The Effect of Mavacamten on Myocardial Blood Flow in Hypertrophy Cardiomyopathy

Methods and Protocols

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This is an internal document summarising the Methods and Protocols of this study.

1 Background & Aims

In Hypertrophic Cardiomyopathy (HCM), mavacamten, an allosteric modulator that stabilises an autoinhibited state of super-relaxed cardiac myosin[1], has shown improvement in exercise capacity and left ventricular outflow tract (LVOT) obstruction[2], regression of left ventricular hypertrophy (LVH)[3], and the overall need for septal reduction therapy.[4] Its effect in myocardial perfusion has not been studied to date, despite 91% of HCM patients having significant perfusion defects.[5] This study aims to investigate the effect of mavacamten on myocardial perfusion using quantitative perfusion Cardiac Magnetic Resonance (CMR).

2 Methods

2.1 Study population

Participants will be recruited through the newly developing Mavacamten in HCM Pathway at Barts Health NHS Trust. Inclusion criteria are a diagnosis of HCM, age 18 years, New York Heart Association (NYHA) functional class II or III, Left Ventricular Outflow Tract (LVOT) gradient 50mmHg (at rest or exertional), LV Ejection Fraction (LVEF) 55%, no concomitant treatment with disopyramide or a combination of beta-blockers and calcium channel blockers (CCBs). Disopyramide will be stopped seven days before starting mavacamten. Beta-blockers or CCBs alone will be continued. All patients are started on low-dose mavacamten 2.5mg OD.

2.2 Baseline assessment

In clinic, this includes the EQ-5D-5L quality of life questionnaire, 12-lead ECG, echocardiogram, cardiopulmonary exercise test, blood tests – Full Blood Count, Urea & Electrolytes, Liver Function Tests, high sensitivity Troponin T, NT-proBNP, and CYP2C19 genotyping.

2.3 Echocardiography

The baseline echocardiogram will be comprehensive. Focused follow-up studies will occur at weeks 4, 8, 12, and at 6 months, to monitor Ejection Fraction and LVOT gradient.

2.4 Cardiac Magnetic Resonance

All scans will be performed at 1.5T field strength. The baseline CMR will take place at least five days after stopping disopyramide. Participants with Cardiac Implantable Electronic Devices will not be excluded from the CMR sub-study.

Follow-up CMR scans will be performed at **8 weeks and 6 months.**

Patient preparation: 2 peripheral venous catheters, one in each arm. Avoid distal positions in the hand. Prefer 20G (pink) and above. A summery of the protocol can be found below (Table 1).

2.4.1 Planning the perfusion sequence

2.4.1.1 Slice position

3 SAX slices and 1 long axis (3 chamber).

SAX slices: increase distance factor to ensure appropriate LV coverage; basal slice at the thick basal septum, apical slice apically enough. 3Ch long axis: to capture perfusion at the LVOT.

2.4.1.2 Slice geometry

Ensure the first prescribed slice (i.e. with shortest Trigger Delay) is the basal SAX, followed by mid SAX and then apical SAX. This assumption is not obvious when prescribing a second slice group for the long axis, which can interfere with slice orientation.

Slice geometry may introduce important confounding effects for appropriate quantification. Firstly, and most importantly, the Arterial Input Function (AIF) curve must be sampled from basal SAX LV blood pool. If the long axis slice is first (shortest TD), the AIF will be sampled from the left atrium, which results in very different curve features (Figure 1). Furthermore, although quantitative CMR measures average gadolinium (Gd) concentration over the entire sampling period, the influence of the position of the slice in the cardiac cycle (Trigger Delay relative to RR interval) has not been conclusively investigated to date, especially in our sequence (study ongoing, Peter Kellman, personal communication). Systolic acquisition may have lower myocardial blood flow (MBF) than diastolic acquisition. Moreover, in systole, HCM patients have been reported to exhibit transient systolic flow reversal[6], which could further exaggerate this potential confounding effect. For all of the above, keeping the convention of measuring from base to apex, then any additional long axis slices, ensures any potential systemtic error is constant in the entire study.

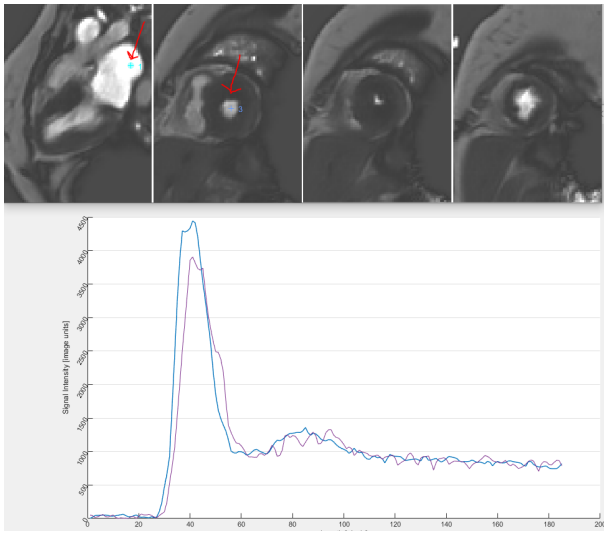

Figure 1: Single pixel time curve sampled from the LA (blue) and the basal LV short axis slice (purple). Note the different delay, upslope and width (Peter Kellman, personal communication)

Practically, start with `Ascending` slice geometry and inspect the test sequence. Modify accordingly. If it is long axis first, then apical-mid-base, changing to `Descending` often resolves the problem. If not, consider manually re-prescribing both slice groups.

If the heart rate during adenosine stress does not allow acquisition of all four slices in one concatenation, drop the long axis slice. Do not go to two concatenations, as this will prescribe the apical and the long axis slices at the beginning of the next RR interval, making them “more systolic”.

2.4.1.3 Number of measurements

Prescibe 120 measurements, as opposed to 60 used in clinical scans.

Our in-line automated software calculates perfusion estimates using a simplified Blood Tissue Exchange (BTEX) model with four variables; tissue blood flow, blood volume, permeability surface area, and interstitial volume[7]. The BTEX partial differential equations are applied to the AIF to calculate the value of each variable which results in the best curve fit, at

each pixel. Therefore, a quantitative map with each pixel's chosen value can be constructed for each variable separately, not just for MBF. This may provide more granular information about the mechanism of change in MBF with mavacamten.

Specifically, each of the four BTEX variable influences a different aspect of Gd's fist pass (Figure 2). Prescribing 120 measurements instead of 60 will provide more data points in the tail plateau of the curve and increase confidence in estimatng interstitial volume (Peter Kellman, personal communication).

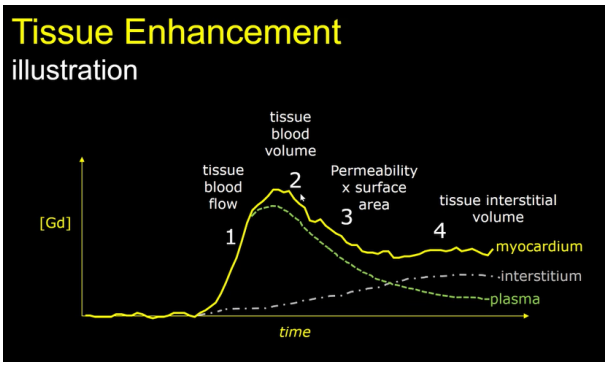

Figure 2: AIF schematic. Each of the four variables of the BTEX model corresponds to a different part of the curve. Acquiring more datapoints in the tail plateau of the curve will increase confidence in estimating interstitial volume.

2.4.2 In participants with Cardiac Implantable Electronic Devices

2.4.2.1 Perfusion

Use FISP perfusion sequence by default, including in participants with Implantable Loop Recorders. In those with pacemakers of ICDs, switch to FLASH perfusion. Note: if a patient is shortlisted for a pacemaker or ICD at the time of inclusion, use FLASH in the baseline scan to ensure quantification can be compared to follow-up scans.

2.4.2.2 Mapping

Here, the first 4Ch T1 is useful to assess off-resonance error through the length of the LV. Consider doing a 3Ch – inspect the SAX pilot for an idea of device artifact. Prescribe a 4Ch T1, inspect the banding artifact, followed by the same 4Ch fat-water DIXON to obtain the field map. If the error is >160Hz it cannot be corrected, so no further mapping is needed.[8]

2.5 Follow-up studies

Mapping is not needed at the 8-week scan. Otherwise, the protocol is identical. Scans at 6 months are identical to baseline.

Table 1: CMR protocol summary

Sequence	Comments
White_Blood_Trans_Stack	As usual
Black_Blood_Trans_Stack	
2ch_Pilot	As usual
5sl_SA_PILOT	Priority to the true apex and slicing the appropriate walls over possible over-riding aorta
Retrogated_cine_4CH	
Retrogated_cine_2CH	
Retrogated_cine_3CH	
4ch_pre_MOLLI (optional)	4Ch optional, to aid planning and quick verification of SAX values.
3SAX_pre_MOLLI	
4Ch_T2 (optional)	
3SAX_T2	
Adenosine stress	Escalate adenosine dose as per guidelines, from 140 g/kg/min, to 175, to 210. In follow-up scans: reproduce adenosine infusion of the baseline scan regardless of HR and symptoms. Continue adenosine infusion throughout the stress sequence. Stop at the end. Measure blood pressure at rest and during stress (~last minute before acquisition)

Sequence	Comments
Stress_SSFP_PERF_AI	Priority sequence. 3 SAX slices and 1 long (3Ch) Increase Distance Factor for appropriate LV coverage. Note this for follow-up studies. Slice geometry: basal-mid-apical-long. 1 concatenation. 120 measurements.
Retrogated cine_SAX	Wait 5 min after adenosine has stopped.
Rest_SSFP_PERF_AI	Identical to stress. Wait ~10 min after adenosine has been stopped to minimise residual vasodilation.
DE_early_2CH	
DE_early_4CH	
LVOT cine	
AoV cine	
LGE	As usual. Consider an additional ~3 mL of contrast ~1min before TI scout acquisition (optional).
TI_scout	
2ch_PSIR	
4ch_PSIR	
SAX_PSIR	
3ch_PSIR	
Post_MOLLI	3 SAX slices.

Analysis of the CMR study and perfusion sequences will be discussed separately.

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