Quantification of Energy Loss in Hypertrophic Cardiomyopathy using 4D Flow MRI

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Introduction: Hypertrophic cardiomyopathy (HCM) is a primary myocardial disease characterized by unexplained asymmetric left ventricular hypertrophy and dynamic obstruction of the left ventricular outflow tract (LVOT). HCM is caused by mutations in sarcomeric contractile proteins and it is characterized by structural alterations, such as cardiomyocyte disarray, scarring and interstitial fibrosis, despite clinically hyperdynamic systolic function[1]. Current diagnosis of obstructive HCM is based on the peak pressure gradient ($\Delta P \geq 30$ mmHg at rest) over the LVOT measured by Doppler echocardiography. However, this technique relies on the single-direction measurement of local peak velocities and may lead to misclassification due to assumptions associated with the simplified Bernoulli equation[2]. Recently, a technique based on 4D flow MRI, that estimates irreversible energy loss (E_L') due to viscous dissipation, showed elevated energy loss in aortic dilatation and aortic valve disease[3]. In this study, we hypothesized that obstructive HCM severity can be characterized by the amount of peak systolic E_L' as calculated from 4D Flow MRI velocity fields covering the entire LVOT. Furthermore, as elevated E_L' may result in increased ventricular loading and lead to worsened myocardial fibrosis, we evaluated myocardial extracellular volume fraction (ECV) with T1 mapping MRI to explore the correlation between E_L' and myocardial ECV.

Methods: Navigator and prospectively cardiac gated 4D Flow measurements in the 3-Chamber view were performed in 19 HCM patients (mean age 51±15 years) and 11 healthy controls (mean age 43±14 years) at 1.5T and 3T (Avanto, Aera and Skyra, Siemens, AG, Germany). Pulse sequence parameters were as follows: TE/TR/FA: 2.2-2.5 ms/4.6-4.9 ms/15º, spatial resolution: 2.1-3.8x2.1-4.1x2.4-3.4 mm, temporal resolution: 37-40 ms, number of cardiac phases: 11-27, FOV: 255-340x255-360x65-132 mm, velocity encoding: 1.5-2.5 m/s. 4D flow velocity data were corrected for Maxwell terms, eddy currents and velocity aliasing and filtered with a median filter (3x3x3 voxels). For all subjects, time-averaged 3D PC-MR angiogram (MRA) data were derived from the 4D flow data. 3D segmentation (MIMICS, Materialise, Leuven, Belgium) based on the 3D-PC-MRA was performed to extract the 3D LVOT geometry. Peak systole was defined as maximum flow through a plane in the mid-ascending aorta (Ensight, CEI Inc, Apex, NC, USA). Similar to strategies reported by Barker at al[3], E_L' in the LVOT was calculated as: $E_L' = \mu \sum_{i=1}^{N} V_i \phi_v$ where μ is the dynamic viscosity of blood (3.2 cP), N is the number of voxels, V is the volume of a voxel and ϕ_v is the viscous dissipation as given by[4]:

$$\phi_v = \frac{1}{2}\sum_i \sum_j \left[\left(\frac{\partial v_i}{\partial x_j} + \frac{\partial v_j}{\partial x_i}\right) - \frac{2}{3}(\nabla \cdot \boldsymbol{v})\delta_{ij}\right] \quad where \quad \begin{matrix} \delta_{ij} = 1 \; for \; i = j \\ \delta_{ij} = 0 \; for \; i \neq j \end{matrix} \qquad (1)$$

in which i and j are the principal directions x, y, z. In addition, the LVOT pressure gradient was estimated from the 4D flow MRI data by the simplified Bernoulli equation: $\Delta P = 4v_{max}^2$. The peak systolic velocity v_{max} in the LVOT was determined by volumetric analysis of the 4D flow data. T1-mapping was performed in 12 of the 19 HCM patients (mean age 50±15 years) using a modified look-locker inversion recovery (MOLLI) technique as described previously[5]. Data for each slice (base, mid, apex) were acquired pre ($T1_{pre}$) and 10-25 minutes post ($T1_{post}$) contrast agent administration (gadopentetate dimeglumine, 0.1 mmol/Kg) using breath holding. Imaging parameters were as follows: spatial resolution = 1.7-2.1 x1.7-2.1x8 mm, slice thickness = 8mm, flip angle = 35°. Patient hematocrit was collected within 48 hours of the cardiac MR exam to allow for calculation of extracellular volume fraction (ECV) values as a marker of microscopic fibrosis. Average T1 values for each slice were calculated using Q Mass MR version 7.5 (Medis Inc, Leiden, Netherlands) by drawing contours along the endocardial and epicardial borders and a region of interest in the left ventricular blood pool in T1 maps. $\Delta T1$ was calculated by the difference of $T1_{pre}$ and $T1_{post}$. The myocardial ECV was calculated using[6]:

$$ECV = (1\text{-}hematocrit) \times (\Delta R1_{myocardium} / \Delta R1_{blood}) \text{ where } \Delta R1 = 1/\Delta T1 \qquad (2)$$

and averaged over the base, mid and apex to estimate whole heart ECV. Differences in E_L' between HCM and controls were evaluated with a Wilcoxon rank sum test. Linear regression was performed to assess a correlation between E_L' and ECV and the coefficient of determination (R^2) was calculated. $P<0.05$ was considered statistically significant.

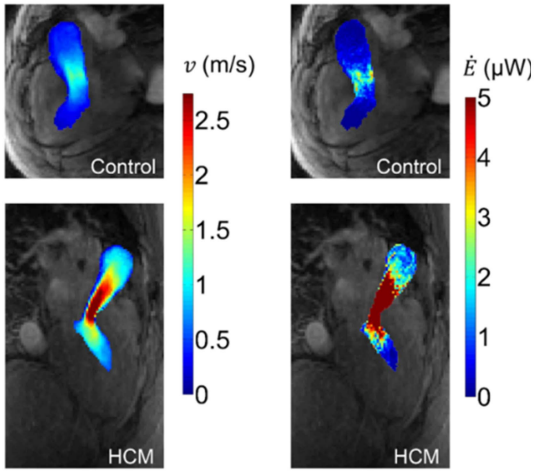

Figure 1: Maximum intensity projections of velocity (left) and energy loss (right) in the LVOT of a control and a HCM patient.

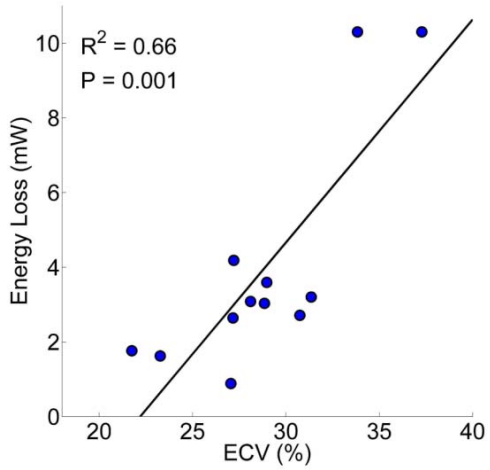

Figure 2: Energy Loss at peak systole compared with myocardial ECV.

Results: Figure 1 shows peak systolic velocity magnitude and E_L' in the LVOT of a control (top) and a HCM patient (bottom). The difference in E_L' between HCM patients and controls was significant (4.0±2.7 mW vs. 1.5±0.6 mW, $P<0.001$). A strong correlation was found between E_L' and the LVOT gradient calculated from 4D Flow MRI ($R^2=0.88$, $P<0.001$). In addition, a significant relationship was found between E_L' and ECV by T1 mapping MRI ($R^2=0.66$, $P=0.001$, figure 2).

Discussion: Increased E_L' in HCM patients may indicate LVOT obstruction and both indicate and lead to remodeling of the left ventricle. The strong correlation found between E_L' and myocardial ECV suggests that increased interstitial tissue is associated with viscous energy loss in the LVOT. Energy loss may help drive myocardial fibrosis in these patients, and longitudinal studies are required to better understand this relationship. 4D Flow MRI analysis of the LVOT and E_L' calculated from this non-invasive technique may be useful in HCM severity assessment and risk stratification without the limitations associated with gradient estimation including the confounding effect of pressure recovery and may aid in improved understanding of HCM pathophysiology.

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References: [1]McKenna WJ, Spirito P. *Heart* 1997;77: 130-32; [2]Pibarot P, Dumesnil, JG. *J Am Coll Cardiol.* 2012 Jul 17;60:169-80; [3]Barker AJ, van Ooij P et al. *Magn Reson Med* 2013; [4]Bird R, Stewart WE et al. *Transport Phenomena*, New York, Wiley, 1960; [5]Messroghli DR, Greiser A et all.*J Magn Reson Imaging* 2007;26:1081-6; [6]Kehr E, Sono M et al. *Int J Cardiovasc Imaging*. 2008;24:61– 68.