Hemodynamic assessment of obstructive hypertrophic cardiomyopathy using 4D flow MRI

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Introduction: Hypertrophic cardiomyopathy (HCM) is an inherited disease with a prevalence of approximately 1:500 in the general population.[1] Patients who have left ventricular outflow tract (LVOT) obstruction are at an increased risk of sudden cardiac death (SCD) and progression to severe heart failure or death from heart failure.[2] Several quantitative markers have been shown to correlate with outcomes and prognosis in patients with HCM including septal thickness, myocardial fibrosis, and peak velocity gradient in the LVOT as assessed by echocardiography.[1] However, at present, diagnosis, risk stratification, and treatment are driven largely by high risk symptoms such as syncope and ventricular arrhythmias or family history of SCD. The pathophysiologic mechanism of high risk events and disease progression is not well understood and a more comprehensive assessment of the individual underlying pathophysiologic mechanisms of HCM is needed to better characterize the disease.

Time-resolved three-dimensional phase contrast (4D flow) MRI allows for quantitative analysis of blood flow within the heart and great vessels with complete volumetric coverage.[4] Patients with obstructive HCM experience dynamic outflow obstruction as a result of basal-septal hypertrophy in combination with systolic anterior motion (SAM) of the mitral valve.[5] Flow assessment using planar techniques such as echocardiography or 2D phase-contrast MRI to assess the complex regional flow dynamics of the LVOT and ascending aorta in these patients is likely to be incomplete. The aim of this study was to employ 4D flow MRI with coverage of the LVOT, left ventricle (LV), left atrium (LA), and mitral inflow. We hypothesize that 3D blood flow visualization and quantification of LVOT and mitral inflow can provide novel insights in altered hemodynamics associated with HCM that may correlate with disease severity and progression.

Methods: Eleven patients (age: 58.5 ± 9.4 years) including 6 men and 5 women referred for cardiovascular MRI (CMR) as part of the routine evaluation of HCM at our institution underwent evaluation with 4D flow MRI at the time of their clinical CMR. All had an echocardiographic diagnosis of HCM. Patients gave written informed consent for this IRB-approved protocol. All measurements were performed on 1.5T MR systems (Avanto, Aera, Siemens, Germany). ECG and respiratory gated 4D flow MRI was acquired in a 3D volume angulated in 3-chamber orientation (LA,LV, LVOT) covering the entire LV (spatial resolution = (2.13-3.75 x 2.13-3.18 x 2.50-3.00) mm³, temporal resolution = 36.8-39.2 ms, venc = 150-250 cm/s). 3D blood flow visualization and quantification was performed using dedicated software (EnSight, CEI, Apex, NC). Analysis planes were placed at the level of the mitral valve (MV), near the apex of the left ventricle, in the LVOT, and in the proximal ascending aorta (AAo). A cylindrical analysis volume was placed along the LVOT. Peak velocity and regurgitant fraction (RF) were calculated in each of the analysis planes. Peak velocity throughout the cardiac cycle was calculated inside the cylindrical analysis volume and peak LVOT gradient was calculated using the simplified Bernoulli equation $P = 4v^2$ (P=peak gradient, v=peak velocity). Time-resolved pathlines generated from each analysis plane depicted the path of blood flow over one cardiac cycle. The visualized pathlines were graded for presence of helical flow in the AAo and regurgitant flow at the MV (absent = 0, mild = 1, severe = 2). Additional patient data were collected including septal thickness from the clinical MRI, peak LVOT gradient from pre-MRI echo, and the presence of symptoms. Pressure gradients were compared using Student's t-test.

Results: Figures 1A and 1B demonstrate flow visualization using 3D streamlines during systole. Figure 1C shows the topography of the peak systolic flow jet through the LVOT as generated by an isovolume velocity threshold (velocity > 1 m/s) inside the cylindrical LVOT analysis volume. Peak LVOT gradients measured in the cylindrical analysis volume were not significantly different compared to echocardiography (41.2 ± 30.8 mmHg vs. 35.23 ± 38.9 mmHg, p= 0.72). Helical flow in the AAo was present in 9 patients and helicity grade was 1.36 ± 0.77. The 4D flow quantitative MV RF was 16.22 ± 15.27%, while the MV RF visual severity grade was 1.09 ± 0.9. The average septal thickness was 1.78 ± 0.3 cm. Symptoms were present in 7 patients (data unavailable on 1 patient), and the most common symptom was exertional dyspnea (DOE). Clinical variables as well as echocardiographic and MRI data of the 11 patients are listed in Table 1. AAo helical grade and 4D flow LVOT peak gradient (Figure 2) both showed positive correlations with maximal diastolic septal thickness as marker of the severity of HCM (r = .459 and r = .496, respectively).

Discussion: CMR is uniquely suited to assess cardiac morphology, function, and tissue characterization in HCM. In this study, we demonstrate the potential of 4D flow MRI to provide additional novel insights into flow characteristics and hemodynamics in patients with obstructive HCM. It is notable that there was no significant difference in peak gradients measured by MRI volumetric velocities compared with those measured by echo. However, the ability to quantify gradients for the full volume of the LVOT throughout the cardiac cycle in a single acquisition may yield a better characterization of dynamic LVOT obstruction and its impact on afterload. Moreover, considering that CMR assessment is the standard of care in this population to assess myocardial fibrosis and wall thickness, incorporating 4D flow assessment adds novel hemodynamic characterization of mitral inflow, intra-cardiac-flow, and LVOT out-flow jet topography, thus providing a comprehensive structural and flow evaluation in a single study. Going forward, markers such as helicity and LVOT dynamic gradients must be correlated with outcomes, symptoms and other quantitative markers, such as myocardial fibrosis, maximum diastolic septal thickness, and ventricular function to aid in risk stratifying these patients and providing insights into the pathophysiology of HCM.

References: 1. Maron BJ. *JAMA*. 2002;287(10):1308-1320 **2.** Maron MS, et al. *NEJM*. 2003;348(4):295-303 **3.**Maron BJ, et al. *JAMA*. 1996;276(3):199-204 **4.** Markl M, et al. *JCMR*. 2011;13:7 **5.**Kim DH, et al. *Circ*. 2010;122(13):1298-1307
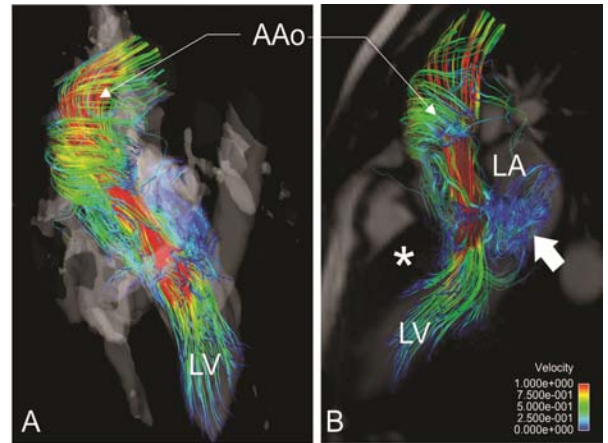
Figure 1:A. LAO view of velocity streamlines during systole demonstrating severe helical flow in the AAo and high velocity in the LVOT. B. Streamlines co-registered with 3-chamber cine MRI showing mitral regurgitation (arrow). C. Volume topography of high velocity systolic LVOT flow jet. Solid arrow – regurgitation through MV; outline arrow – notch corresponding to jet impingement by mitral leaflet; asterisk – thickened septum. LV – left ventricle; LA – left atrium.

Patients	AAo Helical Grading	Gradients (mmHg)		Septal Thickness (cm)	EF (%)	4D flow Mitral Valve RF (%)	Mitral Regurgitant Grading	Symptoms prompting MRI
		Echo	4D flow LVOT Volume					
1	2	92	37.16	2	86	44.90	2	DOE
2	2	23	10.43	1.8	65	5.70	0	DOE, Angina, NSVT
3	1	20.2	14.80	1.8	70	0.00	0	Presyncope
4	0	18.1	67.71	1.5	60	6.08	2	None
5	2	7.3	16.63	1.6	70	1.10	1	DOE, Angina
6	2	N/A	97.00	2.5	75	31.55	2	DOE, Family Hx of SCD
7	1	28.7	85.40	1.8	75	9.78	2	DOE, Family Hx of SCD, Presyncope
8	2	N/A	60.36	1.6	N/A	9.02	1	N/A
9	1	4.7	10.95	1.3	60	4.58	0	DOE, Syncope
10	0	4.1	8.12	1.7	60	29.71	0	None
11	2	119	44.81	2	73	35.99	2	None
Ave	1.36	35.23	41.22	1.78	69.40	16.22	1.09	
St. Dev.	0.77	38.92	30.78	0.30	7.98	15.27	0.90	
Median	2.00	20.20	37.16	1.80	70.00	9.02	1.00	
Min	0.00	4.10	8.12	1.30	60.00	0.00	0.00	
Max	2.00	119.00	97.00	2.50	86.00	44.90	2.00	

Table 1: Obtructive HCM cohort. DOE: exertional dyspnea, NSVT: non-sustained ventricular tachycardia, SCD: sudden cardiac death.

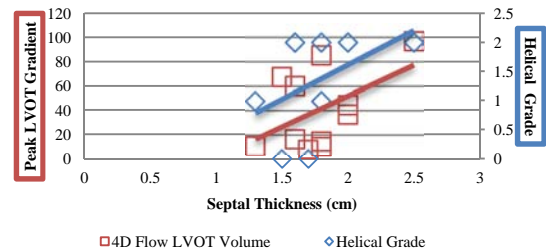□ 4D Flow LVOT Volume   ◇ Helical Grade

Figure 2: 4D flow peak LVOT gradient and helical grade as a function of septal thickness.