SUPPLEMENTAL MATERIAL

Supplemental Methods

Data S1. Cardiac Magnetic Resonance acquisition protocol and analysis

All subjects underwent CMR performed on a 1.5T system (Sola, Siemens, Erlangen, Germany) and abstained from caffeine for at least 24 hours. Cardiac localizers were obtained to plan the cardiac axis views. Using Compressed Sensing-based sequence, cine images in 3 long-axis planes and sequential short-axis slices spanning the entire left ventricle from the base to the apex were acquired. Stress perfusion CMR 90 seconds after hyperemia was induced by regadenoson (400 mcg bolus) using 0.05 mmol/kg of gadolinium (Gadovist, Bayer Schering Pharma AG, Berlin, Germany) followed by 20ml saline flush injected at 5ml/s. Images were acquired apex to base during breath-hold at the first pass of contrast (60 measurements). A gradient echo sequence with a flip angle of 12º, bandwith 651 Hz per pixel, nonsection-selective saturation preparation, field of view 380 mm, acquisition matrix 127x160, slice thickness 10 mm, and standard motion correction was used. LGE images were acquired 10–15 minutes after intravenous administration of additional 0.15 mmol/kg of gadolinium at end diastole, using a breath-held segmented inversion-recovery steady state free precession sequence with a flip angle of 55º, a field of view 400mm, and voxel size of 1.6×1.6×8.0mm after determining the optimal inversion time (TI) using a scout sequence. CMR interpretation was performed by one physician using commercially available software (CMR42, version 5.11, Circle Cardiovascular Imaging, Calgary, Alberta, Canada). LV wall thickness, LV mass, end diastolic volume (EDV), end systolic volume (ESV), and LV ejection fraction (EF) were measured from short axis cine images excluding papillary muscles and trabeculations. Microvascular dysfunction was considered present if a visual perfusion defect was observed. Perfusion defects were considered surrogates for ischemia. For perfusion assessment

and semi-quantification, the myocardium was divided into 32 subsegments (16 American Heart association segments subdivided into an endocardial and epicardial layer). Ischemic burden for each patient was calculated based on the number of involved sub-segments, assigning 3% of myocardium to each sub-segment. Each segment was analyzed for the presence or absence of perfusion defect. Artifacts were assessed by using motion correction in the perfusion sequence and perfusion defects were required to persist for three or more beats throughout the stress perfusion sequence. Perfusion defects sparing the subendocardium and coincident with LGE were not considered, as subendocardial involvement is mandatory for microvascular dysfunction defects. The LGE was analyzed per-segment basis using a signal threshold versus reference myocardium of ≥6 standard deviation. Total LGE was expressed as a proportion of LV mass.

Table S1. Univariable linear regression analysis of left ventricular myocardial work parameters

	Correlation Coefficient (r)	p-value	β-estimate	95% confidence interval	p-value
Global Work Index					
N. segments ischemia (n)	-0.532	**<0.001**	-56.465	-78.163 to -34.767	**<0.001**
Ischemia burden (% of LV mass)	-0.519	**<0.001**	-12.667	-17.778 to -7.554	**<0.001**
MWT	-0.471	**<0.001**	-45.357	-66.554 to -24.160	**<0.001**
LV mass index	-0.558	**<0.001**	-7.319	-10.163 to -4.476	**<0.001**
Concentric hypertrophy pattern	-0.257	**0.028**	-372.156	-701.390 to -42.922	**0.027**
N. segments LGE (n)	-0.331	**0.005**	-29.263	-50.427 to -8.100	**0.007**
LGE (% of LV mass)	-0.285	**0.015**	-15.058	-26.234 to -3.882	**0.009**
Obstructive HCM	-0.163	0.169	-136.897	-359.551 to -85.757	0.224
Diabetes	-0.246	**0.036**	-290.443	-562.397 to -18.489	**0.037**
Hypertension	-0.059	0.619	-45.352	-245.780 to 155.076	0.653
BMI >25 kg/m^2	-0.031	0.868	-60.464	-576.600 to 455.672	0.813
Male sex	-0.040	0.737	-28.073	-237.522 to 181.376	0.790
Global Constructive Work					
N. segments ischemia (n)	-0.519	**<0.001**	-59.373	-80.971 to -37.774	**<0.001**
Ischemia burden (% of LV mass)	-0.532	**<0.001**	-13.788	-18.798 to -8.778	**<0.001**
MWT	-0.504	**<0.001**	-47.400	-68.319 to -26.482	**<0.001**
LV mass index	-0.616	**<0.001**	-8.193	-10.885 to -5.501	**<0.001**
Concentric hypertrophy pattern	-0.321	**0.006**	-447.802	-771.116 to -124.489	**0.007**
N. segments LGE (n)	-0.404	**<0.001**	-37.389	-57.919 to -16.859	**0.001**
LGE (% of LV mass)	-0.372	**0.001**	-17.782	-28.693 to -6.872	**0.002**
Obstructive HCM	-0.105	0.379	-114.085	-337.643 to 109.474	0.312
Diabetes	-0.201	0.091	-248.689	-522.722 to 25.345	0.075
Hypertension	-0.032	0.789	-2.722	-204.462 to 199.018	0.979
BMI >25 kg/m^2	-0.061	0.738	-20.286	-542.004 to 501.433	0.937
Male sex	-0.115	0.337	-72.659	-281.949 to 136.632	0.491
Global Wasted Work					
N. segments ischemia (n)	0.280	**0.017**	5.463	1.902 to 9.024	**0.014**
Ischemia burden (% of LV mass)	0.199	0.094	0.711	-1.016 to 2.438	0.415
MWT	0.210	0.076	4.245	-2.566 to 11.057	0.218
LV mass index	0.258	**0.029**	0.584	-0.369 to 1.537	0.226
Concentric hypertrophy pattern	0.118	0.322	35.833	-62.410-134.076	0.469
N. segments LGE (n)	0.153	0.203	1.919	-4.705 to 8.543	0.565
LGE (% of LV mass)	0.018	0.881	0.269	-3.202 to 3.740	0.877
Obstructive HCM	0.066	0.584	19.423	-45.639 to 84.485	0.553
Diabetes	0.231	0.051	82.361	3.565 to 161.156	**0.041**
Hypertension	0.239	**0.043**	67.500	11.329 to 123.671	**0.019**
BMI >25 kg/m^2	0.338	0.059	75.357	-38.855 to 189.569	0.188
Male sex	-0.110	0.358	-44.321	-104.221 to 15.579	0.145
Global Work Efficiency					
N. segments ischemia (n)	-0.477	**<0.001**	-0.833	-1.244 to -0.422	**<0.001**

Ischemia burden (% of LV mass)	-0.379	**0.001**	-0.156	-0.255 to -0.057	**0.003**
MWT	-0.361	**0.002**	-0.530	-0.931 to -0.130	**0.010**
LV mass index	-0.459	**<0.001**	-0.101	-0.155 to -0.048	**<0.001**
Concentric hypertrophy pattern	-0.200	0.092	-6.138	-11.975 to -0.302	**0.040**
N. segments LGE (n)	-0.263	**0.026**	-0.376	-0.765 to 0.014	0.058
LGE (% of LV mass)	-0.161	0.180	-0.158	-0.363 to 0.048	0.130
Obstructive HCM	-0.193	0.105	-2.758	-6.683 to 1.167	0.166
Diabetes	-0.323	**0.006**	-7.185	-11.834 to -2.536	**0.003**
Hypertension	-0.181	0.127	-2.861	-6.360 to 0.638	0.107
BMI >25 kg/m^2	-0.313	0.081	-6.286	-15.313 to 2.742	0.165
Male sex	0.059	0.625	2.052	-1.627 to 5.731	0.270

p-values were obtained by mixed effects regression models.

LV: left ventricular, MWT: maximal wall thickness, LGE: late gadolinium enhancement, HCM: hypertrophic cardiomyopathy, BMI: body mass index

Table S2. Correlation between myocardial work parameters and ischemia according to obstructive hypertrophic cardiomyopathy (HCM) versus nonobstructive HCM

	Obstructive HCM (n=21)		Nonobstructive HCM (n=54)		
Perfusion defects	Correlation Coefficient (r)	p-value	Correlation Coefficient (r)	p-value	p-value (interaction)
Global Work Index					
N. segments (n)	-0.518	**0.019**	-0.506	**<0.001**	0.953
Ischemia burden (% of LV mass)	-0.524	**<0.001**	-0.414	0.071	0.606
Global Constructive Work					
N. segments (n)	-0.564	**0.010**	-0.520	**<0.001**	0.816
Ischemia burden (% of LV mass)	-0.524	**<0.001**	-0.420	0.065	0.625
Global Wasted Work					
N. segments (n)	0.158	0.506	0.190	0.178	0.904
Ischemia burden (% of LV mass)	0.155	0.514	0.298	**0.032**	0.582
Global Work Efficiency					
N. segments (n)	-0.591	**0.006**	-0.317	**0.022**	0.201
Ischemia burden (% of LV mass)	-0.484	**0.030**	-0.409	**0.003**	0.732

HCM: hypertrophic cardiomyopathy, LV: left ventricular

Table S3. Correlation between myocardial work parameters and ischemia according to the presence of significant replacement fibrosis (LGE ≥15% versus LGE <15%)

	LGE ≥ 15% (n=29)		LGE < 15% (n=45)		
Perfusion defects	Correlation Coefficient (r)	p-value	Correlation Coefficient (r)	p-value	p-value (interaction)
Global Work Index					
N. segments (n)	-0.489	**0.007**	-0.393	**0.009**	0.632
Ischemia burden (% of LV mass)	-0.472	**0.010**	-0.471	**0.001**	0.995
Global Constructive Work					
N. segments (n)	-0.455	**0.013**	-0.359	**0.019**	0.643
Ischemia burden (% of LV mass)	-0.431	**0.019**	-0.408	**0.007**	0.911
Global Wasted Work					
N. segments (n)	0.218	0.165	0.124	0.520	0.697
Ischemia burden (% of LV mass)	0.317	**0.040**	0.209	0.277	0.640
Global Work Efficiency					
N. segments (n)	-0.351	**0.022**	-0.303	0.110	0.829
Ischemia burden (% of LV mass)	-0.474	**0.002**	-0.362	0.054	0.584

LGE: late gadolinium enhancement, LV: left ventricular

Table S4. Segmental univariable linear ventricularregression analysis of left myocardial work parameters.

	Correlation Coefficient (r)	p-value	β-estimate	95% confidence interval	p-value
Global Work Index					
Perfusion defect	-0.294	**<0.001**	-415.325	-502.732 to -327.918	**<0.001**
LGE	-0.227	**<0.001**	-320.131	-405.665 to -234.597	**<0.001**
Wall thickness ≥15 mm	-0.422	**<0.001**	-52.975	-60.801 to -45.148	**<0.001**
Wall thickness 12-14 mm	-0.289	**<0.001**	-85.948	-105.501 to -66.395	**<0.001**
Obstructive HCM	——	——	-158.461	-250.316 to -66.606	**0.001**
Diabetes	——	——	-146.564	-259.618 to -33.511	**0.011**
Hypertension	——	——	-63.451	-146.639 to 19.737	0.135
BMI >25 kg/m^2	——	——	-77.494	-176.738 to 21.751	0.126
Male sex	——	——	-76.704	-162.193 to 8.784	0.079
Global Work Efficiency					
Perfusion defect	-0.242	**<0.001**	-5.635	-7.723 to -3.548	**<0.001**
LGE	-0.133	**<0.001**	-4.408	-6.400 to -2.417	**<0.001**
Wall thickness ≥15 mm	-0.233	**<0.001**	-0.630	-0.821 to -0.438	**<0.001**
Wall thickness 12-14 mm	-0.174	**<0.001**	-0.905	-1.331 to -0.478	**<0.001**
Obstructive HCM	——	——	-3.251	-5.273 to -1.229	**0.002**
Diabetes	——	——	-5.744	-8.318 to -3.171	**<0.001**
Hypertension	——	——	-2.874	-4.745 to -1.003	**0.003**
BMI >25 kg/m^2	——	——	-1.469	-3.749 to 0.810	0.206
Male sex	——	——	-0.050	-1.972 to 1.871	0.959

LGE: late gadolinium enhancement, HCM: hypertrophic cardiomyopathy, BMI: body mass index

Figure S1. Receiver operating characteristic (ROC) curve of the association between Global Work Index and the presence of perfusion defects

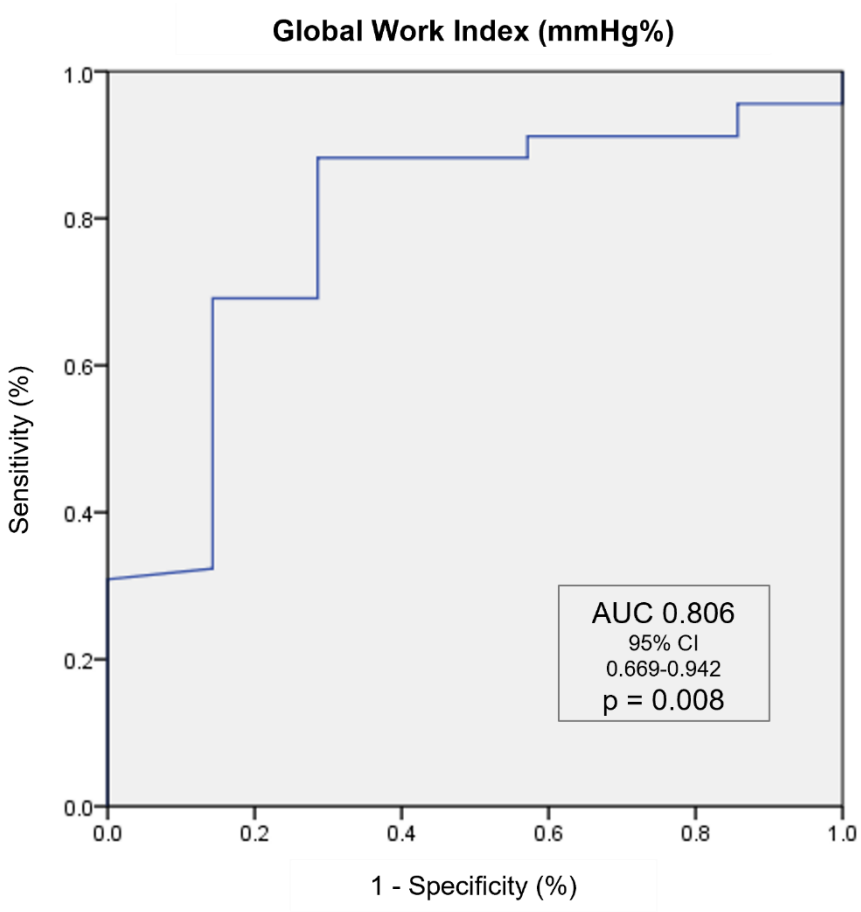


Figure S2. Correlation between myocardial work parameters and ischemia according to obstructive hypertrophic cardiomyopathy (HCM) versus nonobstructive HCM

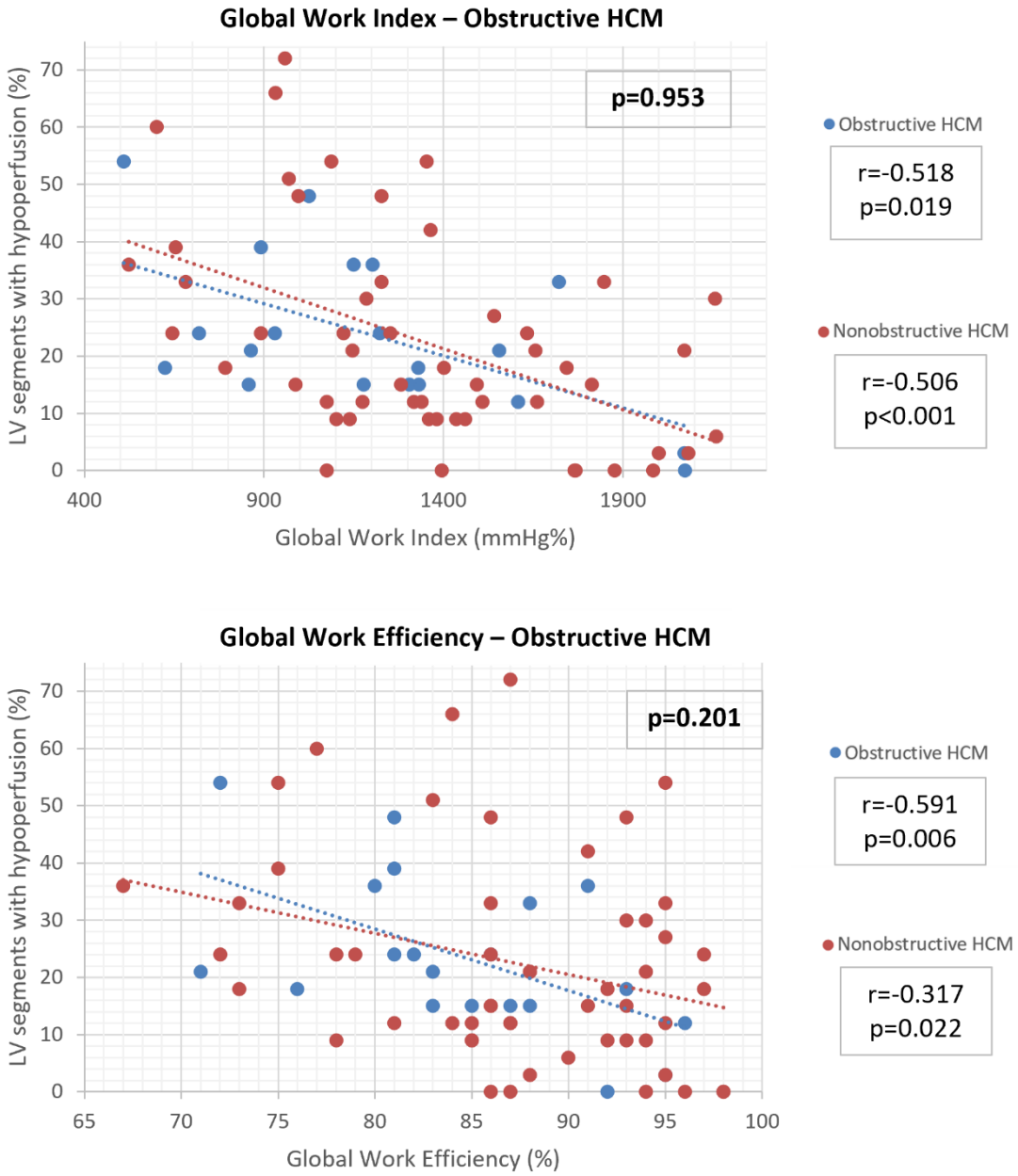
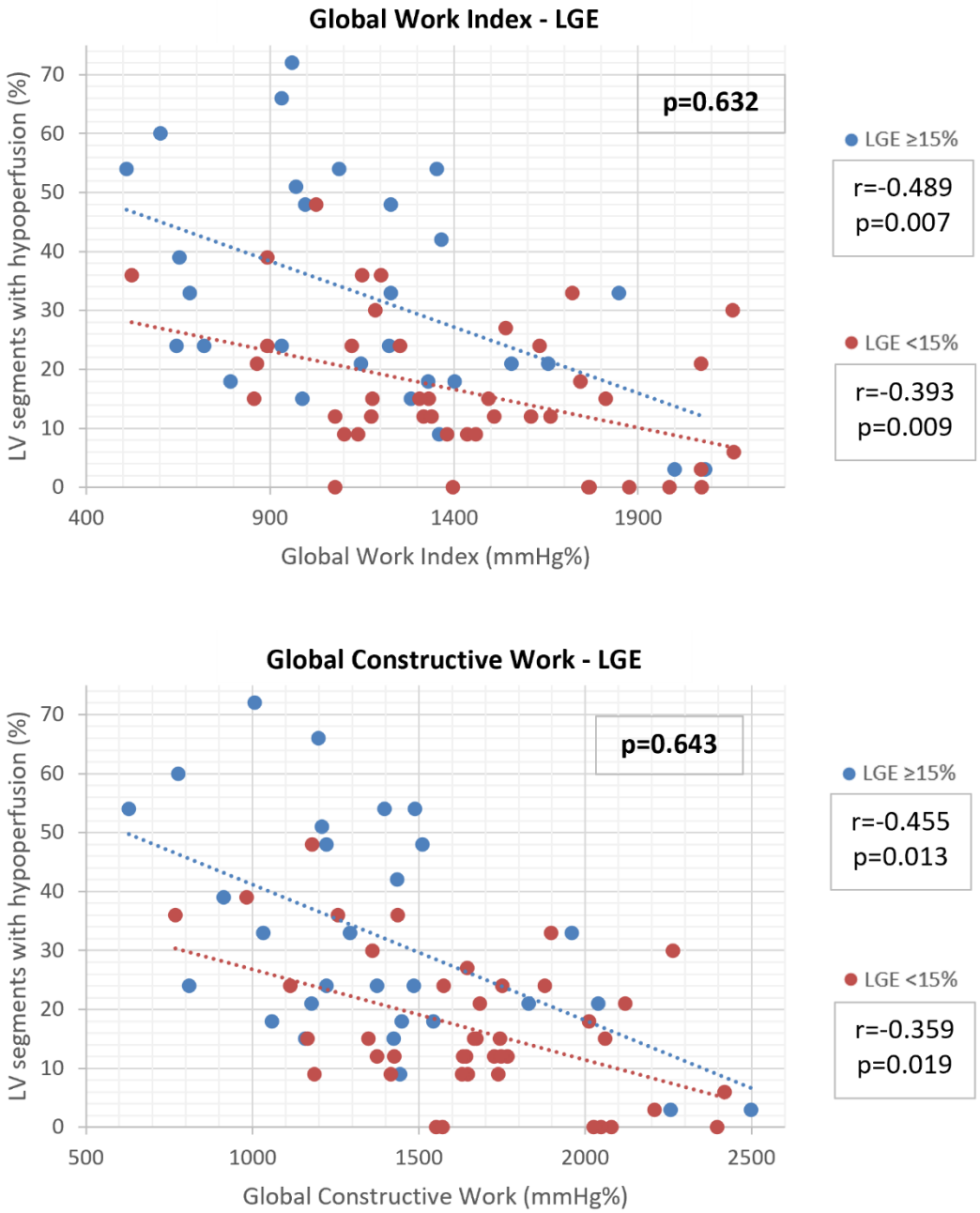


Figure S3. Correlation between myocardial work parameters and ischemia according to the presence of significant replacement fibrosis (late gadolinium enhancement [LGE] ≥ 15% vs LGE < 15%).



LGE: late gadolinium enhancement