SUPPLEMENTAL MATERIAL

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Methods

Tagged MRI studies. Tagged MR images were acquired by whole-body scanners (1.5 CVi, General Electric Medical Systems, Waukesha, Wisconsin, and Sonata/Symphony Siemens Medical Solutions, Erlangen, Germany) using electrocardiograph-triggered segmented *k*-space fast spoiled gradient-echo pulse sequence during breath holds. After completing the standard protocol, 3 tagged short-axis slices (base to apex) were obtained. Parallel striped tags were prescribed in 2 orthogonal orientations (0° and 90°) using electrocardiograph-triggered fast gradient echo with spatial modulation of magnetization (SPAMM) encoding gradients.

Parameters for tagged images were: field of view 40 cm; slice thickness 10 mm; repetition time 6 ms; echo time 3.0 ms; flip angle 10° to 12°; phase encoding views 128 with 6 phase encoding views per segment; temporal resolution 40ms; tag spacing 7 mm.

Harmonic Phase Analysis. Tagged short-axis slices were analyzed by Harmonic Phase (HARP) tool (Diagnosoft Inc, Palo-Alto, Ca).[1;2] HARP is an established method that enables fast determination of myocardial strain. Times to peak systolic circumferential strain (Ecc) and peak systolic strain rate were determined manually for 3 slices, and 3 layers and 4 segments in each slice for each study.

MRI Perfusion Study. Participants were asked to refrain from caffeine intake for 12 hours before their MRI examination. T1-weighted gradient echo imaging with magnetization saturation preparation was used to cover 2 to 3 slices in the short-axis orientation during the first pass of the contrast agent bolus through the LV cavity and myocardium with temporal

resolution equal to the R-to-R duration. Gd-DPTA contrast agent at a dosage of 0.04 mmol/kg of body weight (Magnevist, Berlex, Wayne, NJ) was administered intravenously at a rate of 7 mL/second. The first-pass scan was performed *at rest*, followed by a similar second scan, 15 minutes later, during hyperemia induced by adenosine (0.14 mg/kg per minute for 3 minutes, before the onset of scanning). Adenosine infusion was discontinued after observing the first pass of contrast in the LV, 10 to 15 seconds after starting the perfusion scan.

MRI Perfusion Image Analysis. Region of interest intensity curves were generated with MASS software (Laboratory for Clinical and Experimental Image Processing, Leiden University, Leiden, The Netherlands). The myocardium was divided into eight equal transmural sectors. Myocardial blood flows (mL/min per gm tissue) *at rest* and during hyperemia were determined as previously described.[3]

Statistical Analysis.

The associations of mean time to peak systolic strain, mean time to peak systolic strain rate (averaged across the 12 regions), extent of dyssynchrony (expressed as the SD to time to peak strain or strain rate in 12 regions) with age, gender and LV mass were studied. LV mass index (LV mass/ height$^{2.7}$) and age were studied both as continuous and as categorical variables using quartiles for LV mass index and age groups (45-54, 55-64, 65-74 and 75-85 years). Multiple linear regression models were used to examine relations of time to peak systolic strain, strain rate and their corresponding standard deviations as dependent variables, whereas demographic parameters and risk factors served as independent variables.

Three sets of multivariable models were examined in a hierarchical fashion: These associations were studied in 3 different ways: Model 1: Unadjusted. Model 2: Adjusted for

gender, age (when LV mass index was studied), ethnicity and body mass index (BMI) (when age was used). Model 3: Model #2 with additional adjustments for history of diabetes mellitus (DM), smoking (never, former smoker and current smokers), systolic and diastolic blood pressures (SBP and DBP, respectively), HDL, LDL-cholesterol, and antihypertensive therapy.

Unadjusted differences between continuous variables were studied using ANOVA, while statistical significance of differences between distributions of categorical variables were calculated studied using $\chi 2$ or Fisher Exact tests as appropriate. Relationships between mean blood flow (mbf) *at rest* and during adenosine induced hyperemia and average time to peak strain, strain rate as well as dyssynchrony were determined after adjustment for age, gender, ethnicity, BMI, history of hypertension, diabetes and smoking using multi-variable linear regression. MBF was studied both as a continuous and as a categorical variable (using MBF tertiles). Data are presented as mean±SD.

The normality of residuals from the linear regression models was assessed via standardized normal probability (P-P) plots as well as plotting the quantiles of a variable against the quantiles of a normal distribution showing no deviation from normality in the middle range of data as well near the tails. Skewed plots of residual versus fitted values from age- and LVH-specific regression models did not indicate a discernible pattern or heteroscedasticity in residuals, suggesting that no important deviations from linear model assumptions had occurred. In addition, augmented partial residual plots did not demonstrate nonlinearities in the linear regression models. Variance inflation factor analysis did not demonstrate any multicollinearity in the final regression model. Differences were considered

significant if $p<0.05$. All reported p values are two-sided. Analyses were performed using STATA-8 software (Stata Inc, College Station, Texas).

Table A: Mean, Median and distribution of time to peak strain, strain rate and the extent of dyssynchrony (n=1,100).

Parameter	Mean	Median	S.D	Inter-quartile range	95% confidence intervals
Time to peak systolic strain	315.4	316.9	53.6	282.6 to 348.4	312.2 to 318.5
Time to peak systolic SR	106.6	104.0	29.8	86.6 to 122.5	104.8 to 108.3
SD of Time to peak strain	84.9	80.7	30.6	64.5 to 99.7	83.1 to 86.7
SD of Time to peak SR	47.4	43.7	22.5	35.5 to 54.7	46.0 to 48.7

Table B: Relationship* between age and time to peak systolic strain, strain rate and their variations expressed as SD of time to peak systolic strain/ strain rate.

Variable	Age groups				
	45-54	55-64	65-74	75-85	Trend test (p value)
Time to peak strain (ms)					
Model 1†	Ref	-1.7±5.4 (0.76)	5.9±5.0 (0.24)	6.9±5.4 (0.20)	0.057
Model 2	Ref	-1.1±5.4 (0.83)	6.8±5.0 (0.18)	7.7±5.4 (0.16)	0.052
Model 3	Ref	2.6±5.6 (0.64)	11.8±5.3 (0.027)	12.5±5.8 (0.031)	0.008
Time to peak strain rate (ms)					
Model 1†	Ref	-6.9±3.0 (0.02)	-8.3±2.8 (0.003)	-5.9±3.0 (0.049)	0.082
Model 2	Ref	-6.5±3.0 (0.032)	-7.5±2.8 (0.007)	-5.0±3.0 (0.099)	0.16
Model 3	Ref	-5.3±3.1 (0.088)	-5.3±2.9 (0.072)	-3.6±3.2 (0.26)	0.42
SD of time to peak strain (ms)					
Model 1†	Ref	-3.5±3.1 (0.26)	4.8±2.8 (0.090)	12.9±3.1 (<0.001)	<0.001
Model 2	Ref	0.72±2.3 (0.75)	1.2±2.1 (0.57)	5.6±2.3 (0.015)	<0.001
Model 3	Ref	1.2±2.0 (0.57)	2.1±1.9 (0.27)	5.1±2.1 (0.015)	<0.001
S.D of time to peak strain rate (ms)					
Model 1†	Ref	0.49±2.3 (0.83)	0.71±2.1 (0.74)	5.0±2.3 (0.027)	0.022
Model 2	Ref	0.73±2.3 (0.75)	1.2±2.1 (0.57)	5.6±2.3 (0.015)	0.011
Model 3	Ref	1.2±2.0 (0.57)	2.1±1.9 (0.27)	5.1±2.1 (0.015)	0.010

* Relationship is expressed as regression coefficient using age groups (45-54, 55-64, 65-74 and 75-85 years of age) as a categorical variable and time to peak systolic strain, strain rate or extent of myocardial dyssynchrony [ms]/ age groups ± SD). First quartile (45-54 year of age) is considered as reference.

† Model 1: Unadjusted

Model 2: Adjusted for age gender, ethnicity and BMI.

Model 3: Adjusted for #1+ history of smoking, systolic and diastolic blood pressure, Hx of diabetes mellitus, HDL, LDL, anti-hypertensive and cholesterol lowering medications.

Table C: Relationship* between myocardial blood flow (MBF) at rest and time to peak systolic strain, strain rate and their variations expressed as SD of time to peak systolic strain or strain rate.

Variable	Myocardial blood perfusion at rest (ml/min/gm.)			
Time to peak strain (ms)	Tertile 1	Tertile 2	Tertile 3	Trend test (p value)
Model 1†	Ref	-16.3±13.0 (0.21)	-35.4±13.3 (0.010)	0.009
Model 2	Ref	-15.8±13.2 (0.24)	-51.3±16.6 (0.003)	0.004
Model 3	Ref	-9.8±13.6 (0.47)	-49.9±18.1 (0.008)	0.014
Time to peak strain Rate (ms)				
Model 1†	Ref	-16.7±6.2 (0.009)	-9.7±6.4 (0.13)	0.12
Model 2	Ref	-16.2±6.4 (0.013)	-14.7±8.0 (0.073)	0.024
Model 3	Ref	-12.2±6.6 (0.071)	-12.6±8.8 (0.16)	0.071
SD of time to peak strain (ms)				
Model 1†	Ref	-0.41±8.2 (0.96)	-4.7±8.4 (0.58)	0.58
Model 2	Ref	-1.2±6.2 (0.85)	-17.4±7.8 (0.029)	0.055
Model 3	Ref	-0.65±6.8 (0.92)	-18.5±8.9 (0.044)	0.090
SD of time to peak strain rate (ms)				
Model 1†	Ref	-8.4±3.8 (0.029)	-11.2±3.9 (0.005)	0.005
Model 2	Ref	-7.6±3.9 (0.057)	-11.1±4.9 (0.027)	0.014
Model 3	Ref	-6.2±4.0 (0.13)	-12.0±5.4 (0.029)	0.019

† Relationship is expressed as regression coefficient using myocardial blood flow at rest as a categorical variable, e.g tertiles of increasing resting blood flow. (Time to peak systolic strain strain rate or extent of myocardial dyssynchrony [ms]/ increasing tertile of myocardial blood flow (ml/min/ gm. LV mass ±standard deviation). First quartile is reference. See above (Table A), description for Model 1, Model 2 and Model 3.

Table D:

Relationship between end diastolic volume and time to peak systolic strain (average in 12 regions), time to peak systolic strain rate and dyssynchrony

Parameter	Regression *coefficient	P value	95% CI
Time to peak strain	0.24	0.000	0.12 to 0.36
Time to peak strain rate	0.24	0.000	0.17 to 0.31
SD time to peak strain	-0.04	0.30	-0.11 to 0.35
SD time to peak strain rate	0.08	0.001	0.04 to 0.13

Adjustments were done for the same variables as described above. (Measured as a ratio of time (ms)/ LV volume (ml).

Table E:

Relationship between end systolic volume and time to peak systolic strain (average in 12 regions), time to peak systolic strain rate and dyssynchrony

Parameter	Regression *coefficient	P value	95% CI
Time to peak strain	0.64	0.000	0.42 to 0.87
Time to peak strain rate	0.54	0.000	0.41 to 0.67
SD time to peak strain	-0.12	0.092	-0.26 to 0.19
SD time to peak strain rate	0.14	0.002	0.05 to 0.22

All adjustments were done for the same variables as described above. (Measured as a ratio of time (ms)/ LV volume (ml).

Table F:

Relationship between QRS width and the time to peak systolic strain, strain rate and the extent of dyssynchrony

Parameter	**Regression *coefficient**	**P value**	**95% CI**
Time to peak strain	0.080	0.495	-0.15 to .312
Time to peak strain rate	0.261	< 0.001	0.134 to 0.390
SD time to peak strain	0.0006	0.992	-0.130 to 0.131
SD time to peak strain rate	0.1465	0.003	0.050 to 0.243

* The relationship was studied using multi-variable regression analysis.
Adjustment for gender, race, age and BMI, Hx of smoking, SBP, HDL cholesterol, LDL cholesterol , glucose, history of hypertension, diabetes mellitus, and treatment for hypertension, diabetes and hypercholesterolemia. (Measured as a ratio of time (ms)/ QRS width (ms).

Table G:

Peak systolic strain (mean across regions), strain rate and peak diastolic strain rate (E`) in sex-specific age-groups.

a. Peak systolic strain (averaged across 12 regions) (%)

	Men			Women		
Age-group	n	Mean± S.E	95% CI	n	Mean± S.E	95% CI
45-54	93	-16.8±0.2	-17.3; -16.4	64	-16.9±0.3	-17.4 ; -16.4
55-64	134	-16.5±0.2	-16.9; -16.1	123	-17.1±0.2	-17.5; -16.6
65-74	224	-16.4±0.2	-16.7; -16.1	196	-17.0±0.2	-17.3; -16.7
≥75	141	-16.2±0.2	-16.6; -15.8	124	-16.4±0.2	-16.9; -15.9

Men: test for trend (ANOVA)- F=1.32, (p=0.26)

Women: test for trend (ANOVA)- F=2.01, (p=0.11)

b. Peak systolic strain rate (averaged across 12 regions). (sec^{-1})

	Men			Women		
Age-group	n	Mean± S.E	95% CI	n	Mean± S.E	95% CI
45-54	93	-1.54±0.05	-1.64; -1.44	64	-1.65±0.06	-1.76; -1.54
55-64	134	-1.55±0.04	-1.63; -1.46	123	-1.63±0.05	-1.74; -1.52
65-74	224	-1.57±0.04	-1.64; -1.49	196	-1.66±0.04	-1.74; -1.59
≥75	141	-1.49±0.04	-1.57; -1.42	124	-1.54±0.04	-1.62; -1.46

Men: test for trend (ANOVA) F=0.72, (p=0.54)

Women: test for trend (ANOVA) F=1.30, (p=0.27)

c. Peak diastolic strain rate (E` averaged across 12 regions). (sec^{-1})

	Men			Women		
Age-group	n	Mean± S.E	95% CI	n	Mean± S.E	95% CI
45-54	93	1.69±0.05	1.59; 1.79	64	1.80±0.06	1.68; 1.92
55-64	134	1.54±0.04	1.47; 1.61	123	1.68±0.05	1.58; 1.77
65-74	224	1.59±0.04	1.52; 1.66	196	1.72±0.04	1.65; 1.79
≥75	141	1.51±0.04	1.43; 1.59	124	1.65±0.05	1.55; 1.74

Men: test for trend (ANOVA) F= 2.94 (p=0.03)

Women: test for trend (ANOVA) F=1.38, (p=0.25)

Table H:

Peak systolic strain (mean across regions) (%), strain rate and peak diastolic strain rate (E`) in sex-specific quartiles of left ventricular mass

a. Peak systolic strain (mean across regions) in sex-specific quartiles of left ventricular mass

	Men			Women		
LV mass quartile*	n	Mean± S.E	95% CI	n	Mean± S.E	95% CI
I	137	-16.9±0.2	-17.3; -16.5	119	-16.9±0.2	-17.4; -16.4
II	136	-16.6±0.2	17.1; -16.2	119	-17.0±0.2	-17.4; -16.6
III	138	-16.6±0.2	-17.0; -16.3	119	-16.8±0.2	-17.3; -16.4
IV	135	-15.9±0.2	-16.4; -15.5	119	-16.8±0.2	_17.2; -16.4

Test for trend (ANOVA): Men: F=4.15 (p=0.006) Women: F= 0.08 (p=0.97)

b. Peak systolic strain rate (mean across regions) (sec^{-1}) in sex-specific quartiles of left ventricular mass

	Men			Women		
LV mass quartile*	n	Mean± S.E	95% CI	n	Mean± S.E	95% CI
I	137	-1.67±0.04	-1.76; -1.58	119	-1.75±0.05	-1.85;-1.65
II	136	-1.58±0.04	-1.67; -1.49	119	-1.55±0.04	-1.63; -1.47
III	138	-1.52±0.04	-1.60; -1.44	119	-1.62±0.04	-1.71; -1.53
IV	135	-1.47±0.04	-1.55; -1.39	119	-1.62±0.05	-1.72; -1.52

Test for trend (ANOVA): Men: F= 4.02 (p=0.008) Women: F=2.96 (p=0.03)

c. peak diastolic strain rate (E`) (sec^{-1}) in sex-specific quartiles of left ventricular mass

	Men			Women		
LV mass quartile*	n	Mean± S.E	95% CI	n	Mean± S.E	95% CI
I	132	1.66±0.04	1.58; 1.74	114	1.81±0.05	1.72; 1.91
II	129	1.60±0.05	1.51;1.69	114	1.67±0.05	1.58; 1.76
III	133	1.57±0.04	1.49; 1.64	114	1.70±0.05	1.60; 1.80
IV	130	1.51±0.04	1.42; 1.59	114	1.61±0.05	1.51; 1.71

Test for trend (ANOVA): Men: F= 2.51 (p=0.057) Women: F=3.07 (p=0.027)

* Mean LV mass for each quartile:

Men:

I. 121.9 (70.5; 141.5); II. 153.7 (141.8; 163.5); III.175.4 (163.8; 1885.); IV.218.6 (188.5; 301.3)..

Women:

I. 92.2 (55.71- 104.2); II. 112.2 (104.2-120.6); III. 129.1 (120.6; 138.2); IV. 158.1 (138.3; 254.1).

Reference List

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