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Layer myocardial strain is the most heritable echocardiographic trait

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Abstract

BACKGROUND: Myocardial deformation assessed by strain analysis represents a significant advancement in our assessment of cardiac mechanics. However, whether this variable is genetically heritable or whether all/most of its variability is related to environmental factors is currently unknown.

We sought to determine the heritability of echocardiographically determined cardiac mechanics indices in a population setting.

METHODS: A total of 1357 initially healthy subjects (women 51.6%; 48.2 ± 14.1 years) were included in this study from 20 years follow-up after the 4th visit of the longitudinal familial STANISLAS cohort (Lorraine, France). Data were acquired using state-of-the-art cardiac ultrasound equipment, using acquisition and measurement protocols recommended by the EACVI/ASE/Industry Task Force. Layer-specific global longitudinal strain (GLS) and global circumferential strain (GCS) (full-wall, subendocardial and subepicardial) and conventional structural and functional cardiac parameters and their potential heritability were assessed using restricted maximum likelihood analysis, with genetic relatedness matrix calculated from genome-wide association data.

RESULTS : Indices of longitudinal / circumferential myocardial function and left ventricular (LV) ejection fraction had low heritability (ranging from 10 to 20%). Diastolic and standard LV function parameters had moderate heritability (ranging from 20 to 30%) except for end-systolic and end-diastolic volumes (respectively 30 and 45%). In contrast, GLSEndo/GLSEpi ratio had a high level of heritability (65%). Except for GLSEndo/GLSEpi ratio, a large percentage of variance remained unexplained (greater than 50%).

CONCLUSIONS : In our population cohort, GLSEndo/GLSEpi ratio had a high level of heritability whereas other classical and mechanical LV function parameters did not. Given the increasing recognition of GLSEndo/GLSEpi ratio as an early/sensitive imaging biomarker of systolic dysfunction, our results suggest the possible existence of individual genetic predispositions to myocardial decline.

INTRODUCTION

The intrinsic pathophysiological background of progressive cardiac deterioration leading to heart failure (HF) is poorly understood. Left ventricular (LV) remodeling represents a critical step toward HF, although inter-individual variability in LV remodeling has been studied sparingly. The underlying genetic pathways contributing to myocardial architecture and cardiac mechanics are moreover scarcely defined.

Myocardial deformation assessment of cardiac mechanics has been recognized as an early marker of subclinical LV dysfunction in a variety of clinical settings (1). Global longitudinal strain (GLS) evaluation has been a significant advancement in echocardiographic assessment and has furthermore been implemented in the guidelines related to HF with preserved EF (HFpEF) (2). Recently, our group showed that layer-specific assessment may even be able to discriminate patients with dyspnea in a population cohort, suggesting that this parameter can identify very early stages of cardiac dysfunction (3), potentially preceding the advent of cardiomyopathy and/or HF.

Cardiac mechanics are influenced by LV size, geometry and load (4). However, the weight of heritability versus environmental factors in the inter-individual differences of these parameters has been scarcely studied. Determining whether these features are heritable would improve our understanding of the genetic factors involved in the development of progressive HF (i.e., not subsequent to an acute event such as an MI or myocarditis) (5).

According to the level of heritability of a cardiac parameter, a patient may display an extreme value of this parameter prior to disease diagnosis. In such case, there are two options when facing extreme LV function values in the setting of a cardiac disease: 1) the said value may be related to an underlying heritable feature promoting this cardiac disease or 2) the value may be related to the disease itself. As this pattern cannot be unveiled in “diseased” populations, the heritability of cardiac features must be evaluated in a populational setting. Importantly, if 1) a cardiac trait is highly heritable in populational cohorts and 2) an extreme (low or high) value of this cardiac trait is observed in a given cardiac disease, then this suggests that this particular trait is in all likelihood a (heritable) predisposing factor to the cardiac disease.

Genome-wide association studies of genetic determinants of cardiac function and structure to date have mainly focused to date on LV mass and dimensions, yielding disappointing results (6). Previous studies suggest the potential value of myocardial strain and reported moderate heritability (i.e., the proportion of variance of a quantitative trait due to genetic factors) of longitudinal deformation (16% to 25%) (6,7). Nevertheless, there are currently no studies that have focused on more comprehensive deformation parameters, such as layer-specific assessment.

In light of the above, the present study sought to quantify the genetic component of cardiac mechanics, in particular strain, using heritability estimation.

METHODS

Study population

The STANISLAS cohort is a single-center familial longitudinal cohort initially including 4295 initially healthy subjects of French origin from 1006 families from the Nancy region (Northeastern France). They were first recruited in 1993-95 at the Center of Preventive Medicine and were re-examined approximately every 5 years (8,9). At the fourth visit (V4), conducted in 2011-16, 1705 subjects returned and underwent a medical examination, an interview by trained nurses using a structured questionnaire, including items on socio-demographic characteristics, medical and family history, smoking status, lifestyle, diet and anthropometric data; they were also genotyped. Moreover, subjects without evidence of cardiac disease underwent examination using high-quality echocardiographic imaging at our department.

The study protocols for all examinations were reviewed and approved by the local Ethics Committee of CPP Est 3, France. All participants provided written informed consent to participate in the study.

Two-dimensional standard echocardiography

Examinations were performed in the left lateral decubitus position with a commercially available standard ultrasound scanner (Vivid 9, General Electric Medical Systems, Horten, Norway)

using a 2.5MHz phased-array transducer (M5S). All echocardiographic and Doppler images were recorded in digital raw-data format and, after centralized anonymization, were submitted to the central core laboratory of the Centre d'Investigation Clinique (University of Lorraine, Nancy). Echocardiographic images were obtained from the three standard LV apical views (four-, two-, and three chambers) as well as parasternal short-axis view at the papillary muscles level. All images were acquired at a frame rate of 50–70 frames per second for 2D views and at least three consecutive cardiac cycles were recorded.

Post-processing analysis of deformation parameters

All strain measurements were performed offline by two experienced echocardiographers with dedicated automated software (Q analysis software, Echo PAC PC version 110.1.0, GE Healthcare). This software enables real-time assessment of strain and strain rate, allowing a very rapid and simple analysis of deformation, by manually placing three sample points along the endocardium to define the LV base and the apex on an end-systolic frame and from which mid-wall myocardial layer strain (equivalent to full-wall) was obtained. Each LV wall was divided into three segments (basal, mid and apical), and the quality of tracking was assessed for each myocardial segment. Tracking feasibility in each apical view was rated on visual inspection. All echocardiographic studies with difficult images and/or moderate-to-poor tracking quality (n=415) were reviewed by a second senior echocardiographer. Segments or views with persistent poor tracking quality were excluded from the myocardial deformation analysis. Reproducibility analyses showed that inter- and intra-observer reproducibility of GLS (Endo, Epi and transmural) was good, with intra-class correlations >0.70 for all considered parameters for longitudinal strains (10,11). For GCS, reproducibility analyses showed moderate intra- and inter-observer reproducibility, with intra-class correlations of 0.49 for circumferential GS Epi; 0.51 for circumferential GS Full Wall; and 0.53 for circumferential GS Endo with lower feasibility (n = 949 of 1357 subjects)

Outcomes and strain parameters

The following systolic left ventricular deformation parameters were obtained from 3 apical views and short axis view: a) longitudinal and circumferential global subendocardial strain (GLSEndo

and GCSEndo); b) longitudinal and circumferential global full-wall strain (GLSFull-wall and GCSFull-wall) c) longitudinal and circumferential global subepicardial strain (GLSEpi and GCSEpi), and d) the two endo/epi ratios (longitudinal and circumferential) were also tested (Figure 1). In addition, systolic global strain rate (GSRs) was automatically displayed and calculated from the average of all 17 segments. Moreover, cardiac structure and function were assessed with the following outcomes: left ventricular mass (LVM), left ventricular mass BSA indexed (LVMind BSA), left ventricular thickness (LV thickness), relative wall thickness (RWT), left atrial volume BSA indexed (LAVI), LV end-diastolic volume of BSA indexed (LV End-Diastolic Vol ind BSA), LV end-systolic volume of BSA indexed (LV End-Systolic ind BSA), E/e' ratio and left ventricular ejection fraction (LVEF).

Statistical analysis

The methodology for heritability estimation is based on the genetic relationship between each subject of the cohort. The genomic data from the genome-wide association study (GWAS) were first used allowing to survey thousands of genomic variants, i.e., approx. 600 000 single nucleotide polymorphisms (SNPs) in the present study. A genetic relationship matrix (GRM) was then computed, which was included in a linear mixed model to estimate the variance captured by additive genetic effects via average information restricted maximum likelihood analysis (12). An additional random effect was defined in order to take into account the common household effect resulting from nuclear families (i.e., parental couple and children aged less than 20 years old). In addition to the usual covariates (sex and age), BMI, smoking status, physical activities, hypertension (high blood pressure or treated), heart rate, systolic blood pressure, diastolic blood pressure, fasting blood glucose and diabetes occurrence were also tested for their association with the 14 outcomes using a multivariate linear model.

Analyses were performed using R (version 3.4.1.) and were implemented in the “gaston” R package (version 1.5.6) (13).

RESULTS

Characteristics of study subjects

After exclusion for missing data, a total of 1357 subjects were included in the present study (Supplemental Figure 1). Their clinical characteristics are summarized in Table 1. On average, half of the subjects were women (51.6%) and middle-aged (48.2 ± 14.1 years) due to the family structure of the cohort. A majority of patients were overweight (approximately 50% with $\text{BMI} \geq 25$). About one fifth (21.6%) were current smokers and less than one third (29.8%) had high blood pressure or were on antihypertensive medication. Table 2 summarizes the echocardiographic characteristics of the subjects, from structural parameters to advanced cardiac functions.

Among all tested covariates, sex, age, BMI, hypertension (self-reported or antihypertensive treatment), heart rate, fasting blood glucose and current smoker were retained for further analysis since at least one of these covariates were associated with one outcome in multivariate analysis (Table 3).

Figure 2, Table 4 and Supplemental Figure 2 present the percentage of variance decomposition of all 18 outcomes, the latter of which could be divided into 3 groups: cardiac structure (hypertrophy and remodeling), standard cardiac functions and advanced cardiac functions.

Fixed effects from covariates

The effects of covariates included in the model (i.e., fixed effects) were highly variable among all 18 tested outcomes, from 2% to 50% of the variance (Supplemental Table 1). The portion of variance that could be explained by fixed-effects was removed from the heritability models in the following analyses.

Heritability of cardiac structure parameters (hypertrophy and remodeling)

LVM, LVMind BSA, LV thickness, LAVI and RWT showed moderate heritability, with 25% to 35% of the variance explained by additive genetic effects. Only a small portion of the variance was explained by common household effect (less than 5%), except for LV thickness and RWT (approximately 15%).

Heritability of standard cardiac function parameters

LVEF, E/e' , and GSR_s showed low heritability estimation (from 16.8% to 22.3%) as well as a low common household effect, with more than 70% of the total variance remaining unexplained.

However, LV End-Diastolic Vol ind BSA and LV End-Systolic ind BSA showed relatively high heritability (respectively 45.4% and 31.2%) and moderate effects from common household, resulting in only 28.1% and 52.1% respectively of unexplained variance.

Heritability of layer-specific strain

The three layer strains (longitudinal and circumferential GSEpi, GSFull-wall, GSEndo) presented low heritability and low common household effect, conversely to the longitudinal GSEndo/GSEpi ratio, which presented a (high) heritability of 65%, as well as the highest percentage of variance explained by common household effect (but not for the circumferential GSEndo / GSEpid ratio). Consequently, the residual effect of unexplained variance was very low (only 7%) (Figure 2).

DISCUSSION

In this large population- and family-based epidemiological study with available speckle-tracking evaluation, we found that: 1) most indices of LV myocardial function were genetically driven but with relatively low heritability estimation (10 to 20%); 2) LV volumes were moderately heritable; and 3) GSendo/GSepi ratio was highly heritable (65%) in contrast to all other echocardiographic parameters. These results suggest that GSendo/GSepi ratio could represent a heritable trait. Given the prognostic value of layer specific strain in identifying early impairment in various settings (3,14), the high heritability of GSendo/GSepi ratio may underlie some of the genetic susceptibility to progressive HF development.

HERITABILITY OF LV STRUCTURE AND FUNCTION

The concept of heritability allows a comparison of the relative contributions of additive genetic effects and the common environment to variations in continuous traits such as indices of cardiac structure and function. Previous family studies have demonstrated different genetic contributions to LV geometry depending on the study model, population ethnicity and imaging method used. Most family studies have shown a low heritability of LV structure (15,16). Several studies conducted in various populations have reported heritability estimates for echocardiographic LVM ranging between 24 to 34%, with twin studies reporting much higher estimates (17,18). In light of this previous evidence, the heritability of cardiac parameters is typically perceived as being low. Our results are in line with these previous findings.

Among LV systolic function parameters, ejection fraction exhibited a moderate heritability in previously published studies (from 27% to 47%), whereas we observed a low heritability of LVEF (18%) (18,19). As previously described, we demonstrated a moderate heritability of left ventricular diastolic function as measured by E/e' and LA remodeling (19,20,21). LV function is influenced by numerous changing environmental factors such as loading conditions that are partly related to blood pressure and water/salt intake levels; these key environmental factors may explain the variability of heritability estimates across the various studies.

Speckle-tracking echocardiography provides detailed information regarding LV mechanical function including the extent to which the LV shortens in the long axis (longitudinal strain). Myocardial deformation represents the interaction between contractility and load. The use of longitudinal strain enables the detection of early functional impairment in several medical conditions, including hypertension (22). Several environment/inheritable conditions are known to have an impact on strain values, in particular gender and aging. However, clinical covariates only contributed to a modest proportion of the variation in strain values (23). Transmural longitudinal peak strain is also only moderately sensitive to acute and chronic changes in load (24), whether afterload or preload (25). Despite this relative independence of strain values with environment variables, our study revealed a modest heritability of strain components, especially GLS, possibly resulting from unmeasured factors affecting the values of strain components.

A LAYER-SPECIFIC APPROACH

In the present study, longitudinal GSendo/GSepi ratio was found to be the most heritable of these cardiac mechanics traits. Layer-specific strain, which has superior diagnostic value comparatively to other LV myocardial deformation parameters (14), showed remarkably high heritability (65%).

In healthy subjects, GLS decreases from the endocardial to the epicardial layer of the left ventricle, with emerging data being compiled with respect to normal values for each layer in healthy subjects (26). Similar to transmural strain, longitudinal strain in healthy subjects is associated with sex, heart rate, stroke volume (27) and hypertension. However, clinical covariates account for only a modest proportion of its variability. More importantly, layer-specific LV longitudinal strain is unaffected by aging (28), a feature relatively rare for an echocardiographic variable.

Myocardial fiber function changes according to pressure and volume load; however, anatomical studies showed no impact of these variables on myocardial strand orientation (5). Differences in strain values according to layer is largely explained by the distribution of heart fibers (25). Previous reports showed discordant heritability levels for layer-specific deformation parameters.

Low genetic and environmental contributions for LV longitudinal and circumferential strain have been reported in a twin study, suggesting that different myocardial layers may be genetically independent of each other (29). However, large community-based cohorts identified a relatively strong heritability of circumferential strain (30%) and to a lesser extent longitudinal strain (16%) in families of patients with heart failure (30). In addition to these previous reports, the present study assessed the heritability of GSendo/GSepi in a populational setting. The very high level of involvement of genetic factors (65% heritability) suggests that GSendo/GSepi is under the dependence of inherited anatomical/geometrical cardiac features. Indeed, in human quantitative genetics, the most heritable traits are anatomical, the first of which is height (heritability close to 80%); we could consequently hypothesize that the very high heritability of GSendo/GSepi may be related to intrinsic anatomical factors.

Clinical perspectives

Mechanical changes characterized by the increase in subendocardial dysfunction represent the transition to Stage B HF disease. Prolonged risk factor exposure leads to decreasing subendocardial function, by further reductions in longitudinal shortening, lengthening and suction performance. Of note, a decreasing GSendo/GSepi ratio systematically precedes LV hypertrophy and remodeling in hypertension (31), reinforcing GSendo/GSepi ratio as a very early marker of dysfunction.

Our results suggest the existence of a familial predisposition of GSendo/GSepi ratio pattern, which may have an impact on the further development of subendocardial LV dysfunction, the latter being a turning point in HF genesis (32-34).

LIMITATIONS

The size of the study population is moderate and only 1705 subjects returned for Visit 4; however, their baseline characteristics have been reported to be similar overall to subjects lost to follow-up or deceased (35), hence these missing subjects are unlikely to have substantially modified our results.

Although strain variables exhibit good reproducibility in terms of intra-observer and inter-observer variability, monolayer strain analysis suffers from intervencor variability. Efforts to achieve

standardization between manufacturers would thus be required before advocating the widespread use of this technique (36).

CONCLUSION

We demonstrate that GSendo/GSepi ratio is highly related to genetic factors whereas the importance of environmental factors is limited. Indeed, layer-strain ratio showed the highest heritability among all investigated function and remodeling cardiac parameters. Its dominant inheritance, the sensitive detection of subtle myocardial dysfunction and the reproducible nature of this imaging biomarker reinforce its potential value as a method of choice for population-based screening programs and the early detection of families (rather than individuals) at higher risk of overt heart failure. A better understanding of this heritable cardiac trait may be needed to best prevent HF in a population setting.

Data Availability Statement

The data underlying this article will be shared on reasonable request to the corresponding author.

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Conflict of interest

The authors declare not having conflicts of interest related to the content of this manuscript.

Table 1: Clinical characteristics of the 1357 study subjects

	N (%) or mean \pm SD
Female sex	700 (51.58%)
Age (years)	48.19 \pm 14.12
BMI (kg/m ²)	25.66 \pm 4.43
Overweight (BMI \geq 25)	676 (49.82%)
Current smoker (yes)	293 (21.59%)
Physical activities	669 (42.30%)
24h SBP (mm Hg)	119.92 \pm 10.15
24h DBP (mm Hg)	74.21 \pm 7.20
Office SBP (mm Hg)	125.53 \pm 15.41
Office DBP (mm Hg)	72.41 \pm 8.88
Hypertension (yes)*	405 (29.84%)
HR (bpm)	63.67 \pm 9.12
Total cholesterol (g/L)	2.13 \pm 0.39
HDL (g/L)	0.58 \pm 0.14
LDL (g/L)	1.34 \pm 0.34
TG (g/L)	63.67 \pm 0.54
Fasting blood glucose (g/L)	0.90 \pm 0.16
Diabetes (yes)	50 (3.68%)
eGFR (CKD formula) (mL/min/1.73m ²)	97.01 \pm 15.46
Dyslipidemia	309 (22.77%)

* treated hypertension or high blood pressure

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; HDL, high-density lipoproteins; LDL, low-density lipoproteins; TG, triglycerides; eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease

Table 2: Echocardiographic characteristics of the 1357 study subject

	N (%) or mean \pm SD
LVM (g)	139.54 \pm 42.65
LVM indexed (g/m ³)	75.65 \pm 18.72
LVH (n)	168 (12.44%)
LV thickness (cm)	0.87 \pm 0.17
Left atrial volume indexed (mL/m ²)	22.64 \pm 6.97
Relative wall thickness	0.38 \pm 0.09
LVEF (%)	65.11 \pm 6.43
LV end-diastolic volume indexed (mL / m ²)	48.98 \pm 12.41
LV end-systolic volume indexed (mL / m ²)	17.26 \pm 6.05
E/e'	6.41 \pm 1.78
GSR_s (1/sec)	-1.09 \pm 0.18
Longitudinal strains	
GSEpi (%)	-18.58 \pm 2.91
GSFull-Wall (%)	-20.58 \pm 3.03
GSEndo (%)	-22.91 \pm 3.25
GSendo/GSepi ratio	1.24 \pm 0.08
Circumferential strains (949 subjects only)	
Circ_GSEpi (%)	-9.41 \pm 2.74
Circ_GSFull-Wall (%)	-16.02 \pm 3.52
Circ_GSEndo (%)	-25.84 \pm 5.69
Circ_GSendo/GSepi ratio	2.96 \pm 1.04

LVM, left ventricular mass; LVM indexed, left ventricular mass indexed by BSA (body surface area); LVH, left ventricular hypertrophy; LVEF, left ventricular ejection fraction; LV, left ventricular; GSR_s, systolic global strain rate; GSEpi, global subepicardial GLS; GSFull_Wall, global full-wall GLS; GSEndo, global subendocardial GLS

Table 3: Multivariate regression for the covariate effects included in the model for heritability estimation

	LVM			LVM ind BSA			LV thickness			LAVI		
	beta	(sd, SD)	P value	beta	(sd, SD)	P value	beta	(sd, SD)	P value	beta	(sd, SD)	P value
Age	0.30	0.07	<0.01	0.27	0.04	<0.01	0.003	0.001	<0.01	0.04	0.02	0.02
Female sex	-40.39	1.76	<0.01	-12.37	0.90	<0.01	-0.103	0.008	<0.01	-0.58	0.39	0.13
BMI	3.39	0.21	<0.01	0.76	0.11	<0.01	0.009	0.001	<0.01	0.21	0.05	<0.01
Hypertension	11.15	2.09	<0.01	5.89	1.07	<0.01	0.032	0.010	0.001	1.45	0.46	<0.01
HR	-0.73	0.10	<0.01	-0.34	0.05	<0.01	-0.001	0.001	0.57	-0.18	0.02	<0.01
Fasting blood glucose	-11.00	5.99	0.07	-6.39	3.07	0.04	-0.112	0.029	<0.01	-0.96	1.31	0.46
Current smoker	4.69	2.18	0.03	2.08	1.11	0.06	0.019	0.010	0.07	0.37	0.48	0.44
Physical activities	2.91	1.75	0.10	1.39	0.90	0.12	0.001	0.008	0.87	0.76	0.39	0.05

	RWT			LVEF			LV end-diastolic volume indexed			LV end-systolic volume indexed		
	beta	(sd, SD)	P value	beta	(sd, SD)	P value	beta	(sd, SD)	P value	beta	(sd, SD)	P value
Age	0.002	0.001	<0.01	0.06	0.01	<0.01	-0.09	0.03	<0.01	-0.06	0.01	<0.01
Female sex	-0.016	0.005	<0.01	1.71	0.35	<0.01	-6.38	0.67	<0.01	-3.19	0.32	<0.01
BMI	0.001	0.001	0.029	0.08	0.04	0.05	-0.13	0.08	0.09	-0.08	0.04	0.04
Hypertension	0.010	0.006	0.059	0.79	0.41	0.05	0.54	0.79	0.50	-0.02	0.37	0.96
HR	0.001	0.001	<0.01	-0.01	0.02	0.74	-0.26	0.04	<0.01	-0.09	0.02	<0.01
Fasting blood glucose	-0.055	0.016	<0.01	-0.49	1.20	0.68	-4.27	2.27	0.06	-1.12	1.07	0.30
Current smoker	0.004	0.006	0.445	-0.19	0.42	0.65	-1.38	0.83	0.10	-0.35	0.39	0.38
Physical activities	-0.003	0.005	0.570	-0.18	0.34	0.60	1.26	0.66	0.06	0.59	0.31	0.06

	E/e'			GSR_s			GSEpi			GSFull-wall		
	beta	(sd, SD)	P value	Beta	(sd, SD)	P value	beta	(sd, SD)	P value	beta	(sd, SD)	P value
Age	0.042	0.003	<0.01	-0.001	0.001	0.03	-0.013	0.006	0.04	-0.02	0.01	0.02
Female sex	0.469	0.088	<0.01	0.002	0.010	0.83	-1.217	0.156	<0.01	-1.28	0.16	<0.01
BMI	0.059	0.010	<0.01	0.008	0.001	<0.01	0.137	0.018	<0.01	0.16	0.02	<0.01
Hypertension	0.598	0.104	<0.01	0.019	0.012	0.13	0.409	0.185	0.03	0.39	0.19	0.04

HR	-0.014	0.005	<0.01	-0.003	0.001	<0.01	0.046	0.009	<0.01	0.05	0.01	<0.01
Fasting blood glucose	1.076	0.298	<0.01	0.023	0.035	0.51	0.668	0.530	0.21	0.45	0.55	0.41
Current smoker	0.150	0.109	0.17	0.019	0.013	0.13	0.299	0.193	0.12	0.30	0.20	0.13
Physical activities	-0.055	0.088	0.53	0.004	0.010	0.72	0.002	0.155	0.99	-0.03	0.16	0.87

	GSEndo			GSEndo/GSEpi ratio			Circ_GSEpi			Circ_GSFull_Wall		
	beta	(sd, SD)	P value	Beta	(sd, SD)	P value	beta	(sd, SD)	P value	beta	(sd, SD)	P val
Age	-0.018	0.007	0.01	0.001	0.001	0.30	-0.001	0.016	0.97	0.027	0.009	<0.01
Female sex	-1.344	0.172	<0.01	-0.010	0.005	0.03	-1.131	0.393	<0.01	-0.843	0.239	<0.01
BMI	0.173	0.020	<0.01	0.000	0.001	0.79	0.120	0.048	0.01	0.117	0.029	<0.01
Hypertension	0.360	0.204	0.08	0.009	0.005	0.12	-0.407	0.486	0.40	-0.178	0.296	0.55
HR	0.052	0.010	<0.01	0.000	0.000	0.17	-0.005	0.022	0.84	0.004	0.014	0.78
Fasting blood glucose	0.193	0.586	0.74	0.037	0.016	0.02	-2.530	1.710	0.14	-2.143	1.041	0.04
Current smoker	0.308	0.213	0.15	0.003	0.006	0.56	0.445	0.470	0.34	0.373	0.286	0.19
Physical activities	-0.052	0.172	0.76	0.004	0.005	0.42	-0.234	0.384	0.54	-0.130	0.233	0.58

	Circ_GSEndo			Circ_GSEndo/ Circ_GSEpi ratio		
	beta	(sd, SD)	P value	Beta	(sd, SD)	P value
Age	0.029	0.007	<0.01	0.013	0.003	<0.01
Female sex	-0.678	0.189	<0.01	-0.094	0.073	0.201
BMI	0.086	0.023	<0.01	0.012	0.009	0.193
Hypertension	-0.055	0.233	0.812	0.010	0.090	0.914
HR	0.009	0.011	0.421	0.003	0.004	0.466
Fasting blood glucose	-1.545	0.829	0.063	-0.385	0.322	0.232
Current smoker	0.410	0.225	0.069	0.125	0.087	0.151
Physical activities	-0.076	0.184	0.679	-0.008	0.071	0.908

BMI, body mass index; HR, heart rate; LVM, left ventricular mass; LVM indexed, left ventricular mass indexed by BSA (body surface area); LVH, left ventricular hypertrophy; LVEF, left ventricular ejection fraction; LV, left ventricular; GSR_s, systolic global strain rate; GSEpi, global subepicardial GLS; GSFULL_Wall, global full-wall GLS; GSEndo, global subendocardial GLS

Table 4: Percentage of variance decomposition

	Heritability	Common household effect	Residual effect
LVM	34.82	3.08	62.11
LVM indexed	30.77	2.66	66.57
LV thickness (cm)	30.13	16.66	53.21
Left atrial volume indexed (ml/m ²)	27.65	4.26	68.09
Relative wall thickness	25.60	14.35	60.05
LVEF (%)	18.18	4.06	77.76
LV end-diastolic volume indexed (mL/m ²)	45.41	26.53	28.06
LV end-systolic volume indexed (mL/m ²)	31.16	16.76	52.08
E/e'	22.32	0.68	77.00
GSR_s (1/sec)	16.77	1.28	81.95
Longitudinal Strain			
GLSEpi (%)	18.27	7.98	73.75
GLSFull-Wall (%)	13.41	3.80	82.79
GLSEndo (%)	12.89	1.19	85.92
GLSendo/GLSepi ratio	65.44	27.45	7.10
Circumferential Strain			
GCSEpi (%)	20.78	4.99	74.23
GCSFull-Wall (%)	18.43	13.34	68.23
GCSEndo (%)	11.27	11.09	77.64
GCSEndo/GCSEpi ratio	10.39	0.55	89.07

See Table 2 for abbreviations

Figure 1: Longitudinal and circumferential strain curves measured by speckle tracking echocardiography

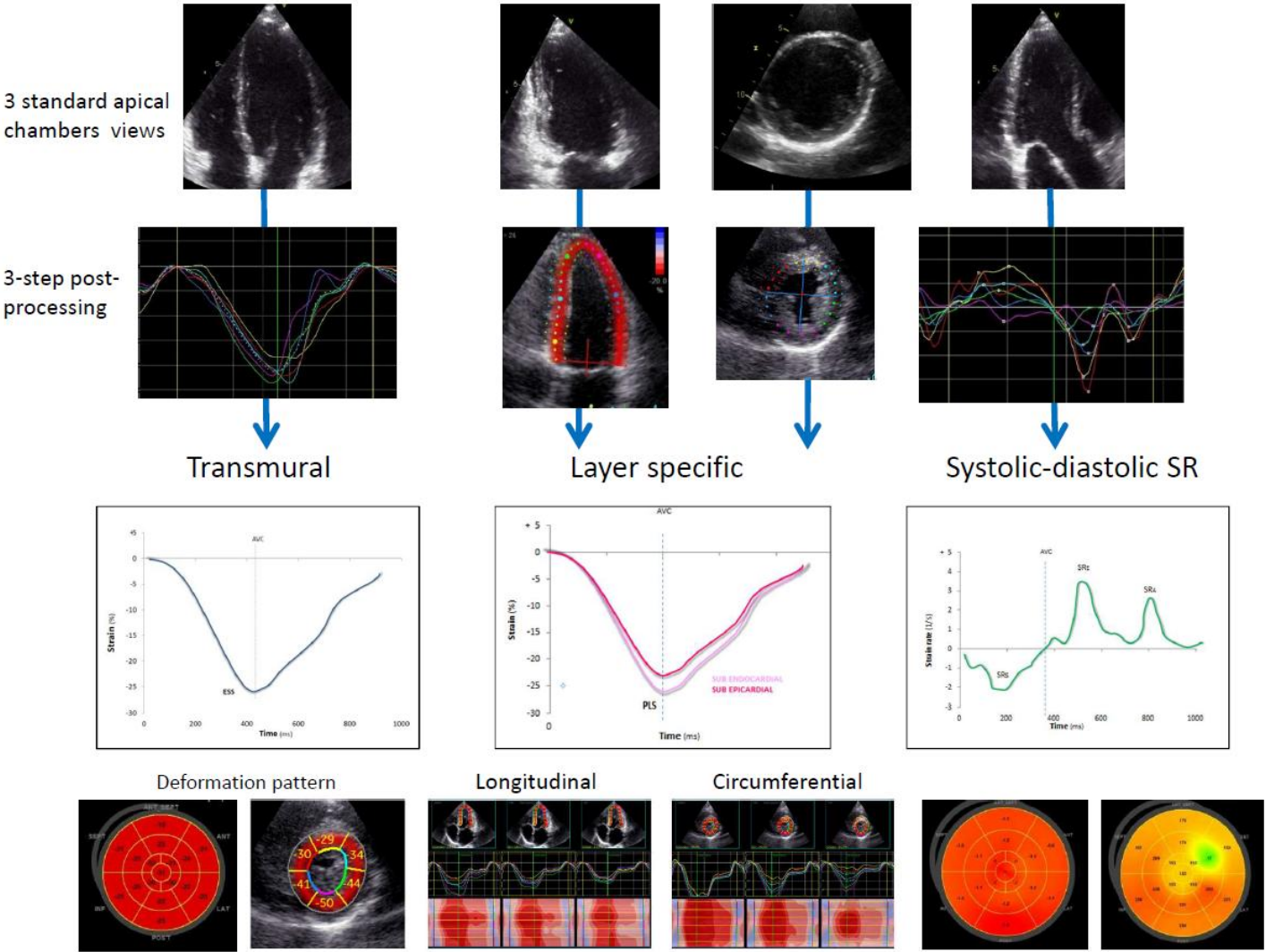
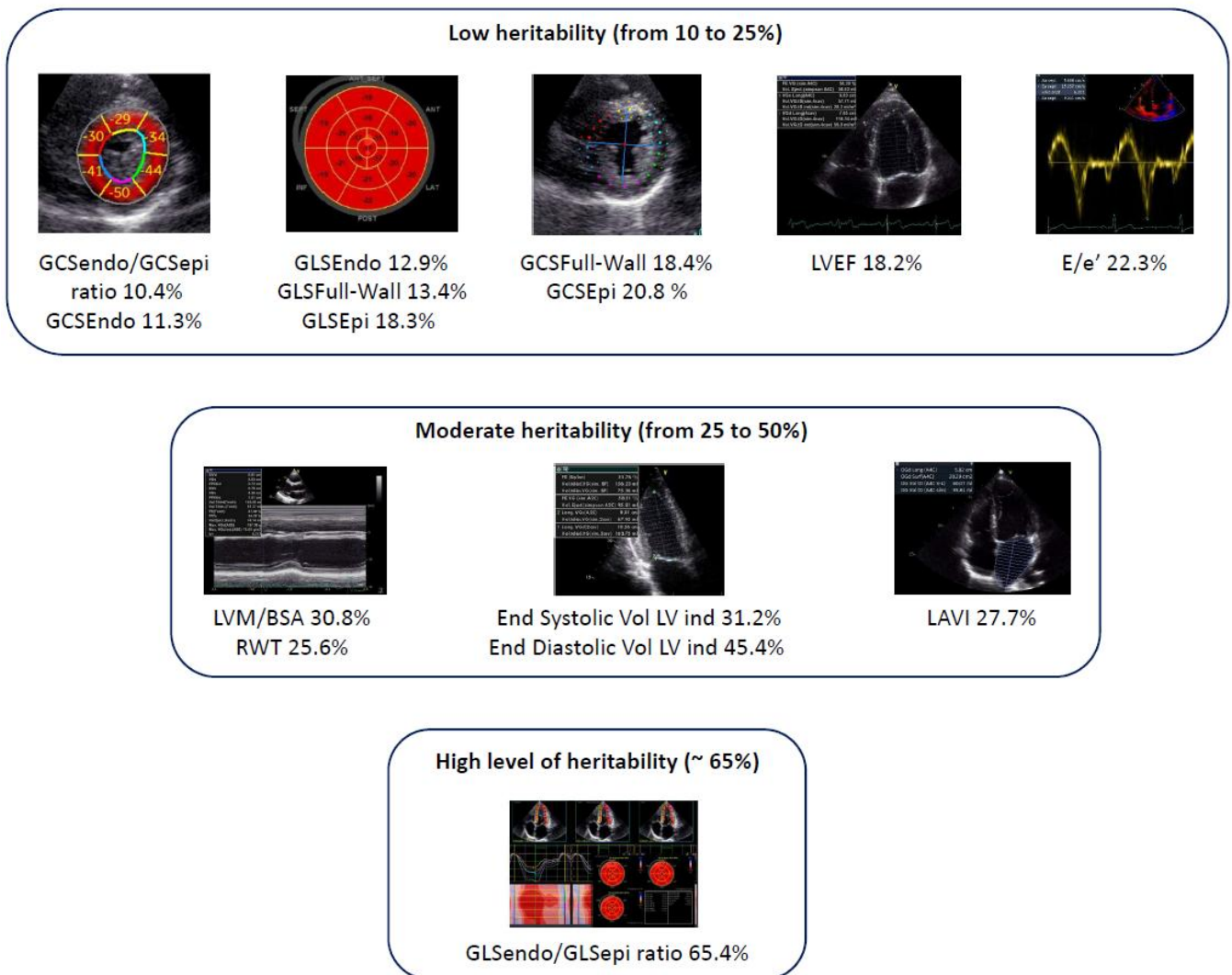
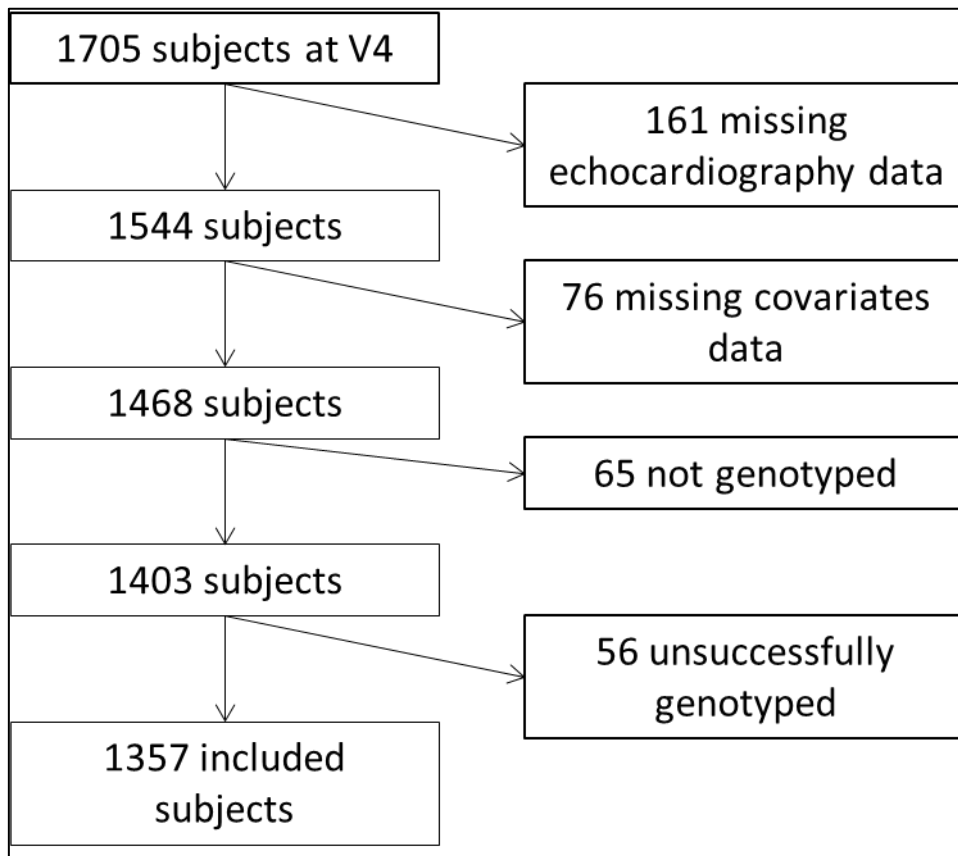


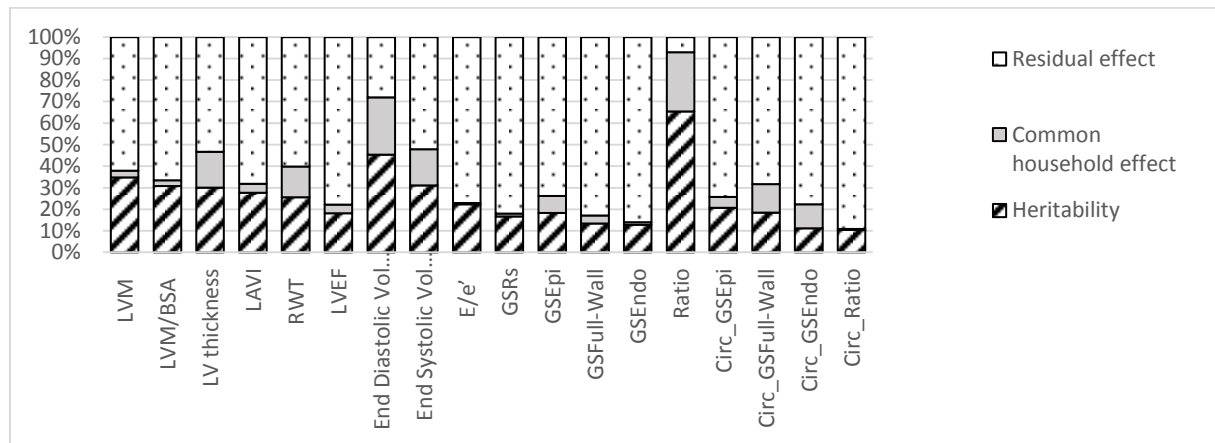
Figure 2: Differences in main standard echocardiographic and deformation parameters according to their level of heritability



Supplemental Figure 1: Study flow chart



Supplemental Figure 2: Variance composition and heritability estimation (%)



LVM, left ventricular mass; LVM/BSA, left ventricular mass indexed body surface area; LAVI, left atrial volume indexed; RWT, relative wall thickness; LVEF, left ventricular ejection fraction; LV, left ventricular; GSR_s, systolic global strain rate; GSEpi, global subepicardial GLS; GSEpi, global full-wall GLS; GSEpi, global subendocardial GLS

Supplemental Table 1: Percentage of variance decomposition (with fixed effects)

	Heritability	Common household effect	Fixed effect*	Residual effect
LVM (mL)	17.66	1.56	49.27	31.51
LVMindBSA (mL/m ²)	20.86	1.73	30.46	46.94
LV thickness (cm)	22.58	12.48	39.87	25.07
LAVI (mL/m ²)	24.91	3.83	9.90	61.35
Relative wall thickness	22.74	12.76	11.14	53.36
LVEF (%)	17.43	3.90	4.09	74.58
LV end-diastolic volume indexed (mL/m ²)	39.23	22.92	13.62	24.24
LV end-systolic volume indexed (mL/m ²)	27.28	14.68	12.44	45.60
E/e'	16.28	0.50	27.06	56.17
GSR _s (1/sec)	15.79	1.20	5.90	77.11
Longitudinal Strains				
GLSEpi (%)	15.86	6.93	13.16	64.04
GLSFull-Wall (%)	11.55	3.27	13.91	71.27
GLSEndo (%)	11.14	1.02	13.56	74.27
GLSEndo/GLSepi ratio	64.32	26.98	1.71	6.98
Circumferential Strains				
GCSEpi (%)	19.88	4.77	4.33	71.01
GCSFull-Wall (%)	17.85	12.92	3.17	66.07
GCSEndo (%)	11.15	10.98	1.04	76.83
GCSEndo/GCSEpi ratio	10.14	0.53	2.33	86.99

* fixed effects are sex, age, BMI, hypertension, heart rate, fasting blood glucose and smoking status
See Figure 2 for abbreviations