

Relationships between Heart Shape, Function and Disease in 38,858 UK Biobank Participants.

Richard Burns^{1,2}, Laura Dal Toso^{1,3}, Charlène A Mauger^{1,4}, Alireza Sojoudi⁵, Avan
Suinesiaputra¹, Steffen E Petersen^{2,6,7}, Julia Ramírez^{2,8,9}, Patricia B Munroe^{2,6,7},
Alistair A Young^{1,4#}

¹ School of Biomedical Engineering and Imaging Sciences, King's College London,
London, UK.

² William Harvey Research Institute, Faculty of Medicine and Dentistry, Queen Mary
University of London, UK.

³ Institute for Biomedical Engineering, University and ETH Zurich, Zurich, Switzerland

⁴ Department of Anatomy and Medical Imaging, University of Auckland, Auckland, New
Zealand.

⁵ Overjet, Palo Alto, USA.

⁶ NIHR Barts Biomedical Research Centre, Queen Mary University London, London,
UK

⁷ Barts Heart Centre, St Bartholomew's Hospital, Barts Health NHS Trust, London, UK

⁸ Aragon Institute of Engineering Research, University of Zaragoza, Zaragoza, Spain

⁹ Centro de Investigación Biomédica en Red, Biomateriales, Bioingeniería y
Nanomedicina, Zaragoza, Spain

#Address for Correspondence: Alistair Young, School of Biomedical Engineering
and Imaging Sciences, King's College London, 1 Lambeth Palace Rd, London SE1
7EU, UK. Email: alistair.young@kcl.ac.uk

Abstract

Background: Cardiac functional metrics such as ejection fraction, strain and valve excursion are important diagnostic and prognostic measures of cardiac disease. However, they ignore a large amount of systolic shape change information available from modern cardiovascular magnetic resonance (CMR) examinations.

Objectives: We aimed to automatically quantify multidimensional shape and motion scores from CMR, investigate covariates, and test their discrimination of disease in the UK Biobank compared against standard functional metrics.

Methods: An automated analysis pipeline was used to obtain quality controlled 3D left and right ventricular shape models in 38,858 UK Biobank participants, 5,149 of whom had one or more diagnoses of cardiovascular or cardiometabolic disease. Principal component analysis was used to obtain a statistical shape atlas and quantify each participant's left and right ventricular shape at both end-diastole and end-systole simultaneously. Systolic strain was obtained from arc length changes computed from the shape model, and mitral/tricuspid annular plane systolic excursion (MAPSE/TAPSE) was computed from the displacement of the valves. Discrimination for prevalent disease was quantified using linear discriminant analysis area under the receiver operating characteristic curve.

Results: The first 25 principal component scores captured >90% of the total shape variance. Significantly stronger discrimination for atrial fibrillation, heart failure, diabetes, ischaemic disease, and conduction disorders ($p < 0.001$ for each) was obtained using shape scores compared with volumes, ejection fractions, strains, MAPSE and TAPSE.

Conclusions: Automatically derived shape and motion z-scores capture more discriminative information on disease effects than standard metrics, including volumes, ejection fraction, strain and valve excursions.

Keywords: strain, MAPSE, TAPSE, shape

Introduction

Heart function is commonly quantified by ventricular mass, volume, ejection fraction (EF), myocardial strain, and mitral/tricuspid annular plane systolic excursions (MAPSE/TAPSE)¹. These metrics provide useful diagnostic and prognostic information on cardiac disease^{2,3}. Strain is commonly computed from image feature tracking or tissue tagging in cardiovascular magnetic resonance (CMR) imaging¹, or speckle tracking in echo², and is a more sensitive indicator of adverse events than EF in hypertension⁴, hypertrophic cardiomyopathy⁵, and cardio-oncology toxicity⁶. However, MAPSE may be more predictive of death and hospitalization for heart failure than strain⁷ and may contain additional prognostic information for death in hypertensive patients⁸. The relationships between geometry, EF, strain and motion are complex⁹. Different metrics vary differently with covariates such as afterload and body habitus^{10,11}. It is currently unclear what is the best metric for evaluation of heart disease, and better functional metrics are needed to provide more complete evaluation of cardiac dysfunction^{12,13}.

Statistical shape atlases enable quantification of most of the multidimensional heart shape information available in modern medical imaging methods such as CMR^{14,15}. The development of these techniques has been facilitated by large cohort studies such as the Multi-Ethnic Study of Atherosclerosis (MESA)¹⁶ and the UK Biobank¹⁷, which utilized CMR to study the effects of disease on heart structure and function. Previous studies have shown that atlas shape scores have stronger associations with risk factors such as hypertension, hyperlipidaemia, diabetes, smoking and obesity than standard mass and volume metrics in 1,991 participants of MESA¹⁸ and 4,329 participants of the UK Biobank¹⁹. Shape models in ~1,500 volunteers have also shown novel relationships with adiposity and titin-truncating

variants^{20,21}. In particular, atlas-based shape scores have shown independent prognostic information for prediction of future adverse events in 4,618 MESA participants²² and in 1,021 patients post-acute myocardial infarction²³. Fully automated analysis pipelines now enable computation of heart shape and scores in >10,000 UK Biobank participants^{24,25,26}. However, previous studies have not compared shape atlas scores with common functional metrics such as strain and MAPSE for ability to discriminate disease.

The aim of this study was to investigate the sensitivity of atlas metrics of cardiac function to disease, and examine their covariates. We hypothesized that atlas-based shape scores would have stronger discrimination of disease than standard functional metrics of mass, volume, EF, strain and MAPSE/TAPSE. We developed an automated analysis pipeline and generated customized shape models and a statistical shape atlas in 38,858 UK Biobank participants. The atlas captured right and left ventricular shape at both end-diastole and end-systole. Standard functional metrics were computed automatically from the shape models. This enabled direct comparison between atlas scores and standard metrics in linear discriminant analysis evaluation of disease discrimination. We show that atlas scores enable more sensitive discrimination of disease effects on heart shape and function than standard metrics, and show how they can be incorporated into the clinical workflow and used to increase the power of studies to detect disease or treatment effects.

Methods

An overview of the automated analysis pipeline is shown in Figure 1. The pipeline steps are detailed below. Briefly, CMR images (Figure 1A) of UK Biobank participants were automatically analysed using a previously validated²⁷ deep learning convolutional

neural network algorithm (cvi42 Version 5.11 1505) (Figure 1B). Contours of the right and left ventricles and valve landmarks were extracted from short and long axis images and merged in 3D (Figure 1C). A biventricular shape model was customized (Figure 1D) to each case using diffeomorphic registration. Principal component analysis (PCA) was used on the ~5800 resulting model vertices (Figure 1D) for unsupervised dimension reduction resulting in a set of PC shape scores for each participant. Participants with cardiovascular or cardiometabolic disease endpoints (8 types), as well as participants with no reported cardiovascular or cardiometabolic disease (reference) were used for subsequent linear discriminant analysis for each disease type.

Study Population

This post-hoc cross-sectional study evaluated data from the UK Biobank (application 2964); a large-scale prospective cohort study with 500,000 participants aged 40-69 at time of enrolment with detailed health, lifestyle, physical measures, and biological samples. The study design and data collection methods have been described previously^{28,29}. At the time of analysis, 45,683 individuals had available CMR images (Figure 1A)²⁹. All participants gave written informed consent and the appropriate institutional review boards approved the study protocol (National Research Ethics Service North-West 11/NW/0382). Systolic blood pressure was averaged between manual and automated readings taken at the imaging visit and adjusted by adding 15mmHg if the participant was taking blood pressure altering medication.

Cardiovascular or cardiometabolic disease prevalence was determined for 8 categories: atrial fibrillation; heart failure; a composite of myocardial infarction and/or ischaemic heart disease; hypertrophic cardiomyopathy; dilated cardiomyopathy; type 2 diabetes mellitus; conduction disease comprising significant atrioventricular block,

1 bundle branch block and fascicular block; and a ventricular arrhythmia composite
2 including ventricular arrhythmia, implanted cardiac defibrillator, sudden cardiac death
3 and/or cardiac arrest. These were chosen to represent common disease categories of
4 interest known to have pathophysiological effects on heart shape and function.
5 Disease categories were determined using ICD9 & ICD10 codes from hospital episode
6 statistics data from the NHS through the UK Biobank. A reference cohort was also
7 identified with no reported cardiovascular or cardiometabolic disease (the reference
8 sub-cohort).

19 **CMR Imaging and Automated Image Analysis**

21 The UK Biobank CMR protocol has been described previously²⁹. Briefly, all imaging
22 was performed on a wide bore 1.5 T scanner (MAGNETOM Aera, Syngo Platform
23 VD13A, Siemens Healthineers, Erlangen, Germany) using a phased-array cardiac coil.
24 Retrospectively gated balanced steady state free precession cine images were
25 acquired with three long axis orientations (horizontal long axis, vertical long axis, LV
26 outflow tract) and a short axis stack covering both the RV and the LV (6mm thickness
27 for long axis, 8mm thickness for short axis, flip angle 80°, TR/TE = 2.6/1.1ms, temporal
28 resolution 32ms interpolated to 50 phases per cardiac cycle, pixel size 1.8 x 1.8 mm).
29 Each slice was acquired in a separate breath-hold.

43 Contours and landmarks were automatically identified using cvi42 post-
44 processing software (Version 5.11 1505, Circle Cardiovascular Imaging Inc., Calgary,
45 Canada). This software used deep learning convolutional neural network algorithms
46 for fully automated analysis, which has been previously validated²⁷. Contours were
47 identified in short and long axis (two-chamber, three-chamber and four-chamber)
48 images. Tricuspid and aortic valve points were defined from landmarks delineated on
49 the two-chamber and three-chamber long axis views respectively, and mitral valve
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1 points were defined on all long axis images. A LV endocardial apex point was defined
2 on the four-chamber image. Since RV free wall myocardium was not detected by the
3 machine learning algorithms, the RV free wall epicardial surface was imputed by
4 displacing the RV endocardial points outwards by 3mm. The cvi42 software provided
5 a report containing ventricular volumes and LV mass computed using slice summation
6 of the short axis contours. The ED and ES frames were selected as the frames with
7 the highest and lowest volumes computed by cvi42.
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10 **Automated Biventricular Shape Analysis and PCA**

11 A biventricular shape model consisting of a subdivision surface template mesh was
12 automatically customized to each case as described previously³⁰. Briefly, breath-hold
13 misregistration was automatically corrected and the shape model geometry was
14 customized using diffeomorphic least squares minimization of the distances between
15 the shape model and the contour points from all the short axis and long axis slices.
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17 A biventricular statistical shape atlas was constructed using PCA as previously
18 described¹⁹. ED shapes were co-registered using Procrustes alignment (without
19 scaling), and the aligned ED and ES shape model vertices were concatenated into a
20 single shape vector. Singular value decomposition of the covariance matrix resulted in
21 a relatively small number of PC scores that described the majority of shape variation
22 across all participants, while accounting for correlations between points in the shape
23 model. The first component explained the most of total shape variance, and each
24 subsequent PC successively explained less variance. For each participant, PC scores
25 were calculated which quantified the amount of each PC present in that individual. The
26 PCs which captured >90% of the total variance were kept for functional analysis.
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29 A series of quality control checks were performed at different stages of the
30 pipeline (details provided in Supplementary Material).
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Geometric Shortening Strain

Geometric % shortening strain was calculated as percent change in arc length:

$$GLS \text{ or } GCS = ((EDL-ESL)/EDL) \times 100\% \quad (1)$$

where GLS and GCS denote global longitudinal and circumferential strains respectively, and EDL and ESL are the corresponding endocardial surface arc lengths at ED and ES respectively. Note % shortening was defined to be positive for contraction. Previous studies have found good agreement between geometric global strain and feature tracking as well as tagging estimates^{31,32}.

MAPSE and TAPSE calculation

Mitral/tricuspid annular plane systolic excursion (MAPSE/TAPSE) was calculated as the mean 3D displacement of valve points from ED to ES in mm.

Covariate Analysis

Univariate and multivariate linear regressions were performed using R (version 4.2.1)³³ to quantify the strengths of relationships between functional metrics and covariates, including age, sex, height, body mass index, and afterload, in the disease-free reference sub-cohort. Afterload, or myocyte stress at ES, is known to be correlated with many functional metrics. Here we estimate afterload using the Arts formula³⁴:

$$Afterload = SBP \left(1 + \frac{3 (LVESV)}{LVWallVolume} \right) \quad (2)$$

where LV ES volume and LV wall volume (at ED) were estimated from the model using numerical integration. This formula has been shown to produce accurate estimates of myocyte stress at ES in a variety of geometries³⁴, validated using a biomechanical model.

Relationships with Disease

Differences in functional metrics between the reference group and each disease category were tested using the Wilcoxon rank sum test. To examine the discriminative

1 ability of the PC scores compared with standard functional metrics, linear discriminant
2 analysis models were constructed for each prevalent disease category. In each model,
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4 positive cases were those with the disease and negative cases were those in the
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6 disease-free reference cohort. For each disease category, two linear discriminant
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8 analysis model were compared, one in which the discriminatory variables were PC
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10 scores and the other in which the discriminatory variables comprised LV and RV end-
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12 diastolic and end-systolic volumes, ejection fractions, global circumferential and
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14 longitudinal strains, and MAPSE and TAPSE. The area under the curve (AUC) was
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16 compared between the two models using the DeLong test. For this comparison the
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18 AUCs were constructed using the test cases from a five-fold cross validation analysis
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20 using the R caret package (version 6.0-93)³⁵. An additional comparison was performed
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22 with covariates age, sex, body mass index, height, and afterload added to the
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24 discriminatory variables of both linear discriminant analysis models.
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31 Although the PC scores are uncorrelated by definition, multicollinearity may
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33 exist between the standard measures (volume and strains). Multicollinearity can have
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35 a large effect on the regression parameters (betas), but may not change the overall
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37 AUC greatly. This was tested by successively excluding variables with variance
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39 inflation factor (VIF) greater than 5, until all variables had $VIF < 5$ ⁵⁰. If both LV and RV
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41 measures of volume had $VIF > 5$, the RV measure was removed first.
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46 To test the benefit of adding standard variables to PC scores, we also compared
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48 PCs plus standard variables plus covariates against standard variables plus
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50 covariates, removing variables with $VIF > 5$.
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53 **Manual Volume and Tagging Analysis**

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55 Volumes and strain results from the automated analyses were compared with manual
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57 analyses previously performed in the first 5000 CMR imaging participants^{36,37}. The
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1 manual volume analysis was performed by drawing short axis ventricular contours and
2 valve landmarks, using cvi42. Calculation of volumes and mass was performed using
3 slice summation in cvi42³⁶. Manual strain analysis of the three short axis slices
4 acquired with spatial modulation of magnetization (SPAMM) tissue tagging was
5 performed using CIMTag2D v8.1.5 software, (Auckland MRI Research Group, New
6 Zealand), which has been validated previously in phantoms and patients³⁸. As
7 previously described³⁷, a tag grid was aligned automatically to the myocardial tagging
8 planes at end-diastole. End-systole was determined visually, and tag tracking was
9 performed using nonrigid image registration, with manual adjustments at key phases
10 during the cardiac cycle including the end systolic and late diastolic frames.
11 Circumferential myocardial strain was calculated by the software from the motion of
12 the tag lines, averaged over the whole slice.
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33 Results

34 Study Population, QC and Automated Analysis

35 Of 45,683 CMR examinations available for analysis at the time of study, 3D shape
36 models could be customized at ED and ES in 43,159 cases (Figure 1A, B, C). PCA
37 was performed on 41,659 cases (Figure 1C). Model QC resulted in 1,500 cases
38 rejected before the PCA. After PCA, 1,261 cases were excluded for high Mahalanobis
39 distance, 463 cases for high PC projection error, and 1,832 cases for volume
40 differences from cvi42 (the total 2,801 in Figure 1E is due to many cases being rejected
41 for multiple criteria). After QC, there was a total of 38,858 cases, 5,149 with prevalent
42 cardiovascular or cardiometabolic disease and 33,709 without.
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58 Table 1 shows participant demographics, comparing the reference sub-cohort
59 with the disease sub-cohorts. In general, those with disease were older, more likely
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male, with higher blood pressure and body mass index. Table 1 also shows ventricular volumes and LV mass computed from the shape models by numerical integration. Those with disease had significantly higher left and right ED and ES volumes, higher LV mass, and lower right and left EF. The reference group volumes and mass were within the reference range for normal cardiac structural and functional measures detailed previously³⁶.

Strain, MAPSE and TAPSE

Table 2 shows global geometric longitudinal and circumferential strain computed from model arc lengths, and MAPSE and TAPSE computed from the displacement of model valve points, in reference and disease groups. Compared to the reference group, most strain measures were significantly ($p < 0.05$) reduced in all disease groups, except for hypertrophic cardiomyopathy in both LV GCS (mid) and RV GCS (mid), ventricular arrhythmia composite in RV GCS (mid) and RV GLS, and diabetes in RV GLS. MAPSE and TAPSE were also reduced in all disease groups compared to the reference ($p < 0.05$).

Figure 2 shows univariate correlations between standard functional metrics and covariates within the reference group. Strain was decreased in males, and also with increased height, body surface area, ventricular volume, LV mass, and LV afterload. Strain was not as strongly correlated with age, body mass index, or blood pressure. In contrast, MAPSE and TAPSE increased with height, body surface area, larger ventricular volume and LV mass, and was not as strongly correlated with sex, body mass index, and afterload. Multivariate regression results are presented in Supplementary Table S1.

Principal Components

We selected the first 25 PCs of shape variation, which represent the largest modes of variation of biventricular shape within the cohort, and together accounted for over 90% of the total shape variance. Figure 3 shows the amount of shape variance explained by each PC. Animations of these can be found in Supplemental Movies. Since these modes result from unsupervised dimension reduction, anatomical interpretation is typically not possible; however, clear interpretations can be made for some modes. In particular, PC1 (34% of shape variance) was associated with overall size at both ED and ES with positive scores associated with larger hearts. PC2 (11%) was associated with systolic motion, with positive scores associated with larger displacement, in particular basal descent of the valves during systole (TAPSE and MAPSE). PC3 (8%) was associated with sphericity of both ventricles at ED and ES, with positive scores related to less spherical shapes. PC9 (2.1%) was associated with systolic basal excursion, PC10 (2%) was associated with sphericity of the right ventricle, and PC13 (1.1%) was associated with ejection fraction.

Figure 3 shows univariate correlations between PCs and demographics, volumes, and strain. PC1 (overall size) was positively correlated with ventricular volumes and mass, male sex, height and body surface area, afterload, and MAPSE and TAPSE. PC1 was negatively correlated with strain and EF. PC2 (longitudinal motion of the valves) was positively correlated with MAPSE and TAPSE, and to a lesser extent strain and EF. PC3 (sphericity) was correlated with RV GCS and MAPSE/TAPSE. PC 9 was correlated with MAPSE/TAPSE and to a lesser extent strain. PC10 was correlated with RV strain and EF, as well as TAPSE. PC13 was correlated with LV and RV strain and EF, and to a lesser extent MAPSE and TAPSE.

Relationships with Disease

Strengths of relationships with cardiovascular or cardiometabolic diseases are shown in Table 3. Receiver operating characteristic curves are shown in Supplementary Figure S1. Comparing linear discriminant analysis models using the first 25 shape PC scores as discriminatory variables against a “standard” model with volumes, mass, ejection fraction, strain, MAPSE and TAPSE as discriminatory variables, the shape scores had significantly stronger relationships with prevalent atrial fibrillation, heart failure, myocardial infarction or ischaemic heart disease, diabetes and conduction disease. Relationships with hypertrophic and dilated cardiomyopathies and ventricular arrhythmia were similar between metrics, however the disease cohorts for these groups were relatively small (n=26, 32 and 152 respectively). When covariates age, sex, body mass index, height, and afterload were added to the discriminatory variables of both models, AUC improved and differences between models were reduced, as expected since the covariates are strongly related to disease and mask the differences between shape scores and strain/volume measures (Table 4). However, relationships with shape were still significantly stronger than those with volumes and strain (DeLong $p < 0.05$) in atrial fibrillation, heart failure, diabetes and conduction disease (Table 4).

To assess effects of multicollinearity, variance inflation factors (VIF) were computed for the discriminator variables in all models. Those with $VIF > 5$ were successively removed. For the PC models, no discriminator variables needed to be removed. For the standard model without covariates, RV end-diastolic and end-systolic volume, LV end-systolic volume, and LV ejection fraction were removed. Results are shown in Table S2, and were very similar to Table 3. For the standard model with covariates, RV end-diastolic and end-systolic volume, LV end-diastolic volume and end-systolic volume, and LV ejection fraction were removed (none of the age, sex,

height, weight, BMI and afterload covariates had VIF > 5). Results are shown in Table S3, and were very similar to Table 4.

We also evaluated the effect of adding standard variables to the PC scores and covariates, compared with the standard variables and covariates. Since standard volume and strain measures are correlated with PCs, those with VIF>5 were removed. For the PC model, all PCs, LV and RV global circumferential and longitudinal strains, and all covariates age, sex, height, weight, BMI and afterload, remained after removal of variables with VIF >5. Results are shown in Table S4, and were very similar to Table 4, and Table S3. This indicates that adding standard functional measures to the PCs has little effect on discriminatory power of the PC scores.

Manual Volumes and Tagging Strain

Within the 5,000 participants who had manual volume analysis, 4,257 had both manual and automatic shape model estimates of mass and volume (669 disease and 3,588 reference). Comparisons between manual and shape model estimates for disease and reference cases within this sub-cohort are shown in Table 5. In general, the LV volumes and mass computed from the shape models using numerical integration were larger than the manual estimates. This is likely due to differences in computation methods, with the model volume and mass including structures up to the valves and at the apex tip whereas manual estimates were performed with short axis slices only using slice summation. LV mass was also larger in the model estimates, partly due to allocation of mass to the LV at the junction of the RV free wall and the septum in the model, which is excluded in standard LV contours³⁹. The differences in volume and mass were consistent between disease and reference cases for both methods (Table 5). Bland-Altman plots of differences between methods are shown in Supplemental Material.

1 Within the first 5,000 participants who had manual tagging strain analysis, 3,845
2 had both manual and automatic shape model strain estimations. Geometric
3 circumferential mid-ventricle strains and tagging strains are shown in Table 5 for each
4 sub-cohort. Bland-Altman plots are shown in the Supplemental Materials. LV global
5 circumferential midventricular strain was higher than tagging circumferential strain,
6 which was expected since endocardial circumferential strain is typically higher than
7 mid-wall and epicardial strain (the tagging estimate being an average over the whole
8 wall)⁴⁰. Differences between disease and reference cohorts were consistent between
9 shape model and tagging strain estimates. Correlations between tagging GCS and
10 covariates (sex, height, afterload, LV volume etc) followed similar patterns to geometric
11 model GCS (Figure 2). Correlations between tagging GCS and PCs (Figure 3) also
12 followed similar patterns to geometric model GCS.

13 **Sensitivity of Combined Metrics**

14 Disease-specific combined PC scores can be used to quantify functional impairment
15 and track changes with disease development or treatment effects. For example, the
16 standardized combined z-score obtained from the linear discriminant analysis models
17 is the linear combination of PC scores which best discriminate the presence of disease.
18 Table 6 shows the disease-specific combined z-scores for each disease category.
19 These disease-specific z-scores are intuitive, in that reference (healthy) cases have a
20 mean around zero and a standard deviation around one, and disease cases have a
21 higher score in units of standard deviations. The differences in z-scores between
22 reference and disease cases are more highly significant for shape scores than
23 standard metrics in all disease categories. Studies designed to detect a change in heart
24 function with disease progression or treatment would therefore have more power to
25 detect an effect. For example, in diabetes the z-scores were 0.00 ± 0.97 (reference) vs

0.99 $\pm$ 1.00 (diabetes) for PCs and -0.03 $\pm$ 0.98 vs 0.68 $\pm$ 1.15 for standard metrics. A power calculation of the number of participants needed for a study of heart function in diabetes would require 32 participants (16 in each group) to detect a difference between patients and controls using PC scores, and 68 participants (34 in each group) for standard metrics, assuming an alpha of 0.05, power of 0.8.

Discussion

Evaluation of cardiac disease typically includes functional assessment including ejection fraction, strain, and valve plane motion, commonly assessed with echocardiography or CMR^{1,41}. However, these metrics do not capture all the shape change information present in modern medical imaging examinations. Here, we showed that shape scores derived from a statistical shape atlas, including both ED and ES shape information, are more strongly discriminative of disease than standard volumetric, strain and valve motion metrics (Table 3). The PC scores can be automatically calculated at the time of imaging (Figure 1), by segmenting the images, customizing a shape model, and computing the PC scores. Combined PC scores (such as linear discriminant analysis z-scores in Table 6) can be used to quantify patient status relative to a reference cohort, such as that provided in the UK Biobank. This provides a potentially more powerful set of functional metrics than is currently available, enables more sensitive quantification of disease effects, and can reduce the number of subjects required for studies of disease status and treatment effects.

In particular, PC scores performed well for discrimination of diabetes mellitus, myocardial infarction, conduction disease, atrial fibrillation and heart failure, suggesting PC scores contain more information on shape and shape changes during systole in

these disease categories. No significant differences were found for hypertrophic and dilated cardiomyopathies, with relatively high AUC for both sets of discriminatory variables, indicating that traditional measures are very discriminative for these diseases. However, the number of hypertrophic and dilated cardiomyopathies cases was low in this cohort and the method should be tested in larger disease cohorts. Ventricular arrhythmia discrimination was also similar between shape scores and traditional metrics, with moderate AUC, which may indicate that systolic shape changes are not as informative in these pathologies.

Our pipeline for atlas shape quantification was fully automated, with some similar characteristics to previously published automated analysis pipelines for quantification of cardiac shape and function^{23,24,25,26,42,43,44}. However, to our knowledge the current study is the first to compare PC shape scores with EF, strain and MAPSE/TAPSE functional indices for the discrimination of disease.

Geometric strain computed from arc lengths had good agreement with tagging strain, as found in previous studies^{31,32}. As expected, endocardial strain was higher than tagging midwall strain. Strain was significantly decreased with most examined diseases (Table 2), consistent with previous studies¹. In particular, a previous study of 3,984 UK biobank participants showed reduced tagging strain in 143 diabetes mellitus participants⁴⁵. The current study corroborates this finding, with the diabetes mellitus group (n=1,656) having reduced geometric strain for both LV and RV GCS and GCS, as well as MAPSE and TAPSE.

There was a significant dependence of strain on afterload, in agreement with previous studies^{10,46}. Also, strain was reduced with male sex and increased body size (body surface area and height), in agreement with previous studies^{24,41,43,47}. Some previous studies have shown that MAPSE may have different prognostic information

1 to strain^{7,8} and has different relationships with body size than strain¹¹. Here, MAPSE
2 had different relationships with age, body size and afterload to strain, with reduced
3 dependence on afterload and body size, but stronger dependence on age. Moreover,
4 some PC scores were highly correlated with MAPSE and TAPSE (PC2 and PC9 in
5 Figure 3) whereas others were more correlated with strain (PC10 for RV strain and
6 PC13 for LV strain), consistent with strain and MAPSE information being captured in
7 the PC scores. Correlations between PC scores and sex, height and afterload were
8 also found, particularly with PC1 which was associated with overall heart size. Other
9 PCs had greatly reduced correlations with body habitus and afterload, including PC2
10 (MAPSE) and PC10 and PC13 (RV and LV strain).
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24 Limitations of this study include use of UK Biobank data, which comprised
25 mainly low-risk participants with selection bias arising from volunteering for the study.
26 Subsequently there is a lack of cases with disease in cardiomyopathy and arrhythmia
27 categories. Although an automated quality control procedure was used to remove
28 outliers, it is likely that additional QC of the automated pipeline including analysis of all
29 frames in the cine sequence such as in Ruijsink *et al.*, 2020⁴² would benefit results.
30 Mistakes in automatic segmentation will lead to errors in the PC scores, although the
31 first 25 scores used in this study are relatively robust to small errors in segmentations.
32 Disease was classified by self-reported incidence or hospital electronic health records
33 and may not fully capture the diseases present in individuals in early asymptomatic
34 stages of disease. Co-morbidities between diseases were not considered since the
35 nature of the relationships between shape score and disease require a detailed
36 analysis of how shape varies with height, sex, age, and co-morbidities, which will
37 require a larger disease cohort (UK Biobank will shortly have 100,000 imaging
38 participants, enabling some disentanglement of these effects). Table 4 shows only
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1 modest AUC improvements when covariates age, sex, body mass index, height, and
2 afterload are included in the discrimination of atrial fibrillation, heart failure, diabetes
3 and conduction disease. This is due to these covariates being highly discriminative,
4 masking differences between PC and standard heart function measures. However, the
5 main utility lies in improved sensitivity of z-scores derived from PCs (Table 6), e.g.
6 enabling 50% fewer diabetic patients to detect differences from a reference group,
7 thereby facilitating studies of mechanistic effects of disease and treatment. LV volume
8 and mass were significantly higher in the models compared to standard slice
9 summation (Table 5). This is likely due to systematic differences in calculation
10 methods, with numerical integration of model mass including muscle up to the RV free
11 wall, and up to the valve locations. Finally, a recent study of 45,700 UK Biobank
12 participants showed feature tracking strain was independently predictive of incident
13 heart failure, myocardial infarction and stroke⁴⁸. Having established improved
14 sensitivity with prevalent disease, future work should study the utility of atlas scores in
15 predicting future adverse events, and assess their utility combined with other data from
16 applicable examinations, e.g. LGE and mapping information, stress perfusion data,
17 calcium scores, aortic distensibility, etc. Such predictive models will need to examine
18 the multicollinearity between predictors seen in Figure 2 and Figure 3. Two previous
19 methods used for incident disease prediction include partial least squares²² and linear
20 discriminant analysis with careful feature selection⁴⁹. The examination of changes in
21 disease specific scores (such as in Table 6) should also be extended to longitudinal
22 studies.

Conclusions

Atlas-based shape and motion scores capture more of the available shape change information present in modern imaging examinations than standard measures of cardiac function. An automated analysis pipeline enables routine evaluation of disease-specific z-scores at the time of imaging. Atlas scores provide more sensitive metrics for the evaluation of disease effects.

Abbreviations

3D: three dimensional

AUC: area under the curve of the receiver

CMR: cardiovascular magnetic resonance

ED: end-diastole

EF: ejection fraction

ES: end-systole

GCS: geometric circumferential strain

GLS: geometric longitudinal strain

LV: left ventricle

MAPSE: mitral annular plane systolic excursion

MESA: Multi-Ethnic Study of Atherosclerosis

PC: principal component

PCA: principal component analysis

ROC: receiver operating characteristic

RV: right ventricle

TAPSE: tricuspid annular plane systolic excursion

Declarations

Ethics approval and consent to participate

UK Biobank was approved by National Research Ethics Service North West (11/NW/0382). All participants gave written informed consent.

Consent for Publication

No identifiable individual information was included in this study.

Availability of data and materials

This research has been conducted using the UK Biobank resource under application 2964. The raw data, the derived data, the analysis and results have been clearly annotated and returned to UK Biobank, which will then incorporate the returned data into the central repository. UK Biobank will make the data available to all bona fide researchers for all types of health-related research that is in the public interest, without preferential or exclusive access for any person. All researchers will be subject to the same application process and approval criteria as specified by UK Biobank. For the detailed access procedure see <http://www.ukbiobank.ac.uk/register-apply/>.

Competing Interests

Alireza Sojoudi was an employee of Circle Cardiovascular Imaging during the period of the submitted work. Dr Petersen has received personal fees from Circle Cardiovascular Imaging outside the submitted work. All other authors have no competing interests.

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Authors' Contributions:

RB, SEP, JR, PM and AY designed the study. AY, LDT, CM, AS developed the methods. AS supervised the Circle analyses. RB and AY performed the model analyses and drafted the manuscript. All authors participated in revision and read and approved the final manuscript.

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Figure Legends:

Figure 1: Automated analysis pipeline. CMR, cardiovascular magnetic resonance; PCA, principal component analysis; APSE, annular plane systolic excursion; PC, principal component; IQR, interquartile range.

Figure 2: Univariate correlations between strain and covariates in the reference cohort. LV, left ventricular; RV, right ventricular; GCS, global circumferential strain; GLS, global longitudinal strain; MAPSE, mitral annular plane systolic excursion; TAPSE, tricuspid annular plane systolic excursion; BMI, body mass index; SBP, systolic blood pressure adjusted for presence of medication; DBP, diastolic blood pressure adjusted for presence of medication; body surface area, body surface area; EDV, end-diastolic volume; ESV, end-systolic volume; M, mass; EF, ejection fraction. Model strains and MAPSE/TAPSE from n=33709 cases; tagging strain from n= 3,280 cases.

Figure 3: Univariate correlations between PCs and demographics, volumes, and strain. The amount of shape variance explained by each PC is shown on the left. LV, left ventricular; RV, right ventricular; GCS, global circumferential strain; GLS, global longitudinal strain; GCSt, global circumferential strain (tagging); MAPSE, mitral annular plane systolic excursion; TAPSE, tricuspid annular plane systolic excursion; BMI, body mass index; SBP, systolic blood pressure adjusted for presence of medication; DBP, diastolic blood pressure adjusted for presence of medication; BSA, body surface area; EDV, end-diastolic volume; ESV, end-systolic volume; M, mass; EF, ejection fraction. All correlations N=33709 cases except tagging N=3,280.

Supplemental Figure S1 ROC curves for linear discriminant analyses (Table 3). Blue: PC model; Green: standard model.

Supplemental Figure S2 Bland Altman Plots: Manual vs Shape Model.

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Tables

Table 1. Participant characteristics for sub-cohorts with and without disease. Values are mean (standard deviation) for continuous variables and count (%) for categorical variables. Conduction disease: bundle branch block, fascicular block or atrioventricular block. Ventricular arrhythmia composite: ventricular arrhythmia, cardiac arrest, sudden cardiac death, defibrillator implantation). All variables were significantly different between Reference and Disease groups (* $p < 0.001$ Disease vs Reference, Wilcoxon rank sum test)

Characteristic	Disease (n = 5,149)	Reference (n = 33,709) ¹
Age (years)	67 (7)	63 (8) *
Sex (male)	3,453 (67%)	14,974 (44%) *
Weight (kg)	83 (15)	75 (14) *
Height (cm)	171 (9)	169 (9) *
BMI (kg/m ²)	28.2 (4.6)	26.3 (4.0) *
SBP (adjusted)	147 (21)	138 (20) *
DBP (adjusted)	86 (12)	82 (11) *
LV EDV (ml)	155 (36)	146 (32) *
LV ESV (ml)	74 (22)	67 (18) *
RV EDV (ml)	153 (35)	147 (35) *
RV ESV (ml)	70 (20)	65 (20) *
LV Mass (g)	131 (27)	123 (26) *
LVEF (%)	52.4 (6.4)	54.2 (4.8) *
RVEF (%)	54.7 (6.7)	56.1 (5.8) *
Heart failure	341 (6.6%)	.
Atrial fibrillation	1,088 (21%)	.
Myocardial infarction, ischaemic heart disease	2,389 (46%)	.
Hypertrophic cardiomyopathy	26 (0.5%)	.
Dilated cardiomyopathy	32 (0.6%)	.
Diabetes mellitus	1,656 (32%)	.
Ventricular arrhythmia composite	151 (2.9%)	.
Conduction disease	635 (12%)	.

Table 2 Geometric strain (% shortening) and MAPSE/TAPSE in different disease categories. Mean (standard deviation). GCS, global circumferential strain; GLS, global longitudinal strain; MAPSE, mitral annular plane systolic excursion; TAPSE, tricuspid valve plane annular excursion; LV, left ventricle; RV, right ventricle; * P < 0.05, † P < 0.001, Wilcoxon rank sum test disease vs Reference.

Group	LV GCS (mid)	LV GLS	RV GCS (mid)	RV GLS	MAPSE	TAPSE
Reference	27.0 (3.6)	20.6 (2.6)	23.8 (5.6)	32.1 (5.3)	12.2 (2.2)	17.6 (3.3)
Atrial fibrillation	25.3 (5.2) [†]	18.6 (3.9) [†]	22.5 (6.1) [†]	29.4 (6.8) [†]	10.9 (2.8) [†]	15.4 (4.5) [†]
Dilated cardiomyopathy	19.6 (4.9) [†]	15.8 (3.6) [†]	17.7 (6.3) [†]	25.5 (6.7) [†]	9.7 (2.4) [†]	14.1 (3.8) [†]
Diabetes mellitus	26.3 (4.4) [†]	19.9 (3.0) [†]	22.7 (6.0) [†]	31.9 (5.9)	11.1 (2.3) [†]	16.0 (3.8) [†]
Hypertrophic cardiomyopathy	26.1 (6.0)	17.8 (3.5) [†]	23.6 (6.8)	28.1 (6.2)*	10.6 (3.3)*	14.9 (4.4) [†]
Heart failure	23.4 (5.3) [†]	17.8 (3.7) [†]	22.2 (6.2) [†]	30.0 (6.6) [†]	10.4 (2.6) [†]	15.2 (4.1) [†]
Myocardial infarction, ischaemic heart disease	25.9 (4.6) [†]	19.5 (3.1) [†]	23.1 (5.9) [†]	31.3 (5.9) [†]	11.4 (2.3) [†]	16.1 (4.0) [†]
Conduction disease	24.8 (4.6) [†]	19.0 (3.1) [†]	22.7 (6.1) [†]	30.3 (6.2) [†]	11.4 (2.4) [†]	16.0 (3.8) [†]
Ventricular arrhythmia composite	25.0 (5.2) [†]	18.7 (3.7) [†]	22.9 (5.0)	30.9 (6.2)	11.2 (2.4) [†]	16.4 (4.0) [†]

Table 3. Comparison of linear discriminant analysis AUC of disease prevalence: PC scores vs standard metrics. Disease: cardiovascular or cardiometabolic disease; AUC, area under the curve; PCs, principal components. LV and RV end-diastolic and end-systolic volumes, ejection fractions, global circumferential and longitudinal strains, LV mass, and MAPSE and TAPSE are all included in the Standard model.

Disease	AUC		DeLong test P-value
	PCs (1-25)	Standard	
Atrial fibrillation (n=1088)	0.76	0.71	8.9E-13
Heart failure (n=341)	0.82	0.78	2.4E-05
Hypertrophic cardiomyopathy (n=26)	0.79	0.83	0.14
Dilated cardiomyopathy (n=32)	0.92	0.91	0.70
Ventricular arrhythmia composite (n=151)	0.73	0.68	0.04
Myocardial infarction or ischaemic heart disease (n=2389)	0.73	0.69	1.0E-20
Diabetes mellitus (n=1656)	0.77	0.68	2.1E-56
Conduction disease (n=635)	0.78	0.74	6.4E-08

Table 4. Comparison of linear discriminant analysis AUC of CMD prevalence, including covariates in both models. CMD, cardiometabolic disease; AUC, area under the curve; PCs, principal components; Standard: LV and RV end-diastolic and end-systolic volumes, ejection fractions, global circumferential and longitudinal strains, LV mass, and MAPSE and TAPSE. Covariates were age at imaging, sex, height, weight, BMI and afterload.

CMD	AUC		DeLong test P-value
	PCs	Standard	
Atrial fibrillation (n=1088)	0.77	0.76	1.8E-03
Heart failure (n=341)	0.85	0.82	4.9E-04
Hypertrophic cardiomyopathy (n=26)	0.82	0.83	0.55
Dilated cardiomyopathy (n=32)	0.94	0.89	0.10
Ventricular arrhythmia (composite) (n=151)	0.74	0.72	0.19
Myocardial infarction or ischaemic heart disease (n=2389)	0.77	0.77	0.18
Diabetes mellitus (n=1656)	0.82	0.81	2.2E-04
Conduction disease (n=635)	0.81	0.79	4.9E-04

Table 5. Model and manual analyses of volume and strain. Mean (standard deviation); *p<0.001 Disease vs Reference, Wilcoxon rank sum test; ¹Strain for n=565 for disease and 3,280 for reference cases with both manual tagging (midventricular) and model strain. GCS: global circumferential strain.

	Shape Model		Manual	
Characteristic	Disease (n=669)	Reference (n=3,588)	Disease (n=669)	Reference (n=3,588)
LVEDV (ml)	157 (37)*	148 (32)	151 (37)*	142 (32)
LVESV (ml)	75 (23)*	68 (18)	63 (23)*	58 (17)
LVM (g)	132 (28)*	123 (26)	99 (26)*	87 (23)
RVEDV (ml)	154 (36)*	148 (35)	158 (37)*	151 (37)
RVESV (ml)	69 (21)*	65 (20)	70 (23)*	67 (22)
LV GCS (mid, %) ¹	26.2 (4.1)*	27.2 (3.3)	21.5 (3.3)*	22.5 (2.9)

Table 6: Linear discriminant scores for each disease category (z-scores). Disease: cardiovascular or cardiometabolic disease; PCs, principal components; Standard: LV and RV end-diastolic and end-systolic volumes, ejection fractions, global circumferential and longitudinal strains, LV mass, and MAPSE and TAPSE.

Disease	PCs (1-25)			Standard		
	Reference	Disease	P-value	Reference	Disease	P-value
Atrial fibrillation (n=1088)	-0.04 ± 0.95	1.32 ± 1.59	9.8E-132	-0.03 ± 0.97	0.99 ± 1.43	1.2E-98
Heart failure (n=341)	-0.02 ± 0.98	1.79 ± 1.58	7.2E-64	-0.02 ± 0.95	1.94 ± 2.69	1.8E-33
Hypertrophic cardiomyopathy (n=26)	-0.00 ± 1.00	2.25 ± 1.63	2.1E-07	-0.00 ± 1.00	2.08 ± 1.46	1.2E-07
Dilated cardiomyopathy (n=32)	-0.00 ± 0.99	3.05 ± 1.56	2.6E-12	-0.00 ± 0.99	3.97 ± 3.59	6.1E-07
Ventricular arrhythmia composite (n=151)	-0.01 ± 0.99	1.27 ± 1.57	2.4E-18	-0.01 ± 0.98	1.56 ± 3.06	4.2E-09
Myocardial infarction or ischaemic heart disease (n=2389)	-0.07 ± 0.94	0.93 ± 1.26	2.9E-251	-0.05 ± 0.93	0.79 ± 1.47	3.9E-148
Diabetes mellitus (n=1656)	-0.05 ± 0.97	0.99 ± 1.00	3.3E-264	-0.03 ± 0.98	0.68 ± 1.15	4.3E-117
Conduction disease (n=635)	-0.02 ± 0.98	1.30 ± 1.36	1.2E-93	-0.02 ± 0.96	1.22 ± 1.84	1.7E-53