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Atlas-based Anatomical Modeling and Analysis of Heart Disease

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Abstract

Heart shape and function are major determinants of disease severity and predictors of future morbidity and mortality. Many studies now rely on non-invasive cardiac imaging techniques to quantify structural and functional changes. Statistical anatomical modeling of heart shape and motion provides a new tool for the quantification and evaluation of heart disease. This review surveys recent progress in the evaluation of statistical shape measures across populations and sub-cohorts, and highlights collaborative efforts to facilitate data sharing and atlas-based shape analysis.

Keywords

Cardiac MRI; cardiac atlas; anatomical models

Introduction

Heart disease is the primary cause of morbidity and mortality around the world, with coronary artery disease, diabetes and obesity being major contributing factors. Changes in heart shape and function are known to characterize the progression of disease. Many studies now rely on non-invasive cardiac imaging techniques to quantify structural and functional changes, which are used as surrogate endpoints [1]. Several large epidemiological studies are employing cardiac imaging to determine morphological determinants of outcome and relationship to other risk factors. The Multi-Ethnic Study of Atherosclerosis (MESA) was initiated in July 2000 to investigate the prevalence, correlation, and progression of subclinical cardiovascular disease in a population-based sample of 6,500 men and women aged 45–84 years [2]. Cardiac magnetic resonance (CMR) imaging was used in MESA to

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Conflict of Interest

The authors have no conflict of interest to declare.

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evaluate cardiac mass and volume [3]. Recently, an imaging extension to the UK Biobank has been announced, with cardiac, abdominal and brain MRI studies to be performed initially on a subset of 6,000 Biobank participants [4]. These studies provide an opportunity to establish quantitative measures of the variation in subgroups and the relationships to outcomes, biomarkers and risk factors.

Anatomical modeling of heart shape and function can utilize cardiovascular imaging studies to enable precise quantitative evaluation of subtle differences in cardiac shape and function among population cohorts [5–7]. In disease groups, anatomical modeling can provide new measures of the progression of disease and the evaluation of severity. In the asymptomatic population, pre-clinical variation may indicate developing disease before clinical symptoms are observed.

This review focuses on the construction and utility of anatomical shape models in the evaluation of statistical shape measures across populations and sub-cohorts, and highlights collaborative efforts to facilitate data sharing and atlas-based shape analysis.

Atlas-based Shape Measures

The ability to integrate data from multiple sources and variables has significant potential for the diagnosis and clinical care of patients. It allows better personalization of patient diagnosis by taking into account the measurements derived from a clinically relevant group [8]. This population-based approach to measure clinical diagnosis has been well established in the brain domain [9]. However for the heart domain, statistical maps of regional cardiac shape and function are only recently being developed [5].

A common clinical application of atlas-based analysis of the heart is to estimate a template and then co-register it into diseased hearts to investigate, for instance, how the LV remodels after the onset of MI [10] or how to select candidates in cardiac resynchronization therapy [11]. Furthermore, the atlas can also provide a platform for ontological labeling of cardiac anatomy to query local shape differences [12].

With the advent of large-scale population databases for atlas-based analysis through data sharing mechanisms, similar studies can be conducted and combined with mathematical and computational models to provide a statistical map of the variation seen in heart disease. Statistical models derived from large populations of patients can provide a range of reference values against which individual patients' data can be compared. A standardized model-based analysis can be used to establish shape and motion with respect to a standard coordinate system.

A mathematical model of the heart can provide anatomical coordinates, which enable point correspondences to be made in consistent locations between all models (Figure 1). Fiducial landmarks placed at the centroid of the LV cavity on the apical and basal ED short axis images, at the hinge points of the mitral valve in the ED long axis image, and at the insertions of the right ventricular free wall into the inter-ventricular septum can be used to register the model with the anatomy of each case [13].

Clinical Shape Indices

Simple measures of ventricular size and shape are known to have prognostic value, particularly to cardiac remodeling. These geometrical changes even precede any detectable global left ventricular (LV) dysfunction. As the heart remodels, its geometry changes to become less elliptical and more spherical [14]. Sphericity has also been associated with decreased survival [15] and adverse remodeling [16]. Sphericity is an even more sensitive predictor of adverse events than LV volumes and EF [15].

Increased end-systolic volumes (ESV) and decreased ejection fraction (EF) are observed in myocardial infarction (MI). ESV is the predictor of mortality in patients after MI [17]. In asymptomatic individuals, left ventricular (LV) chamber dimension was associated with adverse events in the Framingham study [18] and end-diastolic volume (EDV) and mass were predictive of heart failure in MESA [19]. Volume and mass have also been shown to be altered with standard risk factors for prediction of cardiovascular events [20].

Although cardiac remodeling is generally related to the progressive heart failure, it can be adaptive or maladaptive. Some early remodeling in patients after MI was restored to normal within 2–4 weeks [14]. When this transition from adaptive to maladaptive happens, and how patients with such risks are identified, are still open questions. LV volume enlargement is also present in asymptomatic subjects (physiological LV dilatation) due to physical exercise in athletes, but not for all cases. Some asymptomatic relatives of patients with cardiomyopathy also have LV dilatation, which can be used as a marker for preclinical cardiomyopathy risk assessment [21]. Based on these clinical findings, an atlas-based heart shape and function analysis derived from large-scale population cohort may provide novel insights into 1) the remodeling processes of heart disease, and 2) characterising different subclinical groups among population.

Data Sharing

Data sharing is vital for the development of the field and many granting agencies are now requiring a data sharing plan as part of all research proposals. More researchers are now making datasets available to the community for benchmarking and algorithm development as well as characterization of population groups. The Statistical Atlases and Computational Models of the Heart workshops, which have been taking place in conjunction with the annual Medical Image Computer and Computer Assisted Intervention (MICCAI) conferences, have made a series of “challenges” consisting of benchmark data and ground truth available to the community for objective comparison of different processing and analysis methods. These include CMR images for heart segmentation, electrophysiological data for simulating heart activation, tagging and echocardiographic data for the reconstruction of motion, flow data for computational fluid dynamics, and late gadolinium enhancement data for the quantification of scar in the atria and ventricles [22] [23].

Infrastructure and Tools

The Cardiac Atlas Project (CAP) provides infrastructure and mechanisms to facilitate data sharing and has combined data from several studies to construct registered maps of regional

cardiac function [6]. Large-scale cardiac imaging datasets can be classified, annotated and shared in a HIPAA compliant manner via a web-accessible interface with the cardiac research community. The database contains over 3,000 cardiac MRI imaging examinations (approximately 1.5 million images), with the majority of examinations contributed from large research studies such as MESA [2], and clinical studies such as the Defibrillators to Reduce Risk by Magnetic Resonance Imaging Evaluation (DETERMINE) study [24]. In addition, image contours and epidemiological information from the contributing studies are linked to the image data to enable analyses of sub-cohorts and risk factors. Over 20 groups worldwide have used the CAP for a variety of research projects¹, including large-scale generalization of cardiac motion for percutaneous coronary intervention, characterization of shape variation for medical device design, learning-based registration to extract morphological information, quantification of local cardiac remodeling for electromechanical simulations, and automatic identification of wall motion abnormalities.

Anatomical cardiac models are also available from the Anatomical Models Database, a community resource sharing a variety of anatomical and computational models [25]. This resource includes finite element mechanical and electro-physiological models together with benchmarking data and tools for generating meshes from image data.

Shape Representations

One compact representation of the left ventricle comprises 16 bicubic finite elements defined in a prolate spheroidal coordinate system. This enables an efficient representation of the shape of the left ventricle as a radial function of two angular coordinates: $\lambda(\mu, \theta)$ [13,26]. In this representation, shape parameters of the cardiac model are obtained from the finite element control points for each of the epicardial and endocardial surfaces. In order to calculate statistical shape differences, the models can be sub-sampled at high density using a standardized sampling pattern (10×10 points per element) and the positions converted to rectangular Cartesian coordinates.

After removing scale, position and rotation variations among subjects, shape and motion are mathematically mapped and principal component analysis (PCA) can then be used to analyze the modes of variation of the atlas. PCA decomposes the major sources of variation within a multidimensional data set into a set of orthogonal components or ‘modes’ [27]. Eigenvectors of the covariance matrix give the shape modes present in the cohort, and their corresponding eigenvalues give the relative amount of variation present in the cohort for each mode.

For example, the major modes of variation within a cohort of 1,991 MESA participants were calculated using a principal component analysis (Figure 2). The first modes associated with the greatest variation were found to correspond with sphericity, and mitral valve geometry [28]. Projection of an individual’s shape and motion onto these modes (e.g., mode 1 which is associated with sphericity for ED and ES) provides a standardized method for quantifying the amount of each mode present.

¹See Cardiac Atlas Project website: <http://www.cardiacatlas.org>

The distributions of relative position at end-diastole and end-systole enable identification of symptomatic vs asymptomatic wall motion characteristics. In Figure 3, relative distributions enable classification of myocardial infarction patients solely on the bases of regional shape and motion.

Statistical atlases of shape and function also enable automatic characterization of regional wall motion abnormalities (RWMA) [29]. Support vector machines were employed to classify the asymptomatic control and patient groups for each of 16 standard anatomical regions in the heart (Figure 4). Ground truth visual wall motion scores from standard cines and infarct scoring from late enhancement (LGE) were provided by experienced observers. From all configurations, end-systolic shape best predicted wall motion abnormalities (global accuracy 78%, positive predictive value 85%, specificity 91%, sensitivity 60%).

In another study, Lewandowski *et al.* recently showed significant morphological differences between individuals born preterm (30 weeks) and full-term age matched healthy volunteers [7], which are indicative of remodeling associated with the premature switch to post-natal circulation. Significant shape differences between adults born preterm and full term controls were found in the first six principal modes of variation. These included changes in length, wall thickness and apex orientation.

An atlas of right ventricular shape can provide insight into the remodeling and transition to heart failure of the right ventricle after repair in tetralogy of Fallot patients [30]. Leonardi *et al.* studied 38 patients (aged 10–30 years) with repaired tetralogy of Fallot (but not pulmonary valve repair). Regurgitation severity was significantly associated with right ventricle (RV) dilatation ($P = 0.01$) and tended to be associated with bulging of the outflow tract ($P = 0.07$) and a dilatation of the apex ($P = 0.08$).

A statistical atlas of 138 patients with various pathology was constructed from CT data by Hoogendoorn *et al.* [31]. A reference case was chosen to represent a mean case, and then all other cases were warped to match this case using image based non-rigid registration. A mean image was then calculated, and this was manually segmented to form a triangular mesh. Temporal image registration was then applied to warp the surface mesh representation to each frame. A spatio-temporal statistical shape model was then constructed to separate the inter-subject from the temporal sources of variation.

Atlas based analysis of motion can also be performed using motion or velocity data. Duchateau *et al.* formed an atlas from 2D ultrasound cardiac sequences from 21 healthy volunteers, and compared 14 CRT candidates with left ventricular dyssynchrony [11]. Atlases can also be formed of cardiac microstructure. Lombaert *et al.* describe an atlas of human fibre architecture in [32], in which ten healthy human hearts were imaged *ex vivo* using diffusion tensor MRI. The hearts were registered structurally and mean fiber architecture was derived from the registered data.

Towards Automatic Shape Analysis

Although manual analysis of CMR images is the current clinical standard, fully automated analysis methods are now possible for some shape features. These include identification of

fiducial landmarks defining the location of the mitral valve and the apex of the LV in long axis images, and the locations of the intersection of the LV free wall with the interventricular septum in short axis images. Lu *et al.* describe such a procedure to automatically detect landmarks using machine learning techniques [33]. These landmarks can be used to calculate the pose and scale of the heart as well as ventricular length. Accurate and robust results were achieved with a median distance error of 2.6 mm for the mitral valve, 4.7 mm for the RV inserts and 5.4 mm for the base point [33]. Inner and outer contours (epicardial and endocardial boundaries) can also be automatically defined using a variety of methods. In the 2011 MICCAI challenge evaluating automatic and semi-automatic methods for the segmentation of the LV, a fully automated method developed by Jolly *et al.* gave good agreement with manually defined contours [34]. This enabled automated calculation of LV mass, end-diastolic volume and end-systolic volume.

Automated methods for the construction of anatomical models include the method of Lamata *et al.* in which cubic Hermite meshes of patient geometry can be generated from segmented images using a form of non-rigid registration [35]. Atrial anatomy has also been modeled using high-order cubic Hermite elements to combine flexibility of shape with compactness of representation – e.g. 142 elements were sufficient for the left atrium with a accuracy of 0.6 mm [36]. Whole heart modeling can also be performed using variations of these methods [37]. Optical flow or non-rigid registration methods can be used to adapt an existing model to a new subject's images [31,37]. Microstructure fibre and sheet architecture can then be mapped from the atlas to the patient specific model.

Computational Physiology

These models can elucidate the complex interaction of electrical, anatomical, and functional data to provide insight into the processes underlying the normal or pathological function of the heart. Anatomical models can be combined with physiological data to derive patient specific evaluations of heart disease. Pop *et al.* used CMR derived anatomical models with electrophysiology data to generate physiological parameters [38]. Sermesant *et al.* describe a method for the construction of patient specific models from images and electrophysiology data [39].

In one approach, anatomical models derived from non-invasive imaging can be combined with invasive pressure recordings or other data to give information on physiological parameters such as contractility and muscle stiffness. Wang *et al.* have used finite element analysis and parameter identification to show that patients with hypertrophy or non-ischemic heart failure exhibited increased passive myocardial stiffness compared to normal controls [40]. Tissue-specific parameter estimation analysis of this kind can potentially be applied in the clinical setting to provide better characterization of heart failure patients.

Conclusions

Computational models shed light on the physiological and anatomical properties of the heart at various levels: e.g. shape, function, electrophysiology and tissue properties; either independently or conjointly through multi-scale modeling. Some of these measurements can

be readily quantified in today's clinical practices with a range of semi-automatic tools (e.g. volumes from CMR). In particular, atlas-based tools have proven useful for comparing one individual's anatomy to a population or between sub-populations, and in the detection and quantification of disease. Data-sharing initiatives will aid in the validation and further automation of the current state-of-the-art.

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Figure 1.

Model of the right and left ventricles interactively fitted to MRI data (blue wireframe denotes epicardial surface, yellow RV endocardium and green LV endocardium). a) End-diastole; b) end-systole; c) 3D view. Simultaneous viewing of the long and short axis images enables better accuracy of RV volume and function.

Figure 2. Principal components of left ventricular shape variation in 1991 asymptomatic people. Left and right of each mode show ± 3 standard deviations of left ventricular shape variation. ED: end-diastole; ES: end-systole; ED-ES: the difference between ED and ES. Viewpoint is from the septum, posterior wall on the right.

Figure 3.

a) Shape parameter distributions with 95% confidence region (blue epicardial, red endocardial); b) Hotellings T^2 probability for statistical difference for anterior myocardial infarction; c) Fisher discriminant analysis classifying patients with 94% specificity and 93% sensitivity using a combination of modes. S:septal; L:lateral; P:posterior; A:anterior.

Figure 4. Clinical work-flow for RWMA and LGE scoring, (a) acquisition, (b) LV finite element model (AHA regions appear highlighted by differently coloured points in the endocardium) and (c) the scoring on a bull's eye plot where each AHA region is scored visually by a specialist.