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Editorial

Cardiac image modelling: Breadth and depth in heart disease

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ABSTRACT

With the advent of large-scale imaging studies and big health data, and the corresponding growth in analytics, machine learning and computational image analysis methods, there are now exciting opportunities for deepening our understanding of the mechanisms and characteristics of heart disease. Two emerging fields are computational analysis of cardiac remodelling (shape and motion changes due to disease) and computational analysis of physiology and mechanics to estimate biophysical properties from non-invasive imaging. Many large cohort studies now underway around the world have been specifically designed based on non-invasive imaging technologies in order to gain new information about the development of heart disease from asymptomatic to clinical manifestations. These give an unprecedented breadth to the quantification of population variation and disease development. Also, for the individual patient, it is now possible to determine biophysical properties of myocardial tissue in health and disease by interpreting detailed imaging data using computational modelling. For these population and patient-specific computational modelling methods to develop further, we need open benchmarks for algorithm comparison and validation, open sharing of data and algorithms, and demonstration of clinical efficacy in patient management and care. The combination of population and patient-specific modelling will give new insights into the mechanisms of cardiac disease, in particular the development of heart failure, congenital heart disease, myocardial infarction, contractile dysfunction and diastolic dysfunction.

1. Introduction

Heart disease is a leading cause of morbidity and mortality around the world. While substantial advances have been made in the detection and treatment of disease, little is known about the mechanisms and characteristics of disease development. The design of more effective treatments and prevention strategies rely on knowledge of the underlying features of developing disease. For example, patients suffering from heart failure with preserved ejection fraction do not respond well to conventional treatments that work well for other forms of heart failure. It is not known whether these patients exhibit impaired ventricular filling through increased myocardial stiffness or delayed myocyte relaxation. Many heart failure patients with dyssynchronous contraction respond well to pacemaker therapy for cardiac resynchronisation, but approximately one third do not. Patient-specific information to predict response to cardiac resynchronisation therapy, including where to place the pacing device leads and how to select interventricular pacing delays, would be highly beneficial. In sub-clinical disease, interactions between environmental and genetic factors together with adverse events lead to adaptations in cardiac shape and motion. With recent advances in medical imaging, large-scale cohort studies and medical image analysis, it is now possible to address these problems from two perspectives: first by examining how the heart changes its shape and function in response to disease and exposure to risk factors; and second by identifying biophysical parameters that characterise physiological and biomechanical behaviours in health and disease.

Cardiac shape and function continuously adapt (remodel) in response to pre-clinical and symptomatic disease, as well as vascular events. Better quantification of this remodelling could provide more predictive information on the status of heart health and the progression of disease, since these adaptations reflect initially compensatory mechanisms leading eventually to decompensated remodelling and heart failure. For example, concentric remodelling (relative thickening of the heart walls), increased left ventricular (LV) end-systolic volume, and increased LV sphericity have all been

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associated with decreased survival in patients with myocardial infarction (Sutton and Sharpe, 2000). Although remodelling has typically been characterised as changes in morphology due to vascular events, such as myocardial ischaemia or infarction, hypertensive and idiopathic cardiomyopathies (i.e. those of unknown origin) also give rise to remodelling features, which are important clinical markers of disease progression. Pre-clinical remodelling can occur in asymptomatic individuals, prior to the establishment of clinical manifestations of disease, in response to exposure to risk factors and genetic interactions. This type of remodelling has also been associated with adverse outcomes (Bluemke et al., 2008).

Changes in physiological parameters, such as contractility and muscle stiffness, are also indicative of disease processes. For example, resting myocardial stiffness is a major determinant of ventricular function, with large changes in stiffness associated with heart failure and myocardial infarction. Increased muscle stiffness is detrimental to the filling function of the heart, which in turn increases blood pressure and the amount of contraction force required by the muscle. Some forms of heart failure may be associated with increased myocardial stiffness, but it is difficult to characterise patients effectively to determine if the clinically observed symptoms are due to increased passive tissue stiffness, impaired relaxation, impaired contractility or some combination of these.

Mathematical modelling of cardiac shape, motion and physiology is a rapidly developing field with the potential for providing detailed information on the mechanisms of disease processes and cardiac dysfunction. Models of cardiac function can incorporate geometry, motion, microstructure, nonlinear and anisotropic constitutive behaviour, loading conditions, and kinematic constraints. Activation models comprise initiation and propagation of action potentials, calcium transients and cross-bridge activation and deactivation, active force generation and relaxation. Patient-specific biophysical parameters governing myocardial stiffness and contractility can be estimated by optimally matching the behaviour of these models to data from medical imaging. In this way, medical imaging examinations can be augmented with model-based interpretation and thereby provide new information on mechanisms of compensatory and decompensated adaptations.

Medical imaging now enables precise quantification of structural and functional information on cardiac status and performance, but each modality has particular strengths and weaknesses. Multi-detector computed tomography (CT) is very rapid and provides detailed 3D images at approximately 0.5 mm isotropic resolution. However, exposure to ionising X-ray radiation prevents this method from being widely used in routine assessments or evaluation of children with congenital heart disease. Echocardiography provides lower-cost rapid evaluation of function, with more than 50 3D frames per second possible with modern 3D transducers. However, signal dropout due to poor acoustic windows, particularly in the right heart, limits this method in many patients. Transesophageal echocardiography can provide better delineation of the right heart, but it is semi-invasive and the patient may need sedation during acquisition. Cardiac magnetic resonance imaging (MRI) provides a range of contrast mechanisms from motion to T1 mapping and perfusion quantification, but typically cannot be used in patients with implanted devices. Analysis methods that exploit medical imaging must therefore be compatible with a range of modalities, and must integrate information from a variety of sources.

This review will examine applications of model-based analysis of cardiac images, with emphasis on the breadth available in large population-based imaging studies, and depth available in patient specific physiological modelling. We also provide a potential roadmap for the future, which will require closer links between algorithm development and clinical applications.

2. Remodelling in pre-clinical and clinical disease

Much of what is known about multivariable risk factors of cardiac disease has been derived from the large cohort Framingham Heart Study, which does not include cardiac geometry and function. Recently, several cohort studies have used medical imaging as part of a suite of investigations into the effects of risk factors and disease events on heart function. The Multi-Ethnic Study of Atherosclerosis (MESA) was the first major population study to employ cardiac MRI as part of a large-scale epidemiological study to examine the progression of disease from pre-clinical manifestations to clinical symptoms, and apply modern imaging methods to develop new biomarkers and risk factors to augment those identified by Framingham and other population-based studies (Bluemke et al., 2008). Similarly, the UK Biobank is an extensive population-based study that recruited 500,000 people aged between 40 and 69 years in 2006–2010 from across the UK, with over 6000 participants already imaged using cardiac MRI, abdominal MRI, brain MRI, carotid ultrasound, and dual-energy X-ray absorptiometry (Petersen et al., 2013). This is now being extended to image 100.000 participants over the next 6 years. Several other more localised cardiac imaging studies are currently being performed in order to identify novel cardiac disease risk factors based on cardiac shapes and function.

Atlas-based shape analysis is a powerful tool to quantify shape changes in pre-clinical and clinicial disease (Fonseca et al., 2011). Preliminary results in the MESA cohort have shown that atlas-based shape measures are more sensitive than traditional remodelling indices for describing associations with common risk factors (Medrano-Gracia et al., 2014). Principal component analysis (PCA) has been used to quantify the major determinants of shape variation in MESA participants (Fonseca et al., 2011). In 1991 MESA participants, after correction for height, the major principal modes of shape variation were associated with known clinical indices of adverse remodelling, including heart size, sphericity and concentricity (Medrano-Gracia et al., 2014). Geometric variations can also be associated with traditional risk factors and demographic data. For example, significant differences were found between PCA shape modes in sub-cohorts grouped by traditional risk factors including sex, ethnicity, smoking and alcohol. Males and African Americans tended to have larger hearts and females and Chinese tended to have smaller hearts for their height. Heart size increased with history of smoking or alcohol. Female hearts were more spherical than males, and Chinese were less spherical than Whites. Differences in sphericity were also found due to alcohol use (more spherical with current consumption), and presence of diabetes (more spherical with untreated diabetes) at end-systole. Shape indices derived from multidimensional atlas-based analysis were more powerfully associated with known risk factors such as sex, ethnicity, smoking, hypertension and diabetes than traditional imaging markers such as ejection fraction, volume, and LV mass (Medrano-Gracia et al., 2014).

Combinations of shape components may enable calculation of remodelling indices that are specifically associated with traditional risk factors, presence of disease, or adverse outcomes. For example, linear discriminant analysis was used to determine that atlas-based components are more sensitive to traditional risk factors than standard imaging indices such as mass and volume (Zhang et al., 2014). Supervised dimension reduction methods can be used to define a single integrated remodelling component that best describes the remodelling process in relation to a specific disease process (Zhang et al., 2015). As shown in Fig. 1, a single shape mode with the strongest association with myocardial infarction was able to discriminate patients from asymptomatic subjects with 95% accuracy (Zhang et al., 2015).