

Original research

Histo-anatomical structure of the living isolated rat heart in two contraction states assessed by diffusion tensor MRI

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ABSTRACT

Deformation and wall-thickening of ventricular myocardium are essential for cardiac pump function. However, insight into the histo-anatomical basis for cardiac tissue re-arrangement during contraction is limited. In this report, we describe dynamic changes in regionally prevailing cardiomyocyte (fibre) and myolaminar (sheet) orientations, using Diffusion Tensor Imaging (DTI) of ventricles in the same living heart in two different mechanical states. Hearts, isolated from Sprague–Dawley rats, were Langendorff-perfused and imaged, initially in their slack state during cardioplegic arrest, then during lithium-induced contraction. Regional fibre- and sheet-orientations were derived from DTI-data on a voxel-wise basis. Contraction was accompanied with a decrease in left-handed helical fibres (handedness relative to the baso-apical direction) in basal, equatorial, and apical sub-epicardium (by 14.0%, 17.3%, 15.8% respectively; $p < 0.001$), and an increase in right-handed helical fibres of the sub-endocardium (by 11.0%, 12.1% and 16.1%, respectively; $p < 0.001$). Two predominant sheet-populations were observed, with sheet-angles of either positive ($\beta+$) or negative ($\beta-$) polarity relative to a ‘chamber-horizontal plane’ (defined as normal to the left ventricular long-axis). In contraction, mean ‘intersection’-angle (geometrically quantifiable intersection of sheet-angle projections) between $\beta+$ and $\beta-$ sheet-populations increased from $86.2 \pm 5.5^\circ$ (slack) to $108.3 \pm 5.4^\circ$ ($p < 0.001$). Subsequent high-resolution DTI of fixed myocardium, and histological sectioning, reconfirmed the existence of alternating sheet-plane populations. Our results suggest that myocardial tissue layers in alternating sheet-populations align into a more chamber-horizontal orientation during contraction. This re-arrangement occurs via an accordion-like mechanism that, combined with inter-sheet slippage, can significantly contribute to ventricular deformation, including wall-thickening in a predominantly centripetal direction and baso-apical shortening.

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1. Introduction

Detailed knowledge of the histo-anatomy of the heart is crucial for understanding its mechanical (Waldman et al., 1988) and electrical (Kanai and Salama, 1995) behaviour. Myocardial tissue structure is intimately linked to heart function, and both change considerably in cardiac disease. However, a complete and consistent description of cardiac structure, and its deformation during the heartbeat, is lacking, largely due to the complex architecture of myocardial tissue, and the destructive techniques which traditionally have been used to examine it.

Within ventricular myocardium, myocytes are regionally orientated approximately parallel to each other, and the resulting locally

Non-standard abbreviations and acronyms: 2D, two-dimensional; 3D, three-dimensional; ADC, apparent diffusion coefficient; CF, circumferential fibre; DTI, diffusion tensor imaging; FA, fractional anisotropy; FOV, field of view; IDL, inter-active data language; LHF/RHF, left/right-handed helical fibre; LV, left ventricle; MRI, magnetic resonance imaging; NMR, nuclear magnetic resonance.

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prevailing myocyte orientation is referred to as ‘fibre-orientation’. Fibre-orientation was originally studied via histological measurements in sections of transmural ventricular tissue (Streeter et al., 1969; Streeter and Hanna, 1973). It is now understood that fibre-orientation undergoes a transition from a left-handed helical arrangement in sub-epicardial layers, to a circumferential alignment in mid-myocardium, to a right-handed helical direction in sub-endocardial tissue (Jiang et al., 2004). Fibre-orientation is commonly quantified using the helix-angle (α , also known as the ‘fibre-angle’), which describes the deviation from the chamber-horizontal plane (defined as perpendicular to the left ventricular long-axis), as viewed from the outside (Fig. 1).

Building on long-established anatomical records, recent studies have confirmed that the ventricular myocardium is further organized in branching sheets (really ‘sheetlets’, as they do not form continuous extended structures that traverse the entire heart), approximately 4–5 cardiomyocytes thick (Costa et al., 1999; Harrington et al., 2005; LeGrice et al., 1995a; Helm et al., 2005a,b). An extracellular collagen-network provides tight coupling of myocytes within a sheet, and looser connections between adjacent sheets that allow for slippage (LeGrice et al., 1995b). Spaces between sheets appear as cleavage-planes in histological sections throughout the ventricles (Costa et al., 1999; Robb and Robb, 1941). They are also apparent from three-dimensional (3D) reconstruction of the ventricular perimysial collagen-network (Pope et al., 2008).

Detailed knowledge of fibre- and sheet-arrangement, and of their changes during the contractile cycle, is essential for understanding cardiac mechanics. Cardiomyocyte contraction provides the cellular basis for force-generation and shortening, predominantly along the fibre-direction. Given the incompressible nature

and constant volume of the cytosol, cell shortening is associated with radial widening. Interestingly, the increase in myocyte diameter during contraction would raise wall-thickness by only 8%, while in reality systolic wall-thickening by 40% or more is observed. Thus, cell-diameter increases account for a fraction only (about one fifth) of total ventricular wall-thickening during contraction (LeGrice et al., 1995a,b; Rademakers et al., 1994; Spotnitz et al., 1974). Other contributions are believed to arise from lateral shearing and reorientation of sheets. It has been suggested that, in addition to shearing and reorientation, sheets contribute to systolic wall-thickening by extending the in-sheet plane transverse to fibre-orientation (Spotnitz et al., 1974; LeGrice et al., 1995a,b; Costa et al., 1999).

In spite of the role sheets are likely to play in the mechanics of cardiac contraction, sheet-architecture and 3D re-organization during systolic wall-thickening are not well-understood (Gilbert et al., 2007). There appear to be two conceptually different models. The first follows the original description of LeGrice et al. (1995a,b), in which smoothly varying sheets radiate outward from sub-endo- to sub-epicardium. The second model allows for the existence of multiple populations of sheets, referred to as alternating sheet-populations/polarities. Early work by Arts et al., 2001 predicted that two distinct populations of sheets should occur, with sheet intersection angles of about 70–90°, based on the hypothesis that sheets are orientated along the plane of maximal systolic shear, and subject to the constraint that muscle fibre axis is fixed in this plane. This was verified experimentally at various locations throughout the myocardium in the canine heart, with the exception of regions close to the epicardium (Arts et al., 2001). Later studies by Ashikaga et al. (2004, 2005) confirmed the existence of two distinct, approximately perpendicular, sheet populations in the canine heart. Histological measurements of sheet orientation in the ovine left ventricle by Harrington et al. (2005) showed an alternating pattern of sheet polarity across the width of the left ventricular wall, suggesting that sheet populations of opposite polarities are present throughout the myocardium. More recently, combined histological and MR-based studies (Gilbert et al., 2012; Kung et al., 2011) have produced strong evidence in support of the ‘two-population’ sheet model, and it was even suggested by Kung et al. (2011) that when only one sheet population is evident in histological sections, this is likely to be a by-product of sample preparation artefacts, obscuring the second sheet population (Kung et al., 2011). However, as with the majority of previous studies, recent work has been limited to snapshots of ventricular histo-anatomy in only one mechanical state, and an understanding of *dynamic* sheet re-arrangement during ventricular contraction is still lacking. Limited insight into sheet-dynamics may be one of the reasons why even the most-advanced histo-anatomically detailed mathematical models of cardiac contraction, while covering the ventricular twisting motion caused by the transmurally varying fibre orientation, tend to under-represent the atrio-ventricular valve plane shift (many models actually show baso-apical lengthening of the ventricles during simulated contraction). Computational heart models also tend to only partially capture the predominantly centripetal (*from “Centrum” [Latin for: the centre] and “petere” [Latin for: to seek/to aim at] – i.e. directed towards the centre*) wall-thickening, which is achieved with relatively stable epicardial outlines (Fig. 2).

Much of the prior research has been based on inherently tissue-destructive techniques, such as serial histological sections. Not only does this tend to limit analysis to small regions of the heart, but identification of true 3D sheet-orientation is problematic using this approach. This is because myocardial laminae are tightly packed in native tissue, and the predominant sheet-orientation can change abruptly in the space of millimetres (Cheng et al., 2005). In addition,

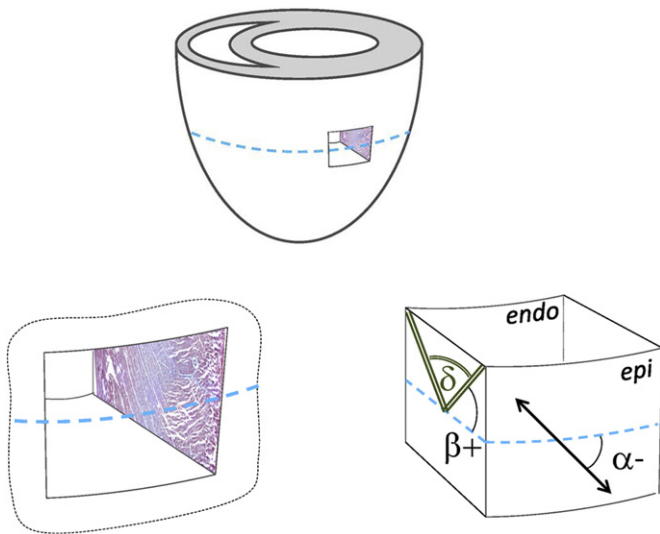


Fig. 1. Schematic illustration to introduce fibre- and sheet-angle definitions. *Top:* conceptualization of the orientation of a ‘transmural tissue block’, removed from the left-ventricular (LV) free-wall, with reference to the heart’s chamber-horizontal plane (blue dashed line). *Bottom-Left:* schematic representation of transmural cut, with indication of long-section tissue appearance (see Fig. 6 for original transmural long-section histology). *Bottom-Right:* excised transmural tissue block with an indication of epicardial fibre-orientation (black arrow) and transmural sheet-orientations (green double-lines). The helix-angle (α) describes the deviation (viewed from the epicardium) of fibre-orientation from the horizontal plane; it is negative if fibres point from top-left to bottom-right (and positive if they go from bottom-left to top-right). The angle β is used to describe the deviation, from the heart’s chamber-horizontal plane, of the apparent sheet-orientation in transmural long-cuts of the ventricles, and is positive if sheet-projections are directed in an apico-basal (‘upward’) orientation, as one follows them from endo- to epicardium (and *vice versa*). Also shown is the sheet intersection-angle δ , discussed in more detail elsewhere in the text.

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