Distributions of myocyte stress, strain and work in normal and infarcted ventricles

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Background
The ventricles of the heart are heterogeneous structures with regional variations in geometry, for example, wall thickness and curvature, as well as variations in cell-level architecture such as myocyte orientation and extracellular matrix structure. Regional heterogeneities are also found in myocyte function: cellular protein expression\(^1\), ionic currents\(^3\), electrophysiology properties\(^4\), action potential morphology\(^5\) and mechanical twitch\(^6\) have been shown to vary with position in the wall of the left ventricle (LV). It is known that these cellular and structural heterogeneities are important determinants of normal and pathological cardiac function. The complex interaction of structural and cellular heterogeneities gives rise to variations in local myocyte mechanical function. The focus of this chapter is to describe the regional and transmural distributions in stress, strain and work in normal and infarcted ventricles as measured experimentally and predicted with a computational finite element model of canine cardiac electromechanics. Experimental data combined with computational simulations show highly heterogeneous distributions of mechanical function in the ventricles. In turn, such distributions in myocyte function contribute to mechanically induced heterogeneity of cardiac electrophysiology via mechano-electric coupling (MEC).

LV structure: arrangement of cardiomyocytes
The cardiac muscle cell or cardiomyocyte is a roughly cylindrical cell that forms attachments to neighbouring cells through gap junctions preferentially aligned with the long axis of the cells, as well as transverse connections via costameres and extracellular matrix attachments. The term ‘fibre’ is also used for cardiomyocytes; in particular we refer to the ‘fibre direction’ as the long axis of these elongated muscle cells, and fibre function will be a mechanical parameter associated with that direction. The cardiomyocytes of the LV are arranged in a helical fashion, with (sub-)epicardial cells oriented in a counterclockwise spiral and (sub-)endocardial cells in a clockwise spiral, viewed from apex to base. In the dog, epicardial myocytes are oriented roughly \(-60^\circ\) from circumferential, mid-wall myocytes are aligned at \(0^\circ\) and endocardial myocytes at \(60^\circ\). This transmural gradient in fibre direction has been shown to have functional implications. It was demonstrated in a numerical model that the distribution of stress and strain in the LV wall is sensitive to the spatial organization of the cardiomyocytes\(^8\) and that their orientation serves to maximize the homogeneity of fibre stress during ejection\(^9\). At low ventricular volumes sarcomere lengths vary transmurally, and they are more uniformly distributed at higher volumes\(^10\) due to cardiomyocyte orientation as well as residual stress\(^11\). There also exists a transmural distribution of myocyte diameter, with cells at the epicardium being larger than those near the endocardium\(^12\). The thinner wall and greater distensibility near the apex (compared to the base) gives rise to longer sarcomere lengths at the apex compared to the base\(^13\).

There is a secondary level of myocardial structural organization. Cardiac myocytes are arranged into discrete muscle layers, termed myocardial laminae or sheets, which are roughly four to eight cells thick\(^14\). Spotnitz was the first to describe the existence of myocardial gaps or ‘sliding planes’ in the rat LV and proposed that these planes could give rise to large changes in wall thickness during systole\(^15\). Like myocyte orientation, sheet arrangement has been shown to vary regionally and transmurally throughout the LV. Through sheet extension and shearing, ventricular wall thickening is accomplished and can be as large as 40% at the endocardial layer\(^16\).

In order to relate regional mechanical function to the orientation of cellular tissue components, a cardiac coordinate system can be defined to represent local circumferential, longitudinal and radial axes. By measuring mean fibre and sheet angles as a function of location, a local fibre-sheet coordinate system can be defined in terms of these angles in order to relate local stress and strain to the underlying anisotropic structure (Fig. 62.1).

Regional ventricular mechanics
The functional role of the heart is to convert metabolic energy into mechanical work in order to generate adequate pressure to eject blood throughout the body’s circulation. In global terms one can describe cardiac function through the pressure–volume relationship,
of contraction and relaxation, direct experimental measurements of stress are few and controversial. Rather than measuring stress directly to assess regional function, some measure of deformation (i.e. strain) is found experimentally, and then mathematical models are used to determine stress. Finite element (FE) models have become state of the art for mathematical modelling of cardiac mechanics. FE models may include accurate measurements of geometry and muscle cell orientations, non-linear passive constitutive laws, active stress relationships and boundary conditions described as pressure or displacement constraints. These models show similar patterns of three-dimensional (3D) strain as measured experimentally and predict substantial regional heterogeneity of ventricular mechanics.

**Material properties of the myocardium**

Distributions of stress and strain in the heart are governed by the underlying 3D tissue structure, the boundary conditions of cavity pressure and volume and the material properties of the myocardium during passive (diastolic) and active (systolic) phases. Fibre and sheet anatomy can be measured histologically and pressures can be measured in vivo; however, quantifying the material properties of the myocardium requires extensive mechanical testing. The importance of understanding the mechanical properties of the myocardium can be illustrated in disease states in which cellular and extracellular remodelling occur and alter the mechanical environment.

The myocardium is a soft biological tissue that is anisotropic, meaning that the material properties are a function of direction. Theoretically, to fully express the material properties of the myocardium, a 3D analysis is required. In reality such tests are practically limited. Therefore the use of uniaxial and biaxial testing has become the norm for mechanical testing to determine the local material properties.

Uniaxial tests using papillary muscles and ventricular trabeculae can be used to define passive stress–strain relationships in the fibre direction. The main findings from these experiments are that the stress–strain relationships are non-linear and time-varying, and that the stiffness–stress relationships are linear. For example, the material properties of the rabbit papillary muscle were characterized by an exponential stress–strain relationship\(^{(21)}\). For a comprehensive review of uniaxial muscle mechanics the reader should consult the review by Mirsky and Parmley\(^{(22)}\).

Due to the incompressibility of cardiac tissue, biaxial tests can be used to infer 3D material properties of myocardial tissue samples. Typically, isolated hearts are sectioned into rectangular slabs cut tangential to the epicardial surface, mounted onto a biaxial stretcher, and then stretched in two in-plane orthogonal directions. The data collected by Demer and Yin suggested that the passive myocardium is non-linear, anisotropic and regionally heterogeneous\(^{(23)}\). Data from Humphrey et al., collected in a single region of the canine LV, illustrated that the myocardium was stiffer in the fibre direction than in the cross-fibre direction\(^{(24)}\).

**Experimental measurements of fibre strain in normal and infarcted tissue**

Due to the impracticality of directly measuring stress in the beating heart, regional myocardial function is typically measured with
some type of deformation analysis, for example tissue strain or muscle cell stretch. While stretch represents a uniaxial length change of tissue (typically quantified as a stretch ratio), strain is classically used to describe the 3D deformation of a material. The relationship between the stretch ratio, $\lambda$, and a component of strain, $E_{ij}$, can be described as:

$$E_{ij} = \frac{1}{2} (\lambda^2 - 1)$$

$$\lambda_j = L / L_o$$

where $L$ is the deformed length, $L_o$ is the undeformed length and $E_{ij}$ is the Lagrangian strain component. In this example, the subscript $f$ of the strain and stretch ratio refers to the fibre direction/component. Experimentally, segment length changes have been assessed with various techniques, including ultrasonic piezoelectric crystals, and show substantial variations in function across the ventricle. The major findings from these studies were that fibre shortening increased from base to apex, and that endocardial shortening exceeded that of the epicardium. Furthermore, mid-wall fibre shortening in the anterior wall exceeded that of the lateral and posterior walls. 2D and 3D strains can be measured in vivo using implantable radiopaque markers. Waldman et al. used implantable markers to measure transmural distributions of cardiac strain. Ashikaga and colleagues showed a significant transmural distribution in fibre strain throughout the cardiac cycle. Wyman and colleagues used tagged magnetic resonance imaging (MRI) to measure regional distributions of fibre strain at the mid-wall and showed significant differences from apex to base and around the hoop axis of the heart, as shown in Fig. 62.2. Specifically, fibre strain was highest in the anterior wall compared to the lateral, posterior and septal walls and increased from base to apex. Experimental measures have also shown that local ventricular electrical pacing results in remote areas of tissue that 'pre-stretch', i.e. lengthening of late-activated tissue segments during the late diastolic and isovolumic contraction phases.

The effect of ischaemia on regional LV function has been assessed using ultrasonic gauges which revealed fibre bulging or 'paradoxical segment lengthening' within the ischaemic tissue during systole. Normal fibre function was characterized by fibre shortening during the isovolumic contraction and ejection phases followed by relengthening during the isovolumic relaxation and early filling phases. During ischaemia, fibres within the ischaemic zone were stretched, indicated by positive strain, throughout systole. This stretching of the muscle cells was due to the reduced contractility of cells in the ischaemic region, in combination with active contraction and shortening of normal myocardium surrounding the ischaemic zone.

The diastolic material properties of the LV during normal and ischaemic conditions have also been studied. Biaxial testing of infarcted tissue revealed increases in circumferential and longitudinal stiffness for 1- to 2-week-old infarcts, along with increased stiffnesses in the circumferential direction. Using MRI tagging and computation modelling, Walker and colleagues showed that infarct stiffness increased nearly 15 times more than non-infarcted tissue in 22-week-old sheep infarcts. Omens and co-workers demonstrated that the increased passive fibre stiffness was due to an increase in collagen fibres that ran parallel to the muscle fibre axis, as depicted in Fig. 62.3. Despite the increase in overall ventricular compliance (Fig. 62.3C), the fibre stiffness was increased substantially in the infarcted hearts.

### Redistribution of work during ischaemic heart disease

Abnormal strain and stress patterns for extended periods of time can alter cardiomyocyte physiology and lead to structural, mechanical and electrical remodelling. During ischaemia, the oxygen supply is less than the working demand of cardiomyocytes, typically due to a change in local blood supply following an obstruction in a coronary vessel. The ischaemic region is said to be akinetic, whereas the non-ischaemic region demonstrates 'hyperkinetic' functionality. This hyperkinesis is in part due to a compensatory adaptation of the non-ischaemic cardiomyocytes that increase their contractile function in response to the dysfunction in the non-contracting ischaemic region (see also Chapter 21). Therefore a result of ischaemia is a reduction of work in both the ischaemic and non-ischaemic regions. Lew demonstrated the effect of varying infarct size on non-ischaemic myocardial function. As shown in Fig. 62.4, pressure–length segment loops reveal that with increasing infarct size, segment shortening increases in the non-ischaemic zone. The distribution of work can be inferred from the area of the pressure–length loops. Increasing infarct size reduced the amount of work done by the anterior and posterior walls. In the infarcted region (anterior wall) work was reduced to that of passive inflation (negative work) compared to that in the actively contracting (positive work) non-infarcted posterior wall.

### Modelling ventricular mechanics in the healthy and infarcted heart

A finite element approach was used to model the regional electromechanics of a cardiac contraction in normal and infarcted canine...
ventricles. This model has been previously described by our group.(20,38). Briefly, realistic geometries of both right and left ventricles were fit in prolate-spheroidal coordinates by 48 (normal) and 60 (infarct) cubic Hermite elements. The normal heart had a cavity to wall volume ratio of 0.27, whereas dilated hearts with infarcts had a cavity to wall volume of 0.57. Realistic myofibre architecture was included in both models. In the infarcted region transmural fibre angle gradient, which represents that of collagen fibres, was larger than in non-infarcted tissue due to the thinner wall thickness in this region.

Passive mechanics were modelled using a transversely isotropic exponential constitutive law with parameters obtained from previous models(19), whereas the passive parameters of the infarct were scaled from experimental data(35). Active mechanics were modelled using a modified Hill’s equation that related tension along the myofibre long axis to intracellular calcium concentration. Model parameters for the normal heart were obtained from previous models(19); in the infarct region parameters were changed such that the peak force was 27% lower than non-infarcted healthy tissue and the force twitch duration was 17% longer(38).

The ventricles were coupled to a systemic and pulmonary circulation, each comprised of two windkessel compartments in series representing arterial and venous blood. Atria were incorporated as time-varying elastance models. The hearts were passively inflated to the end-diastolic pressure and were then activated to contract by prescribing a local activation time from which the myofibres began to develop tension at a delay of 8 ms from activation.

**Distribution of fibre strain, stress and work in simulations of healthy ventricles**

Model results shown below indicate marked differences in fibre mechanics at varying locations. Figure 62.5 shows the transmural distribution of fibre strain (in terms of stretch ratio), stress and work in the anterior wall of the normal LV at three distinct regions: base, equator and apex. Endocardial shortening (stretch ratio less than 1) during isovolumic contraction (IVC) and ejection was
greatest in the anterior apex compared to the base and equator, whereas peak fibre stress was highest for equatorial endocardial fibres and least at the anterior apex. In both the basal and apical regions, a transmural gradient in fibre stretch ratio is observed throughout the ejection phase, with epicardial strain being the least, followed by mid-wall and endocardial strain. At the equator endocardial fibres are stretched during IVC and shorten less than the epicardial fibres during systole. Between the different layers (endo- and mid-wall and epicardial) external work (area within the stress–stretch loop) done by the fibres is highest at the endocardium. The higher tension for endocardial fibres at the equator results in larger work done at the equator. Mid-wall and epicardial work was similar for all three regions.

Figure 62.6 shows the corresponding stretch ratio, stress and work in the posterior basal, equatorial and apical regions. As in the anterior wall, endocardial shortening is highest at the apex and lowest at the base. Additionally in all three regions endocardial shortening exceeds epicardial shortening. Peak fibre stress is highest at the base and equatorial endocardial fibres. Marked transmural gradients are seen in the fibre stretch ratio, stress and work at all sites. Fibre work at the endocardium is similar at all three regions, whereas in the mid-wall fibre work was highest at the base and lowest at the apex.

**Effect of LV anterior infarct on fibre strain, stress and work**

The effect of an anterior infarct on LV function was simulated in the model. The anterior LV infarct occupied 21% of the total LV wall volume. Figure 62.7 shows the fibre stretch ratio, stress and work distributions for infarcted (top), border zone (middle) and remote regions (bottom). Stretch ratio was plotted for each layer (endocardial, mid-wall and epicardial) throughout the isovolumic phase and was referenced to zero LV cavity pressure. At end-diastole, endocardial fibres were stretched more than epicardial and mid-wall fibres in the infarcted and border zone regions. In the infarcted region, all layers were stretched during the isovolumic contraction phase, with endocardial fibres being stretched the most. In the border zone, endocardial fibres were stretched late during isovolumic contraction, whereas mid-wall and epicardial fibres began to shorten. Conversely, in tissue remote from the infarct, endocardial and mid-wall fibres began to shorten, while epicardial fibres lengthened near the end of IVC. Fibre stress was greatest for the endocardial fibres in all regions, followed by mid-wall and epicardial fibres. Compared to the normal fibre stress distributions shown in Figs 62.5 and 62.6, fibre stress in the infarcted and border zone regions at the endocardium was much...
Fig. 62.6 Ventricular mechanics at the posterior wall of the LV. A Location within the wireframe FE model is highlighted, and results are shown at the centroid of each element in these regions. Fibre stretch ratio (B), fibre stress (C) and fibre stress-stress loops (D) are plotted with respect to end-diastole for endocardial (bold lines), mid-wall (dashed lines) and epicardial (black lines) layers in basal (top), equatorial (middle) and apical (bottom) regions. The fibre directions at the various layers are −40° (epicardium), 2° (mid-wall) and 25° (endocardium).

Fig. 62.7 Distribution of cardiac fibre stretch, stress and work in infarcted LV. Location within the wireframe FE model is shaded grey, and results are shown at the centroid of each element in these regions. The epicardial surface of the infarct region is outlined in red. Fibre stretch during the isovolumic contraction phase (B) fibre stress (C) and work (D) in infarcted (top), border zone (middle) and remote regions (bottom). Fibre stretch is referenced to zero cavity pressure, whereas fibre stress and work are referenced to end-diastole. Transmural distributions are shown for epicardial (black lines), mid-wall (dashed lines) and endocardial (bold lines) layers. The fibre directions at the various layers are −45° (epicardium), 5° (mid-wall) and 35° (endocardium).
higher at end-diastole and during IVC. Stress vs stretch ratio plots revealed that all myocytes in the infarcted region displayed akinetic behaviour as indicated by a purely passive stress vs stretch curve. This passive behaviour can also be described by paradoxical systolic stretching of the fibres due to contraction of the surrounding healthy myocardium. In the border zone and remote regions, external work was similar to that of the normal heart, with endocardial work being greatest and epicardial work being smallest.

Conclusions and outlook
In summary, assessments of cardiac function obtained experimentally and through the use of computational models reveal substantial regional variations in fibre stress, strain and work in normal hearts. These distributions are due to the complex structural arrangement of cardiac muscle cells within their extracellular environment, and the anisotropic material properties that depend on these structures. During ischaemic heart disease, scarring can occur and result in an infarct that alters the passive and active state of the myocardium. Experimental findings show that fibre shortening is replaced with paradoxical bulging in ischaemic regions during systole, which results in passive pressure–length loops characterized by negative external work. The passive properties of the chronic infarct scar are as well, observed as increased stiffness in the fibre direction and increased fibre stresses. The results obtained from our computation simulations illustrate the regional differences in fibre function in the normal heart. Fibre shortening is greatest at the apex compared to the base and is largest for endocardial compared to epicardial myocytes. The transmural distribution of fibre stress and work show that endocardial cells are subjected to higher stresses and perform greater work than do midwall and epicardial cells. Simulations of the effect of an anterior infarct on regional function demonstrate that in areas of infarction the cardiomyocytes are stretched through isovolumic contraction, contrary to the fibre shortening displayed by non-infarcted myocardium. Infarcted regions performed the least amount of external work, compared to border zone and remote tissue, thus illustrating the redistribution of work that accompanies ischaemic heart disease.

The altered mechanical state of the infarcted ventricle may have functional implications on cellular electrophysiology and MEC. The ability of cardiomyocytes to sense mechanical loading and the cell's functional response is discussed elsewhere in this book (see, in particular, Chapter 24). Abnormal stretching of the myocytes in infarcted and border zone regions may give rise to abnormal electrical activation and arrhythmias. Therefore, understanding the regional differences in myocyte function in normal and pathological states is a requirement for new insight relevant for diagnosis and treatment of many cardiac diseases. [11]

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