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Transmural Gradients of Myocardial Structure and Mechanics: Implications for Fiber Stress and Strain in Pressure Overload

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Abstract

Although a truly complete understanding of whole heart activation, contraction, and deformation is well beyond our current reach, a significant amount of effort has been devoted to discovering and understanding the mechanisms by which myocardial structure determines cardiac function to better treat patients with cardiac disease. Several experimental studies have shown that transmural fiber strain is relatively uniform in both diastole and systole, in contrast to predictions from traditional mechanical theory. Similarly, mathematical models have largely predicted uniform fiber stress across the wall. The development of this uniform pattern of fiber stress and strain during filling and ejection is due to heterogeneous transmural distributions of several myocardial structures. This review summarizes these transmural gradients, their contributions to fiber mechanics, and the potential functional effects of their remodeling during pressure overload hypertrophy.

Keywords

cardiac mechanics; fiber stress; fiber strain; myocyte fiber angle; transmural gradients; pressure overload hypertrophy

1. Introduction

[1]The motion of the ventricular walls during normal cardiac pump function is highly complex, involving the coordinated activation and contraction of electromechanically coupled myocytes, followed by relaxation, and refilling. Despite numerous studies attempting to describe and model cardiac biomechanics, significant gaps of knowledge remain regarding the mechanisms by which cross-bridge force generation and sarcomere shortening are integrated by the hierarchical intracellular and extracellular organization of the myocardium and the anatomy of the chambers to produce the driving pressures for blood

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[1]Abbreviations: LV, MRI, DT-MRI, ECM, MLC, MLCK, MHC, MHC-α, MHC-β, APD, I_{to}, Kcnk2, TREK-1, Cx43, SERCA2a

flow through pulmonary and systemic circulations. These gaps in knowledge represent potential opportunities for generating therapies or treatments for widespread cardiac disease, which remains the primary cause of death in the United States (Mozaffarian et al., 2016). Hence, it remains of central importance to study structure-function relationships determining myocardial mechanics in the normal and diseased ventricles.

Much work has been done to quantify the three-dimensional deformation patterns in the normal left ventricle (LV) by tracking myocardial tissue during relaxation and filling (diastole), as well as during contraction and ejection (systole). Likewise, efforts have been made to characterize the internal tissue forces (stresses), with experimental measurements and mathematical or computational models. These studies have brought to light the complexity of normal cardiac mechanics, including insights as to the mechanisms by which shortening along the axis of the myocytes drives circumferential and longitudinal shortening in the tissue, with concordant wall (radial) thickening and chamber torsion, to efficiently eject blood during systole, as well as the reverse process during diastole.

One notable feature that has been described is the surprisingly homogeneous transmural distribution of fiber strain and stress across the wall of the normal LV in several mammalian species, including humans. Because simple mechanical theory of thick-walled pressure vessels predicts transmural gradients of strain and stress, with higher levels in the subendocardium, researchers have sought to understand how and how this uniformity (which is an optimal design principle in engineering) is achieved in the normal heart. Studies have shown many structural and functional features of normal LV myocardium that have transmural gradients, that may contribute to maintaining uniformity of fiber stress and strain during LV ejection and filling. Alterations in these structure-function relationships could contribute to adverse remodeling and ventricular dysfunction in heart disease, particular in load-mediated remodeling processes such as cardiac hypertrophy.

In this article, we review studies of transmural gradients of myocardial structure, and how variations in regional architecture affect transmural distributions of strains and stresses in the myocardium. In particular, we aim to summarize the mechanisms by which the structural features that exhibit a transmural gradient may contribute to uniformity of fiber strain and stress, and how these distributions may change during disease. During remodeling processes in which mechanosensing and mechanotransduction are important, understanding mechanisms that regulate the distributions of stress and strain will help define interventions aimed and altering the course of detrimental myocardial remodeling. We focus on examples related to mechanical regulation of concentric hypertrophy due to pressure overload, noting the high prevalence of hypertension, with one in three adults in the U.S. alone having high blood pressure (Mozaffarian et al., 2016).

2. Fiber strain and stress

2.1 Fiber strain

While metrics of whole heart function such as ejection fraction, cardiac output, or wall thickening are informative and useful, especially for clinical classification of patients, the measurement of intra-myocardial deformation within the ventricle wall is imperative to fully

understand regional mechanical function in myocardial tissue, and how load/deformation-related mechanisms of remodeling could be affected by regional variations in mechanics. Since consistent anatomic material landmarks are not readily detected in myocardial tissue, specialized techniques for imaging and recording the displacement of material points within the myocardium have been developed and used to quantify mechanical strain.

The measurement of strain within the ventricle walls has been achieved for decades using various techniques. In general, direct measurement of mechanical strain requires tracking of material points/markers in the tissue. Early, invasive studies involved the implantation of strain gauges, needles, radiopaque beads, ultrasonic crystals, or other markers whose positions were tracked in time (Arts and Reneman, 1980), (Ashikaga et al., 2004), (Cheng et al., 2005), (Cheng et al., 2008), (Costa et al., 1999), (Dieudonn, 1969), (Douglas et al., 1991), (Elshuraydeh et al., 1981), (Fann et al., 1991), (Fenton et al., 1978), (Freeman et al., 1985), (Guccione et al., 1995), (Hansen et al., 1988), (Ingels et al., 1971), (LeWinter et al., 1975), (McCulloch et al., 1987), (McCulloch and Omens, 1991), (Meier et al., 1980), (Meier et al., 1982), (Omens et al., 1991), (Omens et al., 1993), (Osakada et al., 1980), (Prinzen et al., 1984), (Villarreal and Lew, 1990), (Waldman et al., 1985), (Waldman et al., 1988), (Yun et al., 1991). Non-invasive methods have become more available in animal model and humans, such as speckle tracking echocardiography (Bellavia et al., 2010), strain rate magnetic resonance imaging (MRI) (Dou et al., 2003), and tagged MRI (Azhari et al., 1993), (Bogaert and Rademakers, 2001), (Buchalter et al., 1990), (Chuang et al., 2010), (Clark et al., 1991), (MacGowan et al., 1997), (McVeigh and Zerhouni, 1991), (Rademakers et al., 1994), (Young et al., 1994a), (Young et al., 1994b). MRI tagging is a technique whereby regions of myocardium are “tagged” with patterns of magnetization for a limited time as they deform through the cardiac cycle, thus enabling tracking of material point locations and strain calculations. The advantages of using tagged MRI include its non-invasiveness, relative ease of use, and comprehensive coverage of the ventricles at relatively high resolution. Difficulties include potentially low signal to noise ratio and the challenge of converting data from 2D tagged images to 3D displacements, which has been addressed in various ways (Azhari et al., 1993), (Chuang et al., 2010), (Ibrahim, 2011), (Young et al., 1994b), (Zhong et al., 2008). Despite these few challenges, tagged MRI with harmonic phase material point tracking is one of the best methods for a full 3D description of tissue deformation (Osman et al., 1999), (Chuang et al., 2010).

To completely describe three-dimensional deformation in a given volume, the six unique components of the strain tensor are necessary, which can be defined with respect to any chosen coordinate system. Some natural reference frame options which have been used in the heart include “cardiac coordinates”, which locally correspond with circumferential, longitudinal, and radial directions of cylindrical or prolate spheroidal systems, “fiber coordinates”, in which the circumferential direction from cardiac coordinates is rotated by the fiber angle to align with the local myofiber direction resulting in fiber, cross-fiber, and radial directions (Waldman et al., 1988), and “material coordinates”, which align with local fiber, sheet, and sheet-normal directions (Costa et al., 1999). The latter two systems allow for quantifying strain aligned with the fiber axis, which is parallel to the long axis of the myocytes, and therefore the direction along which sarcomeres shorten during systolic contraction.

The strain tensor describes shape change between two time points or states. Fiber strain measured with respect to the unloaded state in passively loaded isolated arrested hearts or measured *in vivo* at end-diastole, with respect to early diastasis, has been used to investigate resting tissue mechanics. End-systolic fiber strain *in vivo*, usually referenced to end-diastole, characterizes the regional systolic mechanics of the myocardium. Using the above-mentioned techniques, researchers have sought to characterize fiber strains in the LV at end-diastole and end-systole to better understand how fiber mechanics relate to pump function and remodeling.

2.1.1 End-diastolic fiber strain—End-diastolic fiber strain gives insight into the passive material properties of myocardium, and describes the state of the sarcomeres at the moment of electrical activation. McCulloch et al. (McCulloch et al., 1987) used radiopaque markers and biplane radiography to measure epicardial end-diastolic strains with respect to an unloaded state (i.e. LV pressure ≈0) in dog and found that epicardial stretch during passive loading is greatest along the axis of the fibers. The same authors in a subsequent study suggested that the consequent torsional shear strain may serve to minimize transmural gradients of fiber lengthening during filling (McCulloch et al., 1989).

Omens et al. (Omens et al., 1991) measured transmural end-diastolic strains with respect to an unloaded state in the canine left ventricle. A major finding of that study, that corresponded well with previous studies of systolic strain (Waldman et al., 1985), (Waldman et al., 1988), was that the end-diastolic principal strain axis did not vary nearly as much with the wall depth as the fiber orientations, and increased in magnitude toward the endocardium. Given the gradient in the orientations of the myofibers across the wall, this result indicated that the maximum principal end-diastolic strain aligned closely with the subepicardial fibers, but was roughly orthogonal to the subendocardial fibers, such that the subepicardial fiber orientation was the axis of maximum passive lengthening, but the subendocardial fibers were aligned with the axis of minimum in-plane strain. To examine this more directly, they used measured myofiber orientations in the tissues at the regions of the markers to resolve the strains with respect to fiber, cross-fiber and radial axes. They found that fiber strain at end-diastole is strikingly uniform across the wall, whereas the radial and cross-fiber strain components displayed transmural gradients (Omens et al., 1991) with significantly higher magnitudes on the endocardium than epicardium. This uniformity of fiber strain at end-diastole has also been shown in other in-vivo studies including the rat (Omens et al., 1993) and dog (Takayama et al., 2002). End-diastolic fiber strain measured in these studies ranged from 0.05 to 0.15 at pressures of ~8 mmHg up to ~0.2 at 18 mmHg.

As early as 1982, mathematical models of the left ventricle were used to test how transmural fiber angle variations and ventricular torsion affect transmural strain (and stress) distributions (Arts et al., 1982). Simplified geometric models of the LV with spherical, cylindrical, and prolate spheroidal geometries, and anisotropy due to fiber orientation, have demonstrated uniformity in fiber strain across the wall at end-diastole with respect to an unloaded state (Choi et al., 2010), (Costa et al., 1996a), (Costa et al., 1996b), (Guccione et al., 1995). In agreement with the above experiments, end-diastolic strain values in these models were uniform and approximately 0.05-0.15 at 1.0 kPa filling pressure.

2.1.2 End-systolic fiber strain—While measurements of fiber strains at end-diastole are necessary to describe myocardial passive mechanics, distributions of fiber strain at end-systole are key to understanding systolic pumping mechanics. Fenton *et al.* (Fenton et al., 1978) were among the first to measure transmural systolic strain distributions using implanted radiopaque beads as material markers. They did not measure fiber orientations, but their results suggested mostly uniform end-systolic fiber deformation. Many experiments following this approach have carefully quantified transmural fiber strain, including those in which the fiber orientations across the wall *were* measured by histology in the same region of the systolic strain measurement in dog and sheep LV (Ashikaga et al., 2004), (Cheng et al., 2005), (Cheng et al., 2008), (Costa et al., 1999), (Takayama et al., 2002), (Waldman et al., 1988). In every case, fiber strains at end-systole with respect to end-diastole were found to be quite uniform transmurally, with values typically around -0.1 (i.e. about 10% fiber shortening) in each case in open-chest anesthetized animals.

Biplane radiography of implanted radiopaque markers is quite invasive, and therefore not typically feasible in humans, though it has been done in donor hearts received by heart transplant recipients (Yun et al., 1991). A more feasible, non-invasive approach to regional strain recording *in-vivo* was developed using cardiac MRI (Buchalter et al., 1990), (Clark et al., 1991). Experiments using these non-invasive approaches, including MRI tagging for material point tracking, have found that transmural fiber strain is uniform at end-systole with respect to end-diastole in several animal species and humans (MacGowan et al., 1997), (Rademakers et al., 1994). The values of these measured end-systolic fiber strains are typically in the range of -0.1 to -0.2, corresponding to a uniform fiber shortening of about 10-20%.

Several models were developed to aid in the description of fiber strains during active contraction of the myocardium (systole), most often at end-systole, with end-diastole or an unloaded configuration as the reference phase. Early models, using a cylindrical shape for the LV, showed that fiber strain was uniform at end-systole (Arts and Reneman, 1989). This result was confirmed by modeling multiple fiber angle distributions in an ellipsoidal model (Bovendeerd et al., 1992), in a more realistic geometry of dog LV (Guccione et al., 1995), and by iterative optimization of the fiber angle, which matched previously published measurements (Rijcken et al., 1997), (Rijcken et al., 1999).

A major result that surfaced from these models of myocardial mechanics is that anisotropy, fiber orientations, and the resultant torsion are key elements of myocardial structure in the development of homogeneous fiber strain distributions across the wall. The myocardium is stiffer in the fiber direction than in the cross-fiber direction, and the direction of torsion is the same at both the epicardium and endocardium. Since torsion is essentially a shear in the circumferential-longitudinal plane, in which the fibers lie, it acts to increase the stretch of epicardial fibers during filling. Conversely the same torsion on endocardial fibers reduces fiber stretch during diastole. During systole these mechanisms are reversed, increasing fiber shortening in the subepicardium and decreasing it in the subendocardium. These important features will be discussed in greater detail in section 3 below.

With these key mechanisms accounted for, the consistent result of these experiments and mathematical models has been that fiber strain at end-systole is transmurally uniform, at a value of approximately -0.10 to -0.20, corresponding to about 10-20% fiber-aligned segment shortening from end-diastole.

2.2 Fiber stress

The direct experimental measurement of stress within the myocardium is extremely challenging, especially while preserving native tissue structure and function, although some groups have attempted to implant stress sensors to achieve this, with limited success (Burns et al., 1971), (Feigl et al., 1967), (McHale and Greenfield, 1973). However, the development of computational tools such as finite element modeling, and the measurement and optimization of tissue material properties *ex vivo* (Dokos et al., 2002), (Novak et al., 1994), (Humphrey et al., 1990a), (Humphrey et al., 1990b), (Yin et al., 1987) provide probably the best approach to estimate regional and 3D stresses given a set of reliable strains (Huisman et al., 1980), (Yin, 1981). A large number of such models have been developed to better understand regional cardiac mechanics (Hunter et al., 2003).

2.2.1 End-diastolic fiber stress—Early models of end-diastolic stress distributions by Beyar and Sideman report circumferential stress rather than fiber stress, but do note that allowing torsion in their prolate spheroidal model reduced the heterogeneity of wall stress at end-diastole (Beyar and Sideman, 1984), (Beyar and Sideman, 1986). Understanding true fiber stress, however, requires measurement of fiber orientations across the wall. One of the first modeling studies that reported end-diastolic fiber stress in models of rat and dog LVs under passive inflation showed relatively uniform fiber stresses, especially in the rat (~1 kPa), but less so in dog (2-9 kPa) (Omens et al., 1993). Other models of end-diastole confirmed transmural uniformity of fiber stress in cylindrical models with papillary muscles and valves (Arts and Reneman, 1989), radially symmetric canine LV geometry (Guccione et al., 1995), and prolate spheroids of varying sphericity (Choi et al., 2010), though still others reported a less uniform distribution in spherical, cylindrical, and prolate geometries (Costa et al., 1996a), (Costa et al., 1996b). The reported fiber stresses were approximately 1.9-2.5 kPa at a filling pressure of 1.0 kPa. In general, the stress distributions follow strain distributions, but several factors and mechanisms can alter this relationship as described in more detail below.

2.2.2 End-systolic fiber stress—As early as 1970, models were developed to quantify stresses at end-systole based on the measured distribution of fiber angles in the LV (Streeter et al., 1970). In this model, it was assumed that fiber stresses during systole were uniform across the wall (~20 kPa), then compared circumferential and longitudinal stresses with those obtained from direct measurement, and found close agreement (Streeter et al., 1970). Subsequently, models wherein fiber stress and strain were calculated found strong uniformity in end-systolic (and end-diastolic) fiber stresses and strains across the wall, as long as appropriate physiological fiber orientations were included (Arts and Reneman, 1989), (Bovendeerd et al., 1992), (Bovendeerd et al., 1994). A model with a more realistic geometry (though still radially symmetric), found strong uniformity of end-systolic fiber stress in the equatorial region, but a more heterogeneous distribution near the base and apex

(Guccione et al., 1995). In this model and others, end-diastolic and end-systolic in-plane (i.e. circumferential and longitudinal) strains matched measured data, but out of plane strain components (i.e. radial) generally did not (Guccione et al., 1995). Modeling the myocardium as orthotropic, i.e. material properties corresponding to both fiber orientation and the laminar sheets of tightly coupled muscle fibers, with these sheets oriented roughly perpendicular to ventricular wall (LeGrice et al., 1995a), improved the estimation of these out of plane strain components, but they still did not match directly measured strains (Usyk et al., 2000). Even recent computational models still cannot accurately predict all deformation and strain tensor patterns, even if bimodal sheet populations, which have been observed in animal studies (Kung et al., 2011), and whose supposed function has been modeled (Arts et al., 2001), are included (see e.g. (Carapella et al., 2014)). This indicates a lack of understanding of the mechanical contribution of sheet structures to material strains. Despite difficulty in predicting radial strains due to the complexity of myocardial structure and contractile function, the majority consensus from these modeling studies has been that fiber stress at end-diastole and end-systole is transmurally uniform.

2.2.3 Mechanisms for uniform fiber stress and strain—Overall, a consistent result from experiments and models is that fiber strain and stress are quite uniform transmurally both at end-diastole and at end-systole in the normal left ventricle. It is worth appreciating that classical engineering analyses of uniform thick-walled pressure vessels predict high stresses and strains on the inner surface (Demiray, 1976), (Mirsky, 1973), with large transmural gradients. This is a natural consequence of deformation of an incompressible, homogeneous thick-walled chamber under an internal pressure load. The endocardial circumference must increase more than the epicardial circumference during filling, and decrease more than the epicardial circumference during ejection, resulting in large transmural gradients of stress and strain. Thus, in both phases of the cardiac cycle, the circumferential filling (diastolic) and ejection (systolic) strains are higher on the endocardium, and experimental measurements consistently show this behavior. How then, can fiber strain (and stress) be uniform, especially since similar arguments can be made for longitudinal strain distributions?

The mechanisms leading to transmural uniformity of fiber stress and strain likely depend on specific transmural non-homogeneities in the myocardium. As mentioned previously and prominent among these is the fiber direction, which, along with chamber torsion, tends to normalize mechanical gradients. This has led several groups to propose that transmural uniformity of myocardial fiber stress and strain, and hence of regional myocardial work, is an important homeostatic principle of myocardial mechanics. It has been postulated that this uniformity may help maximize the efficiency with which regional contractile work is converted to pumping function and minimize vulnerability to ischemia or injury in systole (Vendelin et al., 2002) and diastole (McCulloch et al., 1989), (Omens et al., 1991). All else being equal, this idea implies that there must exist one or more transmural gradient in tissue properties, architecture, or cellular characteristics that normalizes fiber stress and strain across the ventricle wall. In reality, several such transmural gradients have been observed that may explain this phenomenon. Here, we discuss measured transmural gradients from the literature, and how they may contribute to uniform fiber stress and strain. We also

discuss effects of changes in these distributions during cardiac disease, with a focus on compensated concentric hypertrophy due to pressure overload.

3. Transmural gradients as mechanisms of uniform fiber stress and strain

3.1 Fiber angle and torsion

As previously mentioned, one of the most intriguing aspects of normal left ventricular function that has been observed for centuries is torsion or twist during the cardiac cycle. In the 17th century, Lower (Lower, 1669) described this phenomenon during systole as the "wringing of a linen cloth to squeeze out the water", and it has since been well characterized (Sengupta et al., 2008). During isovolumic contraction, the ventricle rotates counterclockwise when viewed from the apex (Young and Cowan, 2012). During ejection, the base changes directions, rotating clockwise, while the apex continues its counterclockwise rotation. Studies have also shown that the heart untwists rapidly during early relaxation independent of any contractile activity (Ashikaga et al., 2004), (Bell et al., 2000), (Rademakers et al., 1992). Many studies have measured torsion using various techniques, with spatial modulation of magnetization tagged cardiac MRI being the gold standard, and speckle tracking echocardiography as a relatively new and potentially valuable clinical approach (Rüssel et al., 2009). Interestingly, a transmural gradient of torsion appears to exist, with endocardial rotations being greater at apex, mid, and basal levels than epicardial rotation (Buchalter et al., 1990), (Lorenz et al., 2000), (Young et al., 1994a), (Zerhouni et al., 1988).

The muscle fiber architecture in the mammalian left ventricle is the fundamental cause of torsion. Since the histological studies of Streeter and colleagues in the 1960s (Streeter et al., 1969) it has been appreciated that the orientation of myofibers in the left ventricle changes gradually from a left-handed helix with a pitch of 50-80 degrees on the epicardium, to a right-handed helix with a pitch of 60-90 degrees on the endocardium, with a smooth, nearly monotonic variation in between. Subsequent studies have verified this fiber architecture, and many have shown that it can be detected via Diffusion Tensor Magnetic Resonance Imaging (DT-MRI) (Holmes et al., 2000), (Hsu et al., 1998), (Scollan et al., 1998).

Of the reports mentioned previously, several models were employed to understand the influence of fiber angle distribution on LV mechanics. It was found that stresses and strains were highly sensitive to the fiber orientation distribution (Bovendeerd et al., 1992), (Guccione et al., 1991), (Huyghe et al., 1992), (Rijcken et al., 1997), (Rijcken et al., 1999). It has also recently been proposed that torsion may be important in stress sensing, which may help to protect the heart from injury due to excessive stresses (van Mil et al., 2016).

Because of the thick-walled shape of the left ventricle, the epicardial tissues have a larger radius from the LV center, and thus a greater lever arm during contraction-induced torsion. If all of the fibers across the wall were aligned with the same helical pitch, then this contractile force in the epicardium would obviously necessitate more shortening in the endocardium. However, because the helical pitches are opposite (approximately 120° separation) from epicardium to endocardium, shortening of the epicardium and its resultant torsion result in shortening in the cross-fiber direction in the endocardium. This allows the sarcomeres in the

endocardial fiber direction to contract relatively independently from (orthogonal to) those of the subepicardium.

It is apparent that the transmural fiber orientation gradient in normal hearts is important in dictating normal torsion and in normalizing fiber stress and strain across the wall. Perturbations to this fiber architecture could contribute substantially to altered cardiac function. Several studies have sought to determine if fiber orientations change during disease. An early study showed a decrease in fiber inclination angle only in the subendocardium in eccentric and concentric hypertrophy, though less so in concentric (Tezuka, 1975). However, a later study reported more longitudinal fibers in pressure overload (concentric) hypertrophy and no change in exercise or volume overload (eccentric) hypertrophy (Carew and Covell, 1979). Omens, *et al.* later found no difference in fiber angle in pressure overloaded rat hearts (Omens et al., 1995), (Omens et al., 1996). However, fiber orientations were measured in mice with left ventricular hypertrophy using DT-MRI, and slight but statistically significant differences in helix and inclination angles were found in the free wall and septum (Schmitt et al., 2009). Also, the fiber orientation and dispersion in the right ventricle changed with pulmonary artery constriction (Hill et al., 2014).

For the most part, it appears that pressure overload hypertrophy minimally affects fiber angle distributions in the LV, though some small changes may occur. Together with the high level of conservation of this pattern in mammalian hearts, this fact suggests that the native fiber orientation is highly important and needs to be preserved in order to maintain normal cardiac function.

3.2 Material Anisotropy

Material anisotropy in most biological tissues is a direct determinant of local mechanical function. Myocardium is no different as it has a distinct fiber architecture, as well as laminar sheets that create a mechanically and electrically orthotropic material wherein fiber, sheet, and sheet-normal directions and function can be defined at any location in the ventricle wall (Anderson et al., 2009), (Gilbert et al., 2011), (LeGrice et al., 1995a), (LeGrice et al., 1995b), (Usyk et al., 2000). Early biomechanical and electrophysiological modeling studies assumed transverse isotropy, however, several invaluable biomechanics studies have shown that ventricular tissue is in fact orthotropic (Dokos et al., 2002), (Novak et al., 1994), and these directional properties related to fiber and sheet architecture play a significant role in determining tissue stress and strain.

Biomechanical experiments by Humphrey and Yin showed that the anisotropy of myocardial tissue may vary as a function of wall depth (Yin et al., 1987), (Humphrey and Yin, 1989). Novak, et al. (Novak et al., 1994) later demonstrated that while myocardial tissue anisotropy is qualitatively uniform (i.e. the form of anisotropy does not change) in the canine left ventricle, it is quantitatively different between epicardium and mid-myocardium. Lin and Yin (Lin and Yin, 1998) also showed that the material properties of active myocardium are different than that of passive myocardium, and are of course anisotropic, with significant development of cross-fiber stresses during contracture. Most recently, Sommer, et al. have shown the orthotropic mechanical properties of human myocardium (Sommer et al., 2015b), (Sommer et al., 2015a).

Arts et al. (Arts and Reneman, 1977) showed the importance of anisotropy in their early models of LV mechanics, but the significance of the orthotropic nature (i.e. the sheet structure) of the myocardium has surfaced more recently (Arts et al., 2001), (Ashikaga et al., 2005), (Ashikaga et al., 2008), (Chen et al., 2005), (Cheng et al., 2005), (Cheng et al., 2008), (Coppola and Omens, 2008), (Costa et al., 1999), (Covell, 2008), (Nikou et al., 2015), (Pope et al., 2008). Since it is commonly argued that sheet structures contribute to wall thickening by allowing large shear deformations to occur (Costa et al., 1999), (Cheng et al., 2005), the orientation, dispersion, and mechanical properties of these sheets are undoubtedly important factors contributing to fiber stress and strain. The conduction of the electrical signal along the sheets is faster than across them, so timing of contraction is also affected by sheet structures (Hooks et al., 2007), which in turn also affects regional stresses and strains (Krishnamurthy et al., 2013).

Pressure overload induces hypertrophic remodeling of the extracellular matrix (ECM) by fibrosis (increase in collagen content) and collagen remodeling by fibroblasts (Bishop and Laurent, 1995), (Bursac, 2014), (Moore-Morris et al., 2014), (Pick et al., 1989). Since the ECM is a major load-bearing component of cardiac tissue, fibrosis directly affects passive tissue properties (Conrad et al., 1995), (Fomovsky et al., 2010), (Hess et al., 1981), (Thiedemann et al., 1983). Additionally, disorder of sheet structures has been measured in hypertensive heart disease (LeGrice et al., 2012). The implications of this reorganization of sheet structures combined with fibrosis, mechanical stiffening, and other forms of remodeling on tissue mechanics require further study. Nonetheless, collagen content and remodeling and fiber and sheet reorganization undoubtedly alter tissue anisotropy and the distribution of fiber stresses and strains.

3.3 Residual stress

Another potential mechanism contributing to uniform fiber stress and strain is that ventricular tissue is residually stressed (i.e. the unloaded, resting ventricle has internal stresses) and that the observed residual stress is non-uniform transmurally. Omens and Fung (Omens and Fung, 1990) first examined residual stress and strain in the rat LV following similar approaches used in other tissues, such as blood vessels (Chuong and Fung, 1986). Residual stress in cylindrical or spherical vessels is known to reduce stress concentrations at the inner surfaces, and this same mechanism is thought to occur in biological tissues. In the heart, it was found that making a radial cut in an equatorial cylindrical slice of rat left ventricle relieves circumferential residual stress, and results in an “opening angle” of approximately 45° (Omens and Fung, 1990). This suggests that resting, unloaded ventricular tissue supports internal, residual stresses. It was shown that this residual stress is regionally variable as expected for the geometry of the ventricle, with endocardial residual stress being compressive, whereas epicardial residual stress is tensile. This work was later extended to show a linear transmural gradient in sarcomere length that becomes uniform when residual stress is released by a radial cut in the rat LV (Rodriguez et al., 1993). Similar results were observed in chick embryo (Taber et al., 1993) and dog (Costa et al., 1997). Subsequent studies showed that 3D residual stress was even more complex with functional implications for distributions of normal and shear stresses during inflation (Omens et al., 2003).

Since normal, resting ventricular myocardium is residually stressed in this manner (with compressive stress in the subendocardium and tensile stress in the subepicardium), it is reasonable to postulate that fiber stress and strain are normalized by residual stress. Indeed, a cylindrical model showed that residual stress, together with anisotropy and torsion, normalize fiber stresses transmurally during filling (Guccione et al., 1991). Rodriguez et al. (Rodriguez et al., 1993) commented that Starling's law likely works in combination with shortening deactivation and force-velocity relationship effects to normalize fiber stresses during systole, and that end-diastolic sarcomere length is likely the primary factor that determines developed tension.

Residual stress has been shown to change in biological tissues due to external pressure overloads (Fung and Liu, 1989). It was postulated that residual stress would increase under pressure overload hypertrophy (Rodriguez et al., 1994). Residual strain of the pressure overloaded left ventricle has been measured in rat (Omens et al., 1996) and chick embryo (Taber and Chabert, 2002). No significant difference in the opening angle was observed in rat, despite the reasonable hypothesis that it would increase with cell cross-sectional area (Omens et al., 1996). Similarly, chick embryo opening angles did not change or even decreased (Taber and Chabert, 2002). Although residual stress has not clearly been shown to change with hypertrophic remodeling in the heart, residual stress does change in other cases such as extra-cellular matrix disease (Weis et al., 2000) and with normal cardiac growth (Omens et al., 1998). With increased wall thickness without chamber dilation in pressure overload, residual stress is likely maintained in the tissue, indicating that the distribution of residual stress may be important for regulating fiber mechanics in both diastole and systole.

3.4 Protein densities

In addition to tissue-scale properties that can modulate stress and strain gradients in the ventricles, molecular-scale distributions and gradients of structural and functional proteins in myocytes and ECM may contribute to uniformity of fiber stress and strain by modulating individual myocyte electromechanical functions, and the interplay between cells and the supporting ECM. Many of the reports summarized in the following sections describe heterogeneous protein distributions in the ventricles, with implications for active and passive function, as well and long-term remodeling in response to altered external loading conditions. We review here several such proteins with transmural gradients that could affect fiber stress and strain distributions, mechanisms by which they might do so, and how disease-induced remodeling of those distributions may alter fiber stress and strain.

3.4.1 Passive structural proteins

3.4.1.1 Collagen: Collagen is a key structural component of the ECM and is therefore important in determining the passive mechanical properties of myocardial tissue (MacKenna et al., 1994), (Fomovsky et al., 2010). Collagen type I is predominant in the ventricles, and although its volume fraction is unchanged as a function of wall depth in rat LV, the form that collagen takes varies from subendocardium to subepicardium, in that the sheet structures mentioned above are clearly defined in the subendocardium and midwall, whereas toward the epicardium, collagen takes the form of longitudinal (parallel to the myocytes) cords (Pope et al., 2008). This implies that the form and organization of collagen, rather than its

content, may play a dominant role in terms of its transmural functional effects (MacKenna et al., 1997).

Fibrosis is a well-documented remodeling response during pressure overload (Bing et al., 1971), (Bishop and Laurent, 1995), (Caspari et al., 1977), (Conrad et al., 1995), (Weber et al., 1989), and will certainly affect stress and strain distributions in this type of remodeling. Although the exact micromechanical-based contributions of ECM components and structure to the anisotropic passive material properties of myocardium in normal and fibrotic tissue are still mostly undefined, the form, distribution, and advanced glycation end-product mediated cross-linking of different types of collagen each can modulate cardiac stiffness (Fomovsky et al., 2010), (Herrmann et al., 2003), (Hess et al., 1981), (Mukherjee and Sen, 1990), (Thiedemann et al., 1983). Thus it is reasonable to expect collagen/ECM remodeling to modulate diastolic mechanics, possibly with regional variations due to the 3D laminar sheet architecture in the ventricular walls.

3.4.1.2 Titin isoform: Titin also represents a major component of passive mechanical properties in the cardiomyocytes. Two major isoforms, N2B and N2BA, are found in cardiac muscle. The shorter isoform, N2B, is stiffer than the larger N2BA isoform, and is predominant in human hearts (Williams et al., 2009). Species-specific differences in the N2BA:N2B ratio exist, and it is thought that changes in this ratio modulate myocyte stiffness, where a higher ratio of N2BA:N2B corresponds with more compliant tissue, and vice versa (Neagoe et al., 2003). Additionally, a transmural gradient of the N2BA:N2B ratio was observed in pig and canine hearts where a higher N2BA:N2B ratio exists in the subendocardium than in the subepicardium (Bell et al., 2000), (Cazorla et al., 2000). Cazorla, et al. (Cazorla et al., 2000) speculated that inter-species variations in cell-to-cell stiffness is related to strain normalization of myocytes in different regions of the ventricular walls. This is consistent with the fact that the endocardial layer deforms more during a normal heart beat than the epicardium. The transmural gradient in the titin isoform ratio could suggest that stiffness along the fiber axis may also vary transmurally, leading to altered regional diastolic anisotropic material properties.

It has been shown that the N2BA:N2B ratio is decreased in spontaneously hypertensive rats (Warren et al., 2003), and in human patients with aortic stenosis (Williams et al., 2009), both of which are forms of pressure overload. In hearts that underwent two weeks of pacing tachycardia, the transmural gradient in titin ratios was exaggerated, and was postulated to contribute to a reduction in restoring forces after systolic contraction (Bell et al., 2000). The changes to this isoform ratio in pressure overload need to be further examined, as well as the functional implications postulated by the resultant changes in muscle stiffness. It is possible that this ratio is modulated to offset fibrotic stiffening during disease in order to maintain ventricular compliance and/or contractility.

3.4.2 Active sarcomere dynamics proteins

3.4.2.1 Myosin regulatory light chain phosphorylation: Myosin light chain (MLC) phosphorylation via myosin light chain kinase (MLCK) has been shown to increase the sensitivity of MLC to Ca^{2+}, and is therefore a key determinant of tensile force produced in

myofibers (Morano et al., 1985), (Olsson et al., 2004). Davis et al. (Davis et al., 2001) observed a transmural gradient of phosphorylated regulatory light chain in normal mouse left ventricle, with increasing levels of phosphorylation from endocardium to epicardium. They postulated that this gradient was required to facilitate normal LV torsion. Additionally, double mutant mice, in which MLC cannot be phosphorylated, had decreased performance and an eccentric hypertrophy phenotype with decreased LV torsion (Sheikh et al., 2012). This study confirmed that MLC phosphorylation facilitates LV torsion, a key component of normalizing fiber stress and strain.

The latter study also proposed that phosphorylation of MLC is indispensable in regulating actin-myosin crossbridge dynamics and plays an important role in heart failure (Sheikh et al., 2012). Toepfer, et al. (Toepfer et al., 2013) also demonstrated that increased phosphorylation in rat trabeculae enhanced myocardial performance and suggested that decreased MLC-phosphorylation in cardiac disease is a key contributor to impaired cardiac contractile function. MLC phosphorylation levels were significantly reduced in pressure overloaded and failing hearts (Kotlo et al., 2012), but heart failure was prevented in MLC kinase-overexpressing mice (Warren et al., 2012). Additionally, constitutively phosphorylated cardiac MLC in mice was sufficient to prevent a hypertrophic cardiomyopathy phenotype (Karabina et al., 2015), (Yuan et al., 2015). Conversely, knockout of MLC induced heart failure (Massengill et al., 2016). These studies highlight the importance of MLC phosphorylation, including its transmural gradient, in the development of normal LV torsion and contraction, and a possible role in heart disease.

3.4.2.2 Myosin heavy chain isoforms: Myosin heavy chain (MHC) forms the head/neck region of the myosin crossbridge. Two major isoforms exist with different functionality. The α isoform (MHC-α) is faster and stronger but less energy-efficient than the β isoform (MHC-β). MHC-β is predominant in human hearts, whereas MHC-α is more highly expressed in rodents. Stones et al. (Stones et al., 2007) measured a transmural gradient in MHC-β mRNA in rat LV, with more found in subendocardium than subepicardium. No gradient in MHC-α was found in rat ventricular myocytes (Campbell et al., 2013), but it has been shown in porcine hearts that greater expression in MHC-α isoform expression in the subepicardium contributes to differing mechanical function and timing, both of which may modify fiber stresses and strains (Stelzer et al., 2008). Specifically, epicardial fibers were activated and developed force at higher rates than endocardial fibers (Stelzer et al., 2008). It is likely that the faster and supposedly stronger contraction of the MHC-α isoform will result in increased compressive stresses and strains in the fiber direction than that of the MHC-α isoform. This difference in the timing and rate of force production between epicardial and endocardial myocytes therefore is likely a major contributor to the distribution of fiber stresses and strains.

In small rodents, shifts in isoform expression toward MHC-α are associated with cardiac disease, including hypertrophy and failure (Herron and McDonald, 2002), (Krenz and Robbins, 2004), (Nakao et al., 1997). This may suggest that cardiomyocytes attempt to improve their efficiency during increased workload demand, but some have reported that this shift may be maladaptive (Krenz and Robbins, 2004). Regardless, even small changes in MHC isoform levels during hypertrophic or other remodeling will likely contribute to altered

LV functional mechanics by regulating the timing and force of contraction (Herron and McDonald, 2002).

3.4.3 Electrophysiological proteins

3.4.3.1 I_{to} proteins: KChIP/Kv4.2/Kv4.3: A well-known feature of myocardium is the difference in action potential duration (APD) across the wall, which, together with the activation sequence results in a positive QRS complex and a positive T-wave of the ECG (Antzelevitch et al., 1991). This transmural gradient in APD is in part due to the transient outward potassium current (I_{to}). This current is comprised of contributions from Kv4.2, Kv4.3, and KChIP proteins. Interestingly, Kv4.2 but not Kv4.3 showed a transmural gradient in rat LV (Dixon et al., 1996). Similarly, there was only a slight gradient in Kv4.3 found in mouse, compared to more marked gradients in Kv4.2 and KChIP (Teutsch et al., 2007). Canine and human LV showed no gradient in Kv4.3 but a significant gradient in KChIP (Rosati et al., 2001), (Rosati et al., 2003). The KChIP and Kv4.2 expression patterns almost universally had higher levels in epicardium than endocardium. These gradients explain the observed phenomenon of differing APD across the wall (Clark et al., 1993).

The Kv4.2 protein is a subunit of voltage-gated potassium channel in cardiac myocytes, partially responsible for generating the I_{to} during the early plateau phase of the action potential, wherein Ca2+ ions are released and bind troponin C to initiate contraction. In rat, human, dog, and other mammals, Kv4.2 is denser in subepicardium than subendocardium. It is well known that endocardial cells are typically activated earlier than epicardial cells, and that the duration of the action potential in endocardial cells is longer than that of epicardial cells, so that they are repolarized after their epicardial counterparts. One of the potential reasons for this is the greater concentration of Kv4.2 in epicardial cells, which are responsible for phase 1 early repolarization of the action potential in these cells. The early repolarization phase of the action potential is nearly nonexistent in subendocardial myocytes. This suggests that the endocardial myocytes are activated for a longer period of time than epicardial myocytes in the same heartbeat. Thus, the potential exists for more cross-bridges to be activated and to a greater extent. This would imply that higher strains (and stresses) may exist in the subendocardium due to this electrophysiology-based mechanism.

Wang et al. (Wang et al., 2007) confirmed the native gradient in Kv4.2 in mice, and found that pressure overload reduced subepicardial Kv4.2 levels and current, eliminating the transmural gradient found in normal mice. Thus action potential-mediated myocyte function could play a role in hypertrophic remodeling.

3.4.3.2 Kcnk2 (TREK-1): The potassium channel subfamily K, member 2 (Kcnk2), or 2-pore domain potassium channel TWIK-related K^+ (TREK-1) has been extensively studied, and is thought to modulate the APD regionally and during sympathetic activation (Bodnár et al., 2015). The TREK-1 gene, mRNA, and protein expression levels were greater in endocardial cells than epicardial cells (Kelly et al., 2006), (Stones et al., 2007), (Tan et al., 2004), (Wang et al., 2013). Interestingly, the gradient of this potassium channel is in the opposite direction to that of the Kv4.2 and KChIP channels, all of which contribute to

repolarization, though with differing kinetics they are responsible for acting during different portions of the action potential (Grant, 2009), (Nerbonne and Kass, 2005).

In hypertrophy, the levels of TREK-1 increased everywhere, such that the normal transmural gradient was maintained (Wang et al., 2013). Similar to the discussion for the I_{to} proteins above, this protein's expression level is important in determining the sequence of activation and deactivation, and can thus impact regional stress and strain by impacting regional APD.

3.4.3.3 Connexins (Cx43): Another important determinant of electrical conduction through cardiac muscle tissue is its anisotropy, which is dictated in part by the presence of gap junction channels, which primarily localize to the ends of the long, rod-shaped myocytes, reducing resistance to electrical conduction along the fiber direction. Connexin plaques are also found coupling adjacent cells, contributing to lateral propagation of activation (Lackey et al., 2011). The presence of the sheet structures makes this conduction orthotropic (Hooks et al., 2007). In ventricular myocytes, gap junctions are primarily formed by connexin-43 (Cx43). Yamada et al. (Yamada et al., 2004) found transmural gradients of Cx43 in the mouse LV, with a greater abundance in the subendocardium and mid-myocardium than subepicardium. This pattern, however, was not observed in rat LV. A similar pattern to that in the mouse was seen in dog (Poelzing et al., 2004) and rabbit (McLachlan et al., 2003). It is not straightforward to draw a connection between increased Cx43 expression and fiber strain, especially considering that expression may not necessarily influence conduction velocity per se. The use of finite element modeling of electromechanics in the ventricles with regionally variable fiber conduction would therefore be a useful study to help define the role of this transmural gradient for regional mechanical function.

Poelzing and Rosenbaum (Poelzing and Rosenbaum, 2004) also showed that Cx43 expression is significantly reduced uniformly in dogs with heart failure, such that the gradient observed in normal dogs was preserved. In humans with aortic stenosis, connexin-43 amounts increased during compensated hypertrophy, then decreased during decompensated hypertrophy (Kostin et al., 2004). An important feature of Cx43 remodeling during disease, including pressure overload and MI, is that of lateralization, which undoubtedly affects conduction anisotropy and velocity (Emdad et al., 2001), (Kostin et al., 2004), (Qu et al., 2009), (Schwab et al., 2013). The effects of such remodeling on electromechanics require further study.

3.4.4 Calcium handling proteins

3.4.4.1 SERCA2a: The sarco-/endoplasmic reticulum calcium ATPase pump (SERCA2a) is a primary factor in removing Ca^{2+} ions from the cytosol following activation. Laurita et al. (Laurita et al., 2003), (Laurita and Katra, 2005) determined that more SERCA2a is expressed in the subepicardium than in the subendocardium in canine hearts, then showed using optical mapping how such differences may lead to altered activation patterns. Others confirmed this pattern in dog as well as both non-failing and failing human hearts (Anderson et al., 2011), (Lou et al., 2011), (Prestle et al., 1999). However, this pattern was not observed in rat (Feldman et al., 1993).

Cordeiro et al. (Cordeiro et al., 2004) also showed a difference in calcium transients in epi-, mid-, and endocardial cells from canine hearts. Their results suggested that differences in calcium homeostasis regulate synchronization of ventricular contraction across the wall, despite different electrical activation times. Computational models of these differences in Ca^{2+} dynamics within a finite element model of LV mechanics showed that this was not a factor in regulating end-systolic fiber strain, but that the effect of these gradients on fiber and cross-fiber strains in the LV is most apparent at early systole, rather than end-systole (Campbell et al., 2009). Even so, SERCA2a activity has been shown to affect contractility and relaxation in disease (Erkens et al., 2015), (Frank et al., 2003), and changes in regional distributions may play a role in mechanical function of the myocardium.

In severe pressure overload, SERCA2a expression was decreased in the whole rat heart (de la Bastie et al., 1990), (Wong et al., 1997). This reduction in SERCA2a level was found to be nonhomogeneous throughout the LV (Anger et al., 1998), however the transmural pattern of SERCA2a decrease has not to our knowledge been reported.

4. Summary and Conclusion

Transmural uniformity of fiber stress and strain at end-diastole and end-systole appears to be a common finding from both experiments and mathematical models. Researchers have sought to understand the fundamental reasons for this homogeneity in function, postulating that uniform fiber stress and/or strain is likely important in improving ventricular pump efficiency. Several structural and functional factors in the normal myocardium that vary transmurally may be mechanisms contributing to the normalization of fiber stress and strain. In diseases such as pressure overload hypertrophy, several structural factors in myocytes and ECM may change, mediating the role of stress and strain in cardiac remodeling. The “holy grail” of work in this field would be to fully describe the contributions each transmural gradient to ventricular mechanics, and the mechanisms by which they do so. Computational modeling, in conjunction with continued experimental measurements, constitute a challenging but tractable method to accomplish those goals.

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Competing interests

ADM and JHO are co-founders, equity holders and scientific advisors to Insilicomed Inc., a licensee of UCSD software used in this research. This relationship has been disclosed to the University of California San Diego and is overseen by an independent conflict of interest management subcommittee appointed by the university.

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