Progress in Biophysics and Molecular Biology 122 (2016) 215–226

Contents lists available at ScienceDirect

Progress in Biophysics and Molecular Biology

journal homepage: www.elsevier.com/locate/pbiomolbio

# Transmural gradients of myocardial structure and mechanics: Implications for fiber stress and strain in pressure overload

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ARTICLE INFO

*Article history:*
Available online 11 November 2016

*Keywords:*
Cardiac mechanics
Fiber stress
Fiber strain
Myocyte fiber angle
Transmural gradients
Pressure overload hypertrophy

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.



**Contents**



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http://dx.doi.org/10.1016/j.pbiomolbio.2016.11.004
0079-6107/

## 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 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).

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

## 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