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Integrative Models for Understanding the Structural Basis of Regional Mechanical Dysfunction in Ischemic Myocardium

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Abstract—Myocardial ischemia and many other cardiac pathologies are associated with regional ventricular dysfunction. Since the distributions of stress and material properties cannot be measured directly in intact myocardium, understanding how regional alterations in myocardial strain or segment function are related to underlying cellular dysfunction must be deduced from theoretical models. Here, we describe how anatomically detailed, three-dimensional computational models can be used in conjunction with experimental or clinical studies to elucidate the structural basis of regional dysfunction in acutely ischemic and ischemic-reperfused (''stunned'') myocardium *in vivo*. Integrative experimental and computational analysis shows that: (1) in acutely ischemic myocardium, the transition from abnormal systolic strain in the ischemic region to normal shortening in adjacent, normally perfused tissue is governed primarily by systolic blood pressure and regional fiber orientation rather than the geometry of the perfusion boundary; and (2) in stunned myocardium, the degree of reperfusion injury to the contractile apparatus may be uniform across the wall thickness despite observations that the extent of ischemia and the impairment of regional strain during reperfusion are both significantly greater in the subendocardium. © *2000 Biomedical Engineering Society.* [S0090-6964(00)01208-X]

Keywords—Stunned myocardium, Finite-element model, Diastolic properties, Functional border zone, Transmural function, Regional blood flow.

INTRODUCTION

Myocardial ischemia causes regional alterations in stress, strain, and material properties. A detailed understanding of ventricular mechanics in regional ischemia and reperfusion injury (stunning) is important because: (1) left ventricular wall stress is a primary determinant of myocardial oxygen demand and hence the risk and extent of ischemic injury;[28,46] (2) coronary vascular resistance and blood flow are affected by wall stress, and myocardial mechanics are affected by coronary pressure and volume;[13,80] (3) knowledge of ventricular stress and strain distributions is needed to understand the interactions between normal and injured tissue;[3,19,61] and (4) injury and structural failure, recovery and healing, remodeling, and hypertrophy of ischemic myocardium are all thought to depend on wall stress and strain.[16,29,59,79]

Since there are no reliable methods for measuring the components of the three-dimensional stress tensor experimentally,[39] researchers have used continuum models to predict stress based on the conservation laws of physics, the structural and geometric properties of the ventricular walls, and measured hemodynamic loading conditions.[12,30,86] To validate and optimize these models, regional strain distributions must be measured. By modifying material parameters to optimize the agreement between model and experiment, new insight into the three-dimensional structural properties of the intact myocardium during acute ischemia and stunning can be obtained. Thus, understanding regional structure–function relations in intact myocardium requires an integrative approach to combine *in vivo* and *in vitro* experimental measurements with mathematical models of ventricular function, to investigate underlying mechanisms of dysfunction, and test hypotheses in a detailed quantitative and mechanistic approach (*integration of in vivo and in silico data*).

ACUTE MYOCARDIAL ISCHEMIA

Acute myocardial ischemia occurs when the reduction of coronary flow is so severe that the supply of oxygen to the myocardium is inadequate for the oxygen demand of the tissue. Under basal conditions, myocardial oxygen extraction is nearly maximal so that an increase in myocardial oxygen demand must be met by an increase in coronary blood flow rather than by an increase in oxygen extraction. The presence of a significant coronary occlusion, for example, a stenosis due to an atherosclerotic plaque, reduces coronary reserve and limits capacity of the coronary blood supply to meet an increase in myocardial oxygen demand.[46]

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Ischemia and hypoxia lead to activation of a defense mechanism in the myocytes to achieve a new balance between oxygen demand and supply, by a combination of downregulation of contraction and upregulation of anaerobic energy production by glycolysis. This mechanism leads to an increase both in inorganic phosphate (P_i) and adenosine diphosphate (ADP). On the other hand, there is an accumulation in protons (H^+) and neutral lactate as byproducts of glycolysis. Both of these lead to displacement of calcium ions (Ca^{2+}) from myofilament binding sites and inhibition of actin–myosin interaction, ultimately resulting in loss of myofiber contractile ability.[1,58]

Myocardial ischemia and infarction activate both vagal and sympathetic sensory nerve endings in the ischemic myocardium, resulting in reflexes. The vagal afferents are either mechanosensitive or chemosensitive, whereas sympathetic afferents may be mechanosensitive, chemosensitive, or both.[70] However, autonomic responses depend on which region of the myocardium is ischemic. Vagal afferents are mainly distributed in the posterior wall of the heart, compared with sympathetic afferents that are more predominant in the anterior regions.[2,49,70] This difference may explain the syndrome of bradycardia and hypotension in the posterior wall infarct.[70] Conversely, the presence of anginal chest discomfort and an increase in blood pressure and tachycardia during the periods of anterior wall ischemia may be associated with the presence of sympathetic afferents in this region.[51]

REGIONAL FLOW–FUNCTION RELATIONS

Tennant and Wiggers[69] showed that systolic segment shortening ceases within the first 50 heartbeats following complete coronary occlusion. After 30 s of ischemia, the ischemic region performs little or no work[72] and systolic shortening is replaced by systolic lengthening or bulging. After 3–5 min of ischemia, the ischemic region demonstrates marked lengthening during isovolumic systole and akinesis during the ejection phase.[45,69]

There is a sensitive coupling between regional myocardial blood flow and systolic segment shortening during myocardial ischemia. Vatner[76] showed that during acute ischemia in conscious canines, there is a strong coupling between subendocardial loss of blood flow and loss of segment shortening. Gallagher and co-workers[21] found a nearly linear relation between reduction in regional left ventricular subendocardial blood flow and regional systolic wall thickening in resting conscious dogs. These studies on regional flow–function relations during ischemia at rest indicate that a close coupling exists between the supply of myocardial substrates, e.g., oxygen, of which the regional coronary blood flow provides a rough measure, and myocardial energy demand, as reflected in the steady-state level of regional contractile function. Thus, under these acute conditions, contraction decreases and remains at a reduced steady-state level ‘‘matched to’’ the available blood supply.[10,64]

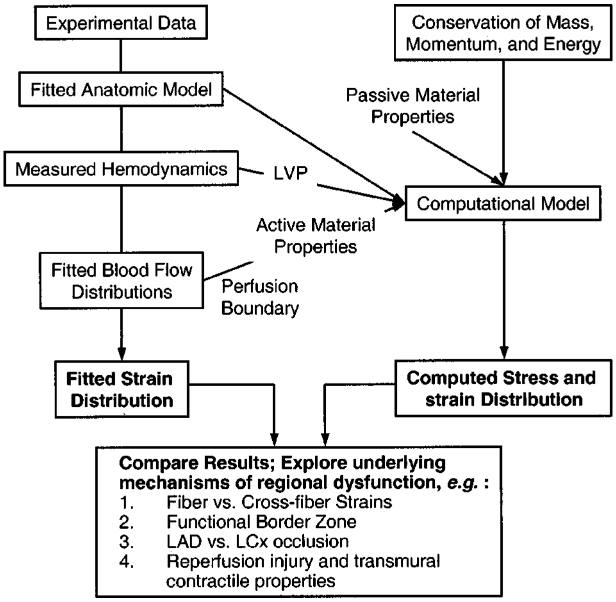

FIGURE 1. Flow chart summarizing the methods used to integrate experimental data and computational models of the contractile myocardium. Equations governing the finite element model of the left ventricle were based on conservation of the mass, momentum, and energy. In these studies, the measured anatomy of the left ventricle provided the geometry and regional fiber angles for the model; the measured left ventricular pressure (LVP) provided the traction boundary conditions; and the measured regional blood flow was used to estimate the perfusion boundary and was included in the model as another field value. Active material properties were altered in the ischemic region defined by the blood flow (see Fig. 3). The model provided regional stresses, which are impossible to measure experimentally in the intact tissue, and strains. Regional strains calculated from the model were compared to experimental strain distributions and once agreement was obtained, perturbations were made in the model to answer questions that experiments alone could not answer (see the text for examples).

However, the flow–function relation is not necessarily one to one: *nontransmural ischemia* due to partial coronary artery occlusion; the presence of regional dysfunction across the lateral margin of the ischemic zone (‘‘*functional border zone*’’); and systolic dysfunction in ischemic/reperfused *stunned* myocardium are all instances in which the relation between regional blood flow and regional function is not unique. This review focuses primarily on the presence of regional systolic dysfunction in the lateral margin of the ischemic boundary (i.e., *functional border zone*) and the stunned myocardium, and its relation to regional blood flow. We describe how *in vivo* and *ex vivo* experimental measurements can be integrated with computational models of contractile myocardium to elucidate underlying structural mechanisms of regional dysfunction. Figure 1 illustrates how experimental measurements were integrated with a mathematical model of the contractile left ventricle (LV) to elucidate the underlying mechanisms of regional dysfunction in acutely ischemic and reperfused myocardium. This method was utilized to test hypotheses and answer questions that could not be answered experimentally alone.

NONTRANSMURAL MYOCARDIAL ISCHEMIA

Within a few seconds of coronary artery occlusion, end-systolic myocardial dysfunction can be seen.[69] This dysfunction is augmented during the first 5 min of occlusion, and by 5 min, complete dyskinensis is a common.[77] However, patterns of dysfunction are altered during graded stenosis of the coronary artery. Gallagher and co-workers[18] showed that the inner half of the ventricular wall is responsible for the majority of the end-systolic wall thickening. Even during partial coronary occlusion with only endocardial layers at risk, transmural function is impaired.

The flow–function relation is important clinically for distinguishing between conditions such as stunning where function is depressed with normal flow versus hibernation where flow and function are both impaired. However, measuring the flow–function relation is complicated by the methods with which function is measured. Coupling between segment shortening and blood flow[71,76] is influenced by the direction of the segment measured in relation to local myofiber direction. There is no direct correlation between regional flow and wall thickening.[14,20] Often in these studies, epicardial function is correlated well with endocardial blood flow and not with epicardial blood flow. Weintraub and co-workers[78] explained this phenomenon first by introducing the concept of transmural ''tethering'' within the myocardial layers. Later, other researchers showed similar results to Weintraub and postulated that tethering is the main mechanism involved.[14,20]

More recently, McCulloch and co-workers[55] in anesthetized open-chest dogs, using transmural bead sets, found that there is a close relation between local myocardial blood flow and fiber function, independent of transmural location, during graded left anterior descending (LAD) occlusion. However, such a close relation does not exist for cross-fiber segment, due to the effect of transmural tethering. Radial strain is similarly coupled between adjacent layers of myocardium, hence the local function. Conversely, fiber stress and strain are more tightly coupled to blood flow than cross-fiber and radial strain.[55]

FUNCTIONAL BORDER ZONE

The transition in function across the lateral margin of the ischemic zone and its relationship to blood flow has been studied in detail. During coronary artery occlusion, there is a sharp transition in blood flow across the perfusion boundary.[85] Studies have shown that this transition region is less than 3 mm wide.[36,56] Studies related to regional myocardial metabolism during acute ischemia have also shown that the transition in the metabolic substances follows the regional changes in blood flow. Hearse and co-workers[35]reported a significant correlation between flow and ST segment change, ATP, creatine phosphate (CP), and lactate after 20 min of LAD occlusion in dogs. Wall motion abnormalities, however, do not directly follow the regional blood flow distribution. The presence of abnormal wall motion (the *functional border zone*) in the well-perfused region adjacent to the ischemic zone was first reported by Kerber *et al.*[41] The functional border zone is a manifestation of mechanics in the lateral bordering region between ischemic and nonischemic zones, and has been used as a convenient way of quantifying the level of interaction between the two neighboring regions.

The findings of Kerber and colleagues[41] have been confirmed in many subsequent studies in anesthetized and conscious animals, though estimates of the width of the functional border zone have varied by an order of magnitude averaging about 1 cm (see Table 1).[18,19,22,32,47,60,66,75] For example, Van Leuven and co-workers[75] measured regional variations in the width of the functional border zone in anesthetized pigs, after 90 min of left circumflex occlusion. They found that the width of the functional border zone decreased from 13 mm at the base to approximately 1 mm at the apical region. Prinzen *et al.*[60] measured two-dimensional area strain during ejection (using epicardial markers), in anesthetized dogs during left anterior descending coronary artery occlusion. They found a 15-mm-wide functional border zone in the fiber direction, and a 20-mm-wide border zone using surface area.

Using two-dimensional (2D) echocardiography for measuring wall thickening, Lima *et al.*[47] observed a functional border zone greater than 25 mm wide in anesthetized dogs, after 40 min of left circumflex occlusion. Guth and co-workers[32] reported a 10–20-mm-wide border zone by measuring wall thickening using ultrasonic dimension gauges, in conscious pigs during left circumflex occlusion. Gallagher and co-workers[22] compared the width of the functional border zone between the anterior and posterior occlusion sites, by measuring wall thickening across the perfusion boundary. They found that occlusion of the left anterior descending coronary artery produced a border zone with the mean of 29 mm compared with 8 mm produced by left circumflex occlusion.

TABLE 1. **Summary of selected previously published data characterizing the functional border zone. Anesth., Anesthetized; Cons., conscious; occl., occlusion; LAD, left anterior descending coronary artery; LCx, left circumflex coronary artery.**

Preparation	Function	Border zone	Reference No.
Cons. Pig; Acute LCx occl.	Systolic wall thickening	10–20 mm	32
Anesth. Pig; LCx occl. (15 min–2 h)	Subepi. fiber shortening	9.2–12.2 mm	66
Anesth. Dog; LCx occl. (15–40 min)	Systolic wall thickening (echo)	>25 mm	47
Anesth. Dog; LCx occl. (5–7 min)	Systolic wall thickening	8±4 mm (30°)	19
Cons. Dog; LCx occl. (10 min–3 h)	Systolic wall thickening	32°±17° and 27°±10°	18
Anesth. Pig; LCx occl. (90 min)	Epicardial 2D strain	13 mm (base) 8–9 mm (mid) 0–1 mm (apex)	75
Anesth. Dog; LAD occl. (5–10 min)	Epicardial area strain	20.5 mm	60
Anesth. Dog;	Systolic wall thickening		22
Acute LAD occl.		29±8 mm	
Acute LCx occl.		8±3 mm	

Therefore, there are substantial variations in the width of the border zone characterized, possibly associated with differences in segment orientation, occluded vessel, region, and method used to measure segment function.

Most researchers have attributed the functional border zone to mechanical interactions or ‘‘tethering’’ between normal and ischemic muscle rather than to a transitional region of impaired contractility.[18,22,32,60,66,75] Some have suggested that this interaction depends on the orientation of the perfusion boundary with respect to the local myofiber axes. For example, in 1976, Wyatt *et al.*[84] proposed the ‘‘parallel fiber hypothesis’’ to explain the degree of interaction between two neighboring myofibers across the perfusion boundary. The intact ventricular tissue is a complex, interwoven network of muscle fibers and ‘‘a muscle fiber acts only as its neighbor allows it to act.’’[67] According to the parallel fiber hypothesis, an ischemic myofiber ‘‘in parallel’’ with a nonischemic myofiber acts like a parallel resistance, particularly if contraction is dysynchronous, transmitting to its adjacent nonischemic myofiber its noncontractile characteristics. In contrast, an ischemic myofiber ‘‘in series’’ with a nonischemic myofiber will allow the nonischemic myofiber to contract with greater shortening.[73,82] The latter case in turn would result in hyperfunction in the nonischemic region.[38]

In an attempt to define and characterize these mechanical interactions more precisely, some investigators have suggested that wall stress is amplified in the border zone region.[14,18,23] Mathematical models of ventricular mechanics support this interpretation,[3,7] though these models are too simplified to reproduce many specific details of mechanics observed in the border zone. For example, a recent model by Bovendeerd and co-workers[7] showed stress alterations in the border zone, consistent with fiber lengthening in the same region. However, these researchers did not assume a sharp transition in contractility across the perfusion boundary. Moreover, their model did not include accurate left ventricular geometry and fiber orientation.

Therefore, there is a need for a model-based approach in which structural factors, such as local fiber orientation and ventricular geometry, are included. Moreover, more accurate mathematical models that include all the factors mentioned above might explain the mechanisms governing the shape and width of the functional border zone. The effect of perfusion boundary orientation relative to fiber orientation has to be investigated quantitatively, by comparing two occlusions sites of left anterior descending and left circumflex coronary arteries that provide different perfusion boundary orientations with respect to the local myofiber orientation. Analyzing three-dimensional segment function in local fiber axes and correlating them to blood flow and wall geometry may elucidate factors contributing to the width of the functional border zone during acute myocardial ischemia.

Recently, we developed a new parametric model-based method that allows epicardial strain distributions to be computed on the left ventricular free wall in normal and ischemic myocardium and integrated with the regional distribution of anatomic and physiologic measurements so that the underlying relations can be explored.[54] Since the myocardial markers used in our experimental approach were inevitably sparse in relation to the heterogeneous structure of the ventricular wall (especially during conditions such as acute ischemia), we used a penalty method to regularize least-squares fits of high-order parametric polynomials to the deforming surface geometry.[8,34,54] However, the choice of correct smoothing weights for penalizing amount of stretch and bending energy of these surfaces had not previously been systematically investigated or optimized. An objective method for optimizing these penalty weights was developed. This validation analysis showed that a regularizing function can be optimized to minimize both fitting errors and numerical oscillations in the computed strain fields. These smoothing procedures are likely to be useful for myocardial strain analysis using other measurement techniques and imaging modalities such as MRI tagging.[87] Moreover, this approach is not limited to large animal studies, and flow–function relations; any number of measurable experimental fields could be integrated in this parametric approach. This provides a framework to integrate physiological with anatomic and kinematic measurements. For example, the relation between regional deformation and blood flow can be explored as a function of longitudinal position within the anterior wall or occluded coronary vessel.

Using this method, we analyzed two-dimensional epicardial strains, resolved with respect to local fiber axes, in anesthetized canines.[52] Either the left anterior descending or left circumflex (LCx) coronary artery was occluded to test the effects of the ischemic region. This enabled us to look at the relation between local fiber orientation and perfusion boundary, since LCx occlusion results in a more longitudinal perfusion boundary compared with LAD. Strains were used to validate a three-dimensional (3D) computational model of LV systolic mechanics based on the assumption that there is a one-to-one relation between regional myocardial blood flow and myofilament activation. Once the model was validated, regional stresses in the ischemic, nonischemic, and the border zone were characterized. Numerical perturbations were then performed in the model to pose mechanistic questions that we were not able to answer by experiments alone.

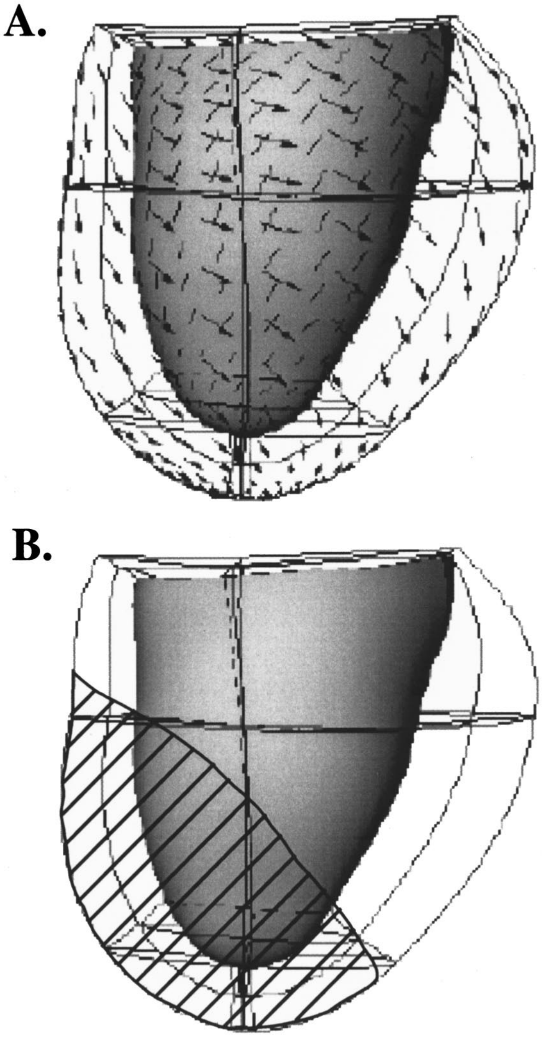

FIGURE 2. Three-dimensional model of the canine left ventricle. Epicardial (vectors, with arrows) and endocardial (vectors, no arrows) fiber angles are shown (A). Ischemic region is shown as the hatched area (B).

A 3D finite-element model of LV mechanics based on comprehensive measurements of canine geometry and myofiber architecture[57] (Fig. 2) was used to simulate filling and ejection using the measured mean diastolic and systolic LV pressures. Systolic stresses were computed from the sum of passive and active stresses in fiber coordinates.[30] Active isometric tension was a function of sarcomere length and intracellular calcium concentration.[40] In this model, transverse systolic stresses were also added as a function of developed fiber stress and fiber and transverse strain (Fig. 3), which matched recent biaxial test results of Lin and Yin.[48] To model ischemia, myofiber calcium sensitivity was reduced by increasing Ca_{50} in the ischemic region from 4.2 to 7.9 μM with a step transition across the perfusion boundary[1] (Fig. 2). Hence the parameter for ''contractility'' in the

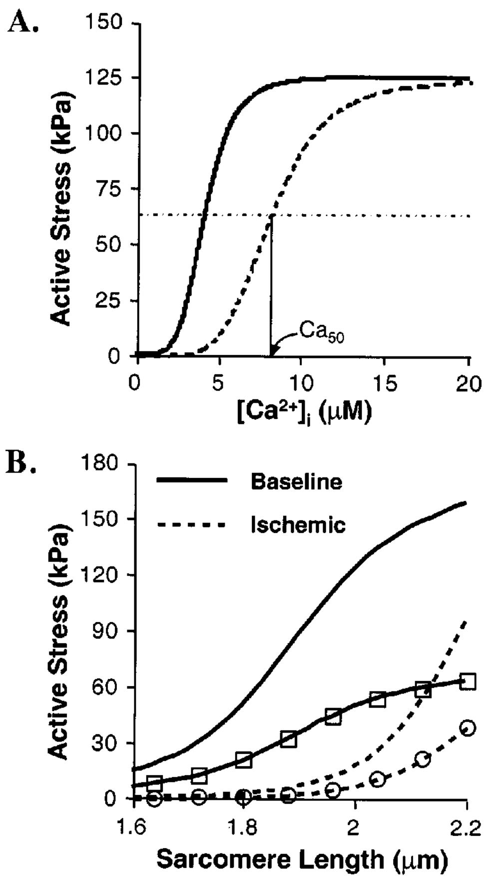

FIGURE 3. Active systolic tension as a function of intracellular calcium concentration (A), and sarcomere length (B) in the normal (solid lines) and ischemic region (dashed lines) are shown. Active stress in the cross-fiber direction (lines with symbols) was also added in the continuum model of the LV. Active material properties were altered abruptly across the perfusion boundary in the ischemic region. Ischemia was simulated by a rightward shift in the tension–calcium relation (increase in Ca_{50}) across the perfusion boundary.

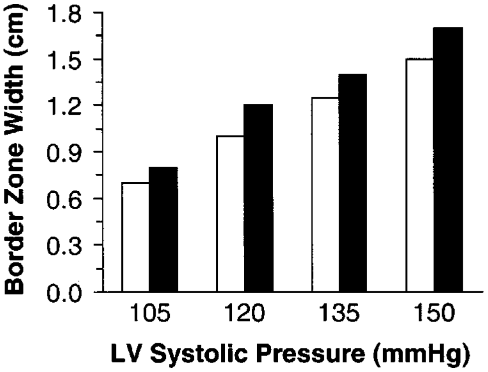

FIGURE 4. Width of the functional border zone as determined by the continuum model of the left ventricle (LV) as a function of LV systolic pressure for left anterior descending (LAD) (open bars) and left circumflex (LCx) occlusions (filled bars). The width of the functional border zone was highly dependent on the left ventricular stresses as defined by LV systolic pressure. At matched pressures, there was little difference in border zone widths in the two regions (i.e., LAD vs LCx).

model was not arbitrary but directly related to the biophysics of myofilament activation. The pressure boundary conditions in these models were based on the experimental means, and displacement boundary conditions were motivated according to the experimental preparations.

We found that the functional border zone of fiber shortening was narrower for LCx occlusion than LAD occlusion. Both occluded vessels resulted in a wider border zone for cross-fiber function than fiber function. Moreover, LAD occlusion resulted in more systolic lengthening in the ischemic zone and less systolic shortening in the remote nonischemic region compared with base-line values, consistent with hyperfunction in the nonischemic region during LCx occlusion.[52]

We found that a sharp transition in regional myofilament activation across the perfusion boundary is sufficient to explain the observation in a 3D model with no region of transitional contractility. Widths of the functional border zone characterized from the models of LAD and LCx occlusion, agreed well qualitatively with our experiments. For example, the functional border zones obtained from the model for LAD and LCx occlusion were 1.3 and 1.8 cm wide, respectively, in the fiber direction, compared to 1.2±0.2 and 2.3±0.2 cm from experimental observations. Similar agreement was also obtained in the cross-fiber direction. The model also resulted in nonischemic zone hyperfunction during LCx occlusion and more dysfunction in the ischemic zone during LAD occlusion, consistent with our experimental findings. Fiber and cross-fiber stresses were elevated by 2.2- and 4.7-fold, respectively, in the border zone region during the ischemic period compared with base line.

Increasing the angle of the perfusion boundary in the LAD perfusion bed to match the LCx's perfusion boundary orientation (with respect to the circumferential axis) did not decrease the width of the functional border zone for fiber function. This result is contrary to the parallel fiber hypothesis[84] that would predict a narrower border zone for a more longitudinal perfusion boundary. The effects of systolic pressure were also determined in the model and we found that systolic blood pressure does significantly affect the width of the border zone in both occlusion models. More importantly, we found that at matched systolic pressures, both coronary vessels would have resulted in similar border zone widths (Fig. 4). By varying the angular dispersion in the local myofiber orientation, we altered the level of systolic anisotropy in the model. We found that decreased systolic anisotropy decreases the width of the cross-fiber border zone and increases the width of the fiber border zone. This result is consistent with higher coupling between regional blood flow and fiber stress and strain than cross-fiber stress and strain.[55]

Therefore, a combination of *in vivo* and *ex vivo* data analysis, and continuum models of the LV enabled us to put some of the previously proposed mechanisms, such as parallel fiber hypothesis, into test. We were able to confirm that mechanical interactions across the perfusion boundary are dependent on the direction in which function is measured (i.e., fiber versus cross-fiber border zone). A new parametric method for data analysis enabled us to integrate *in vivo* and *ex vivo* measurements (e.g., location of ischemia and the perfusion boundary) into a mathematical analysis. Moreover, the addition of transverse active stresses in our 3D continuum model,[53] taking into consideration different structural mechanisms, not only provided a better agreement in the results, but also enabled us to make perturbation in the model to further evaluate underlying mechanisms (e.g., the relation between the level of systolic anisotropy and cross-fiber function).

MYOCARDIAL STUNNING

Myocardial stunning is the development of impaired mechanical function after transient myocardial ischemia despite complete restoration of blood flow; the impairment is temporary and therefore there is eventual spontaneous recovery. In 1975, Heyndrickx[37] defined myocardial stunning as ‘‘mechanical dysfunction that persists after reperfusion despite the absence of irreversible damage and despite return of normal or near-normal perfusion;’’ this occurs in the absence of histologically detectable necrosis.[4,9] This phenomenon is regarded as an entity separate from contractile abnormalities occurring during temporary periods of ischemia and from those associated with irreversible injury. Myocardial stunning has been described in various clinical situations including exercise induce ischemia, open heart surgery, cardiac transplantation, cardiac catheterization and revascularization, unstable angina, and acute myocardial infarction with early reperfusion.[42,62]

Systolic regional dysfunction has been observed in stunned myocardium previously.[5,63] Bolli *et al.*[5] in conscious dogs, after 15 min of occlusion and 7 days of reperfusion observed that at 2 h of reperfusion, the percent thickening fraction averaged 34% of the base line in endocardial layers, 62% in midwall, and 51% in epicardial layers. They concluded that slower recovery in endocardial layers compare to epicardial layers is consistent with maximal ‘‘stunning’’ phenomena in endocardium compared to epicardium. These researchers hypothesized that transient coronary occlusion produces greater injury in subendocardial layers which results in more prolonged dysfunction. Rynning *et al.*[65] in open-chest anesthetized cats, after 10 min of occlusion and 60 min of reperfusion, found that systolic dysfunction in stunned myocardium was more severe in longitudinal than circumferential direction. They concluded that stunning was more pronounced in longitudinal orientated subendocardial fibers. Therefore, it is evident that systolic dysfunction in the stunned myocardium not only depends on transmural location within the left ventricular wall, but could also depend on the orientation in which function is measured.

Researchers have attempted to describe the underlying mechanism of systolic dysfunction in stunned myocardium. Bolli *et al.*[6] in conscious dogs, after 15 min of LAD occlusion showed that wall thickening was depressed after 24 h of reperfusion to 85% of base-line values. They reported that recovery was complete within 30 min if coronary blood flow was greater than 50% of the nonischemic zone. They did not observe recovery at 24 h in those hearts with coronary blood flow less than 25% of the nonischemic region. They concluded that the rate of recovery is determined primarily by the severity of blood flow reduction during ischemia. Przyklenk *et al.*[62] looked at the compilation of four previous studies of anesthetized open-chest canines and determined circumferential segment function in the midmyocardium layer. Correlating effects of various parameters such as: (1) regional myocardial blood flow during occlusion and after reperfusion; (2) high-energy phosphate content; (3) systemic hemodynamic parameters: heart rate, mean arterial pressure; (4) occluded bed size; and (5) segment shortening during coronary occlusion on segment shortening 2 h after reperfusion were determined. Contrary to the findings of Bolli and co-workers[6] in conscious dogs, they found that recovery of the systolic contractile function is determined primarily by the degree of dysfunction during the preceding period of ischemia. These researchers concluded that in anesthetized canine preparation, specific values of ischemic blood flow during occlusion do not accurately predict specific values of segment shortening after reperfusion.

Researchers have also characterized regional diastolic abnormalities associated with myocardial stunning.[15,63,83] Przyklenk *et al.*[63] found that in addition to systolic contraction and isovolumic relaxation, diastolic relaxation time was also impaired for at least 3 h after a brief, transient period of coronary artery occlusion in dogs. Rynning *et al.*[65] reported that diastolic function was deranged in longitudinally oriented segments during the reperfusion period; at 60 min of reperfusion the end-diastolic pressure–length relation was still shifted rightwards in the longitudinal segment, while it was normalized in circumferential segments. However, there are significant discrepancies between the diastolic dysfunction observed *in vivo* with those described in isolated hearts and muscle. Moreover, mechanisms of diastolic dysfunction may vary depending upon the way in which the myocardium was ''stunned.'' For example, a significant amount of endomysial collagen damage and loss has been reported in stunned myocardium.[11,88] But this degradation requires repeated cycles of ischemia and reperfusion[81] and therefore does not apply to all situations.

At the cellular level, contractile dysfunction associated with myocardial stunning is probably a multifactorial process that involves a complex sequence of cellular perturbations and results from the interaction of multiple pathogenic mechanisms.[4] The two proposed hypotheses regarding the pathogenesis of myocardial stunning are the oxyradical hypothesis and the calcium hypothesis. The oxyradical hypothesis postulates that stunning is caused by oxidant stress secondary to the generation of reactive oxygen species.[4,42] The calcium hypothesis postulates that stunning is the result of a disturbance of cellular calcium homeostasis.[44] Gao *et al.*[26] in isolated trabeculae of the right ventricle of rat hearts used two exogenous oxygen free radicals (OFR) generating systems to produce hydroxyl radicals and/or superoxides. They showed that only in muscles exposed to superoxides for 20 min, Ca_{50} increased significantly, with no change of the Hill coefficient. They concluded that exogenously generated OFRs, particularly superoxides, mimic the effects of myocardial stunning on cardiac excitation–contraction coupling. In another study, Gao and co-workers[27] measured the steady-state force–calcium relation before and skinned thin ventricular trabeculae from control or stunned (20 min ischemia, 20 min of reperfusion) rat heart. They found that the maximal calcium activated force ($F_{\max}$) was significantly depressed and Ca_{50} was increased for both skinned and intact stunned muscles. They concluded that reduced calcium responsiveness of stunned myocardium reflects alterations of myofilaments themselves, not of cytosolic factors, which can be reproduced by exposure to calcium-dependent protease. Consistent with these findings, Kusuoka *et al.*[43] also showed that contractile failure in stunned myocardium is due to a decrease in the myofilament sensitivity to calcium as well as reduction in $F_{\max}$. This decrease in calcium sensitivity of tension (force) appears to be due at least in part to alterations in the cardiac troponin regulatory complex.[25,74]

Significant and rapid endomysial collagen damage and loss has been observed in stunned myocardium[11,88] and could contribute to increase end-diastolic strain.[50] However, the degradation requires repeated cycles of ischemia and reperfusion.[81] Increased diastolic stiffness of stunned myocardium *in vitro* has been associated with increased diastolic cytoplasmic Ca^{2+},[24,33] but other studies have shown increased diastolic pressure with no change in diastolic calcium.[43] Recently, Stuyvers *et al.*[68] proposed that diastolic elastic properties may be regulated by calcium-dependent actin–titin interactions.

How these findings at the cellular level translate to regional diastolic and systolic dysfunction in the *in vivo* models of the stunned myocardium is not well understood. Moreover, interpretation based on isolated stunned muscle preparation and relating them to *in vivo* findings is often hard since there are no available data on 3D functional in the stunned myocardium, especially with respect to the local fiber axis.

Recently, we measured three-dimensional transmural function with respect to local fiber axes during 15 min of left anterior descending coronary artery occlusion and 2 h of reperfusion,[52] to determine if impairment of intrinsic myofiber contractile function following coronary artery occlusion and reperfusion is nonuniformly impaired. 15 min of complete coronary occlusion and reperfusion resulted in a significant diastolic and systolic dysfunction in the reperfused region relative to base-line values. Consistent with previously published results, there was a significant difference in the degree of systolic dysfunction between subepicardial and subendocardial layers in radial and cross-fiber segments. However, there was no transmural variation of systolic lengthening in the myofiber direction, despite a gradient in blood flow reduction transmurally. There was also a significant difference in the degree of diastolic dysfunction between subepicardial and subendocardial layers in radial segments, but not the fiber and cross-fiber directions.

A 3D computational model of the LV showed that a transmurally uniform loss of myofilament Ca^{2+} sensitivity and calcium activated maximal force generation, consistent with findings of Gao *et al.*,[24] was sufficient to reproduce these systolic findings. Thus desensitization of myofilaments to calcium may be transmurally uniform in the stunned myocardium, and systolic dysfunction during the preceding ischemic period may be the main determinant of myocardial dysfunction during stunning.

In an attempt to explain diastolic abnormalities observed in stunned myocardium, we hypothesized that strain softening associated with paradoxical systolic stretch during the ischemic period may be responsible for diastolic dysfunction observed during reperfusion periods. Consistent with the findings of Emery *et al.*[17] in rat myocardium, regional strain softening was introduced in our 3D model (Fig. 5), only in the ischemic region, by varying the diastolic material properties.[31] These preliminary models were able to partly explain end-diastolic remodeling observed in our experiments (Fig. 6).[52] Therefore other factors, such as a disruption in diastolic intracellular calcium, may also be contributing to the diastolic properties of the stunned myocardium that were not accounted for here in our model. Moreover, the computational model used here, did not take into consideration many other factors that may also contribute to alterations in diastolic properties of the intact myocardium such as regional coronary perfusion pressures.

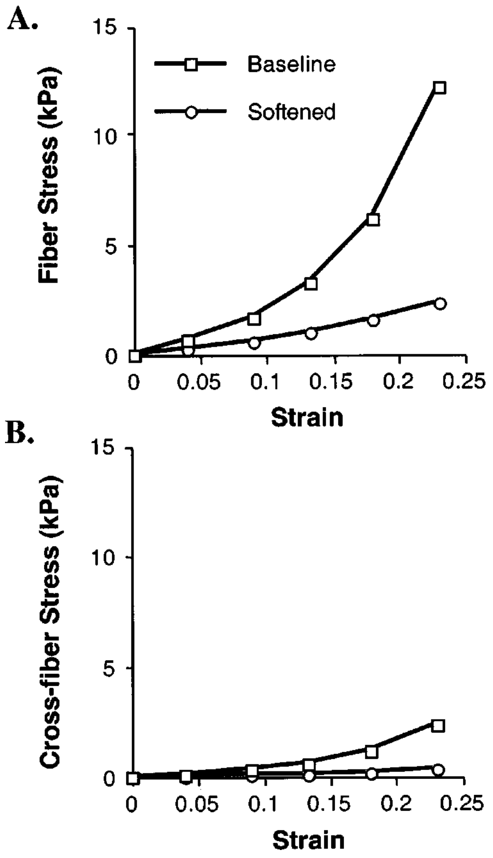

FIGURE 5. Stress–strain relation for the baseline and strain-softened tissue in the fiber (A) and cross-fiber (B) directions. Passive material properties were altered abruptly across the perfusion boundary (Fig. 2) in the ischemia/reperfused region to the softened material description shown.

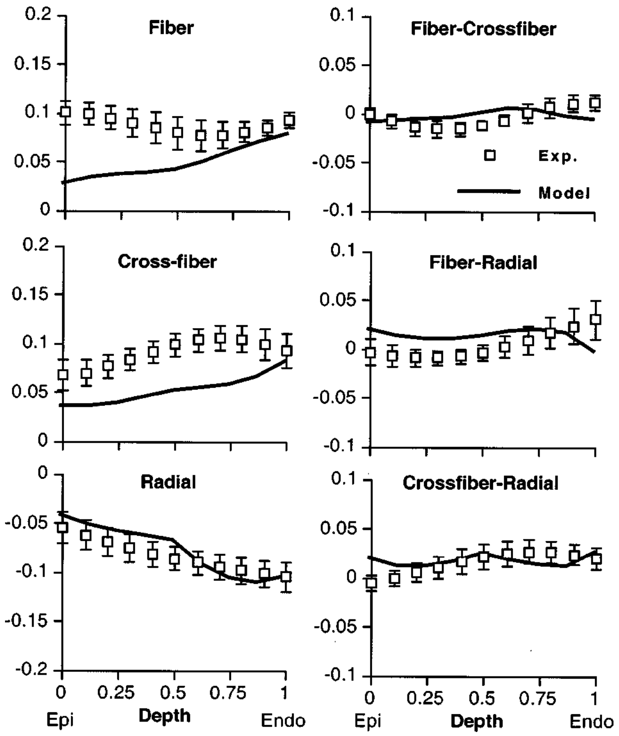

FIGURE 6. Transmural experimental end-diastolic remodeling strains (mean±SE, $n=8$) at 120 min of reperfusion, compared with the model results (solid lines). Strains in the normal directions (fiber, cross-fiber, and radial) are shown in the left panels; shear strains are shown in the right panels. Epi, epicardial and Endo, endocardial.

CONCLUSIONS

The regional flow–function relation can be influenced by mechanical interactions. These interactions tend to be larger (i.e., act at larger distance) for cross-fiber strain than for fiber strain, which is more tightly coupled to regional blood flow. The underlying mechanism is altered stress distribution and the important new development is that computational models have now reached point where they can make reliable predictions. The main advantage of these models is that they included three-dimensional geometry of the heart and the fiber architecture, nonlinear active and passive material properties, all based on previously measured experimental data.

A 3D computational model of the LV showed that a transmurally uniform loss of myofilament Ca^{2+} sensitivity and calcium-activated maximal force generation, was sufficient to reproduce our experimental systolic findings in the ischemic-reperfused myocardium. Thus desensitization of myofilaments to calcium may be transmurally uniform in the stunned myocardium, and systolic dysfunction during the preceding ischemic period may be the main determinant of myocardial dysfunction during stunning.

In this review, we have shown it is necessary to account for 3D mechanics of the ventricle in order to interpret the cellular basis of regional dysfunction in complex regional disorders such as ischemia and stunning. Moreover, three-dimensional contractile models that include details of ventricular anatomy, perfusion, three-dimensional material properties, and myofilament activation are able to elucidate how alterations in cellular properties affect regional flow–function relations in the intact myocardium. These models have to be validated qualitatively and more importantly, quantitatively using elaborate experimental findings and once a level of accuracy has been achieved, perturbations can be made in the models to investigate the underlying mechanisms of dysfunction. The approach used here is not by any means limited to flow–function relations; relationships between regional metabolism and function or regional structure and electrical activity of the myocardium can be explored in a similar manner.

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