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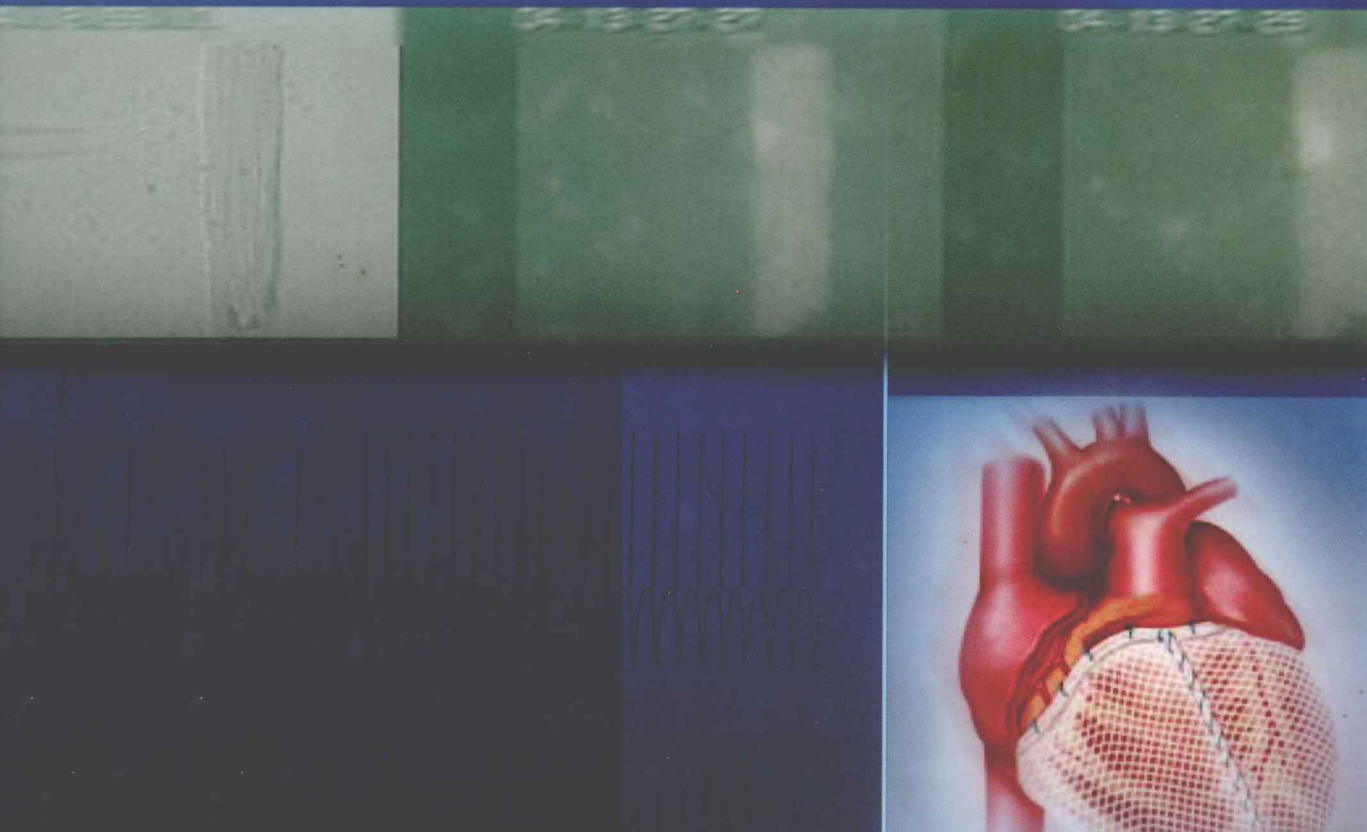
CARDIAC MECHANO-ELECTRIC FEEDBACK & ARRHYTHMIAS

From Pipette to Patient



CARDIAC MECHANO-ELECTRIC FEEDBACK *and* ARRYTHMIAS

From PIPETTE To PATIENT

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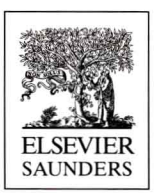

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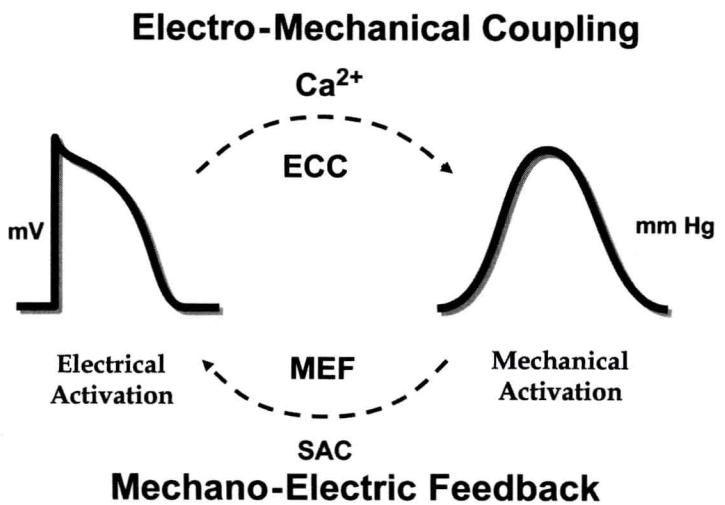
FOREWORD

Stretching Our Views of Cardiac Control

The transduction of electrical impulses into changes in the rate and mechanical force of muscle contraction, known as excitation–contraction coupling (ECC), is a fundamental concept essential to both a basic and clinical understanding of the heart. Modulators of ECC, and hence of cardiac muscle performance, include neurohumoral transmitters such as catecholamines, as well as many other regulators, notably those that affect intracellular calcium handling. This affects actin–myosin interactions and adjusts hemodynamics in accord with changing requirements on a beat-by-beat, year-by-year basis.

The complementary concept that cardiac mechanical function changes that occur in response to neural and hormonal influences impact on the excitatory and conductive electrical properties of the heart, i.e., mechano-electric coupling or feedback (MEF) is a less established idea whose role in normal and pathological physiology has become an exciting new chapter in contemporary biology. Mechanisms and pathways whereby mechanical events, changes in tension and force, and spatial displacement alter the heart's electrical properties are now recognized as an important dimension for development of new approaches in therapeutic cardiac control.

The figure provides a simplified but conceptually useful view of this emerging bi-directional dynamic. Although the left-to-right pathway, ECC, is a familiar element in current therapeutic strategies, the right-to-left pathway, MEF, has only recently begun to be explored as a topic of medical interest. However, although it has become well established that dysfunction in pathways of ECC is important in a number of cardiac pathologies (e.g., in various cardiomyopathies), there are only a few clues for a parallel influence of factors in pathways of MEF. This situation appears likely to change as greater attention is given to mechanisms involved in acute and chronic processes of cardiac remodeling. These include some of the most common forms of heart disease such as dilative failure, atrial fibrillation, and post-infarction scarring. Although we now suspect MEF to play a role in both electrical and mechanical pathological remodeling, direct evidence of this has remained elusive. Thus, although much basic



Simplified conceptual view of the complementarity in coupling between electrical activation of contraction and the influence of mechano-electric feedback (MEF) in cardiac muscle. Electrical activation and excitation-contraction coupling (ECC) are believed to be mediated by convergence of signaling pathways altering cellular calcium (Ca^{2+}) levels, resulting in activation and alterations in actin–myosin interactions. Pathways by which mechanical influences and changes in tension, length, and directional displacement alter cardiac electrical function are believed in many cases to be mediated by stretch-activated ion channels (SAC), which affect intracellular electrical potential and excitation. *(Modified from a figure provided by Michael Franz, with permission.)*

information is becoming available on topics such as how MEF may facilitate normal physiological processes, we still have few clues on how they may be applied in prevention or reversal of disease.

This book represents an important step in documenting the elusive yet important role of MEF. Here, assembled in one source, are the current thoughts and findings of many of the leading investigators in the field. As one reads the pages that follow, it becomes apparent that MEF is indeed a topic whose "time to shine" has arrived, and that this volume contributes much to lighting this path. The three editors are among the field's pioneers, and their selection of topics has resulted in an excellent summary of much of the world's current thinking. The book continues the momentum established by their leadership of a number of important international symposia on MEF that addressed many of the field's outstanding questions in forums encompassing most of its working investigators. The synthesis and distillation of these efforts have contributed much to the pages that follow by providing coverage of important concepts that proceed from basic physiology and move toward an integrated understanding of cardiac control and the exploration of new targets of largely unexplored therapeutic potential.

Classic studies on MEF and how it might contribute to well established events are discussed, such as the Bainbridge response, the function of stretch-activated channels, and the fatal phenomena of commotio cordis. In addition, new approaches by many of today's cutting edge MEF exponents employ a wide range of molecular, biophysical, and genetic tools. Thus, the various sections of the book detail not just the potential impact, influence, and implications of MEF, but they also provide clues to future directions.

The core concepts of cardiac MEF are covered in the initial sections of the book, and there are many interesting additional clinical presentations. Highlights are likely to be different for each reader. For this observer, the chapters that explore chronic influences, as well as the more well-known acute influences of MEF, and those that pertain to atrial fibrillation and other arrhythmias, were highlights. Here is the groundwork that illustrates how changes in MEF may determine disease reversibility and refractoriness to various therapies. Other unique and fascinating topics include how MEF responses vary in different cardiac cell types, (e.g., cardiac myocytes versus cardiac fibroblasts), and several that touch on new questions about the submembranous cardiac cell architecture.

The network of filamentous cytoskeletal proteins has recently been recognized as important in diseases as varied as inherited monogenic arrhythmias and rare forms of cardiomyopathy. Yet, we have little idea of how these phenotypes arise at a cellular or physiological level. Are they parts of the MEF response mediated by alterations in process, such as the organization or anchoring of cell surface receptors and signaling complexes, or even interactions among various ion channel subunits that may be involved? Lastly, this reader noted several intriguing new approaches in studies that deal with still mysterious topics, such as how changes in transcellular electrical and physical communication influence expression of specific proteins that, in turn, determine "who says what to whom" in the close world of in situ cardiobiology.

In conclusion, I'd like to express the personal view that further discoveries concerning the integration of pathways of cardiac mechanical and electrical control, between ECC and MEF, are likely to provide new clues to the treatment and prevention of many forms of recalcitrant cardiac disease, especially those causative of life-threatening arrhythmias. Given that bias, it also seems worth suggesting that work on cardiac MEF, within all its extensions in man, should be supported nationally and internationally with elevated level of priority than has been the case recently. Despite decades of attempts at developing efficacious therapies for disturbances in the heart's electrical system, effective treatment and prevention options are few, and either problematic with respect to efficacy and side effects or increasingly more difficult to justify on a cost-effectiveness/resource utilization basis. The imperative for improvements in arrhythmia therapy is, nevertheless, but one of a number of reasons that speak to a need to expand fundamental and model studies on cardiac control to improve clinical translation and therapy. This book presents an excellent view of how such progress can be successfully achieved, and it illustrates its potential applications.

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MARCH 2005

PREFACE

Cardiac Mechano-Electric Feedback: From Pipette to Patient

Peter Kohl, Frederick Sachs, and Michael R. Franz

The heart is a mechano-sensitive organ.

Stretching of cardiac tissue affects a wide range of structural and functional characteristics including gene expression, protein turnover, connective tissue properties, electrical and mechanical coupling, contractility, and electrophysiology. This book focuses on mechanically induced changes that, directly or indirectly, affect heart rate and rhythm.

Effects of stretch in man range from heart rate responses to changes in venous return, mechanical induction of premature ventricular beats (e.g., during cardiac catheterization) and tachyarrhythmia (e.g., *commotio cordis*), to chronic rhythm disturbance during cardiac volume or pressure overload and the use of mechanical intervention (e.g., pre-cordial thump) to reset dysrhythmic hearts.

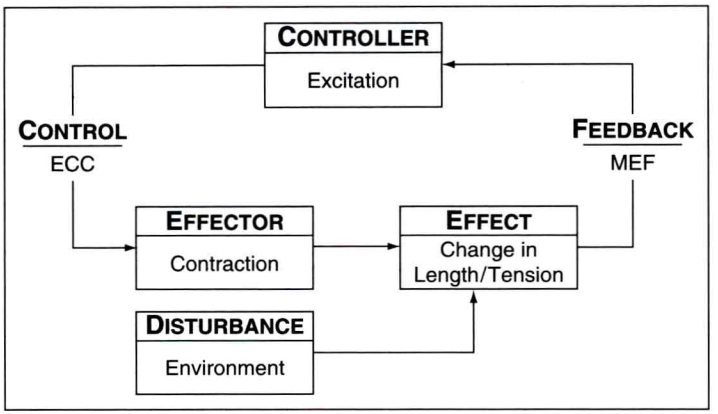
Documented reports of cardiac mechanosensitivity date back well over a century. One of the earliest descriptions of mechanical effects on cardiac function is from 1763, when Akenside gave an account of heart rhythm disturbance after a chest impact.[1] His case report involved severe tissue trauma, however, and it was not until 1882 that Riedinger and colleagues highlighted that, under certain conditions, chest impacts may induce arrhythmia in the absence of structural damage—*commotio cordis*.[2] In 1915, Bainbridge reported his famous observation of a mechanically-induced increase in cardiac beating rate,[3] and five years later, Schott described "pre-cordial percussion" as an effective means of keeping Stokes-Adams sufferers conscious during periods of complete atrio-ventricular block.[4]

The notion of cardiac mechanosensitivity rings a bell with any life sciences student who had an opportunity to conduct practical classes involving Langendorff heart preparations that, quite literally, can be kick-started when quiescent by a finger tap. Similar taps are employed by cardiac surgeons to restart a heart upon weaning from induced arrest.

What are the underlying mechanisms of these phenomena? Are there tools to study them quantitatively? Is there a conceptual framework for cardiac mechanosensitivity?

The last question may, perhaps, best be approached on the basis of regulation theory, which would view mechanosensitivity not as a peculiar, but a necessary, property of any electrically controlled mechanical system. As illustrated in the figure, electro-mechanical control (excitation–contraction coupling, ECC) must be accompanied by a feedback pathway (mechano-electric feedback, MEF) to form a regulatory loop. This concept was first applied to stretch-induced augmentation of spontaneous and ectopic automaticity in atrial and ventricular multicellular preparations by Kaufmann and Theophile (a.k.a. Ravens) in 1967, who labeled their observations as a manifestation of "*mechano-elektrische Rückkoppelung*"—MEF.[5]

The mechanisms underlying cardiac MEF have begun to be explored by both intracellular and extracellular electrical recording techniques. The latter, monophasic action potential recordings, are most helpful in studying stretch effects in the intact heart.[6] Transmembrane recordings, most notably patch clamping, have identified stretch-activated ion channels[7] in



Simplified scheme of the cardiac electro-mechanical regulatory loop. The process of electrical excitation controls cardiac contraction via excitation–contraction coupling (ECC). The resulting changes in cell length and/or tension affect the process of excitation via mechano-electric feedback (MEF). MEF occurs independently of whether a mechanical effect is caused by cardiac contraction itself, or through changes in the mechanical environment of the heart; in the absence of MEF, the system would therefore not be stable. *(From Kohl P, Hunter P, Noble D: Stretch-induced changes in heart rate and rhythm: Clinical observations, experiments and mathematical models. Prog Biophys Mol Biol 71(1):91–138, 1999, with permission.)*

many cardiac cells, including pacemaker cells, atrial and ventricular myocytes, and fibroblasts. Their clinical relevance is starting to emerge,[6] aided significantly by the identification of a first selective blocker for these channels.[8] Advanced optical imaging and molecular techniques have helped to further establish cellular calcium handling and second messengers, such as nitric oxide, as key players in cardiac MEF.

While acute stretch effects are well documented, chronic cardiac pathology involving mechanically induced electrical and structural tissue remodeling is more complex and multifactorial, making it difficult to establish a causal chain of response.

There is strong evidence to suggest that chamber dilatation plays a key role in the development of atrial fibrillation. Similarly, arrhythmogenesis in heart failure and ventricular overload have been linked to the changed mechanical environment. In keeping with this concept, clinical interventions that reduce cardiac distension (such as diuretics and afterload-reducing agents or active and passive cardiac assist devices) and cardiac resynchronization therapy have beneficial effects, not only on pump function, but also on cardiac electrophysiology. Future studies hold the promise of revealing more specific pathways of these phenomena, as there is virtually *no* aspect of cardiac function that is insensitive to the heart's mechanical environment.[9]

Cardiac mechanosensitivity and its effect on electrical function undoubtedly form a very complex system. Increasingly, fragments of this jigsaw are falling into place, as illustrated by the chapters in this book. There are, however, still large gaps to be filled, and we are far from a comprehensive understanding of the detailed mechanisms, physiological role, and clinical relevance of MEF.

The editors are indebted to the many contributors who investigate and clarify the role of MEF. Their work is truly interdisciplinary and translational, and it emphasizes the importance of a field that has gone relatively unnoticed for many decades. Research into MEF has developed from many different perspectives, from *E. coli* to cardiac myocytes, from computer modelling to clinical observations, from hitherto under-appreciated causes of cardiac arrhythmias to potentially providing new therapies.

In presenting the combined insight from basic science and clinical research, this book provides an up-to-date account of the current state of the MEF puzzle. There are potentially far-reaching cardiovascular health implications of a better understanding of the heart as an integrated electrical and mechanical closed-loop

system. The editors hope that the readers will be as provoked as we are and that this text will stimulate further study into the many undiscovered facets of the mechanosensitive heart.

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Wall Stress and Arrhythmogenesis in Patients with Left Ventricular Hypertrophy, Dilation, or Both

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Mortality from Heart Failure: Hemodynamics Versus Electrical Causes

Olga Solovyova, PhD
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Mechano-Electric Heterogeneity in Physiologic Function of the Heart

Peter M. Spooner, PhD
Executive Director, D.W. Reynolds Cardiovascular Clinical Research Center, Johns Hopkins University; Associate Professor, Division of Cardiology, Johns Hopkins University Medical Institutions, Baltimore, Maryland; Director (Emeritus), Arrhythmia, Ischemia and Sudden Cardiac Death Research Program, National Heart, Lung and Blood Institute, NIH, Bethesda, Maryland.
Foreword: Stretching Our Views of Cardiac Control

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Membrane–Cytoskeleton Interface and Mechanosensitive Channels

Borys Surawicz, MD
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Is the U Wave in the Electrocardiogram a Mechano-Electric Phenomenon?

Peter Sutton, PhD
Associate Director, Hatter Institute, Department of Cardiology, University College Hospital; Senior Lecturer, Department of Physiology, University College London, London, England.
Load Dependence of Ventricular Repolarization; Termination of Arrhythmias by Hemodynamic Unloading

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Stretch Effects on Second Messengers and Early Gene Expression

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Load Dependence of Ventricular Repolarization; Termination of Arrhythmias by Hemodynamic Unloading

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Mechanical Modulation of Cardiac Function: Role of the Pericardium

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Wall Stress and Arrhythmogenesis in Patients with Left Ventricular Hypertrophy, Dilation, or Both

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Electro-Mechanical Remodeling in Hypertrophy

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Temporal Modulation of Mechano-Electric Feedback in Cardiac Muscle

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Stretch Effects on Second Messengers and Early Gene Expression

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Atrial Fibrillation and Dilated Cardiomyopathy

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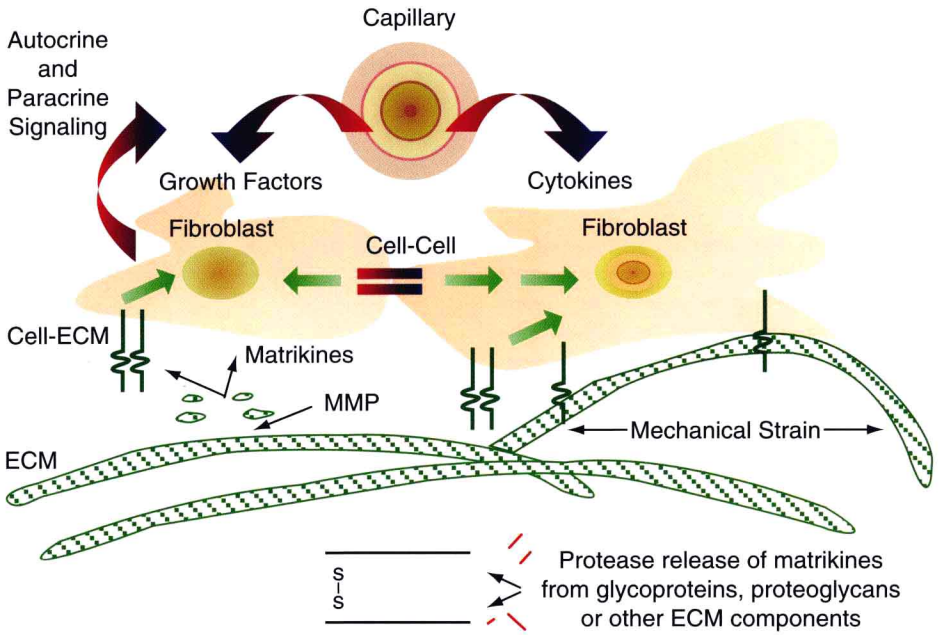
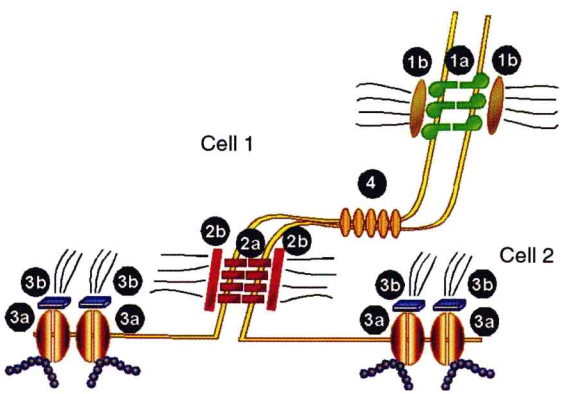
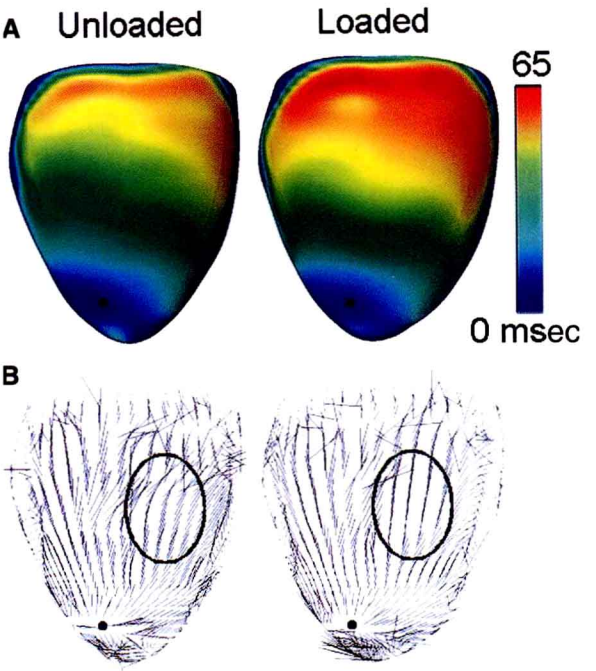
Mechanical Triggers and Facilitators of Cardiac Excitation and Arrhythmias



■ **Figure 10–2** Schematic representation of the dynamic interaction among components of the acellular extracellular matrix (ECM) and the cardiac fibroblasts. MMP, matrix metalloproteinases; s-s, fibronectin disulfide bond.



■ **Figure 11–1** The cell membranes of two adjacent cardiomyocytes are connected by fascia adherens junctions *(1)*, desmosomes *(2)*, and gap junctions *(4)*. The surface membranes are connected to extracellular matrix proteins through cell adherens molecules *(3)*. Fascia adherens junctions consist of the transmembrane-spanning Ca^{2+}-dependent adherens proteins (N-cadherins, *1a*) that are anchored in a submembranous scaffold *(1b)* consisting of several proteins (plakoglobin, catenins). The submembranous complex binds to the microfilaments of the cytoskeleton (actin). Desmosomes are formed by the transmembrane-spanning proteins desmocollin and desmoglein *(2a)* and are anchored in a submembranous scaffold of plakoglobin and desmoplakin *(2b)*. The latter proteins are bound to intermediate filaments (desmin). Gap junctions *(4)* consist of clustered gap junction channels each formed by two juxtaposed hemi-channels (each formed by six connexin proteins). The extracellular matrix is connected to integrin *(3a)* through fibronectin. Intracellularly, integrins bind to cytoskeletal proteins through a number of intermediate proteins *(3b)* that cluster integrin molecules and can induce intracellular signals when activated by extracellular mechanical stimuli.



■ **Figure 14–2** Activation time fields *(A)* and conduction velocity vector fields *(B)* before and during application of 30 mm Hg ventricular volume load in isolated rabbit heart, using methods from Sung and colleagues.[29] The *small solid circle* indicates the approximate position of pacing. The ellipses outline a region in which the apparent direction of conduction has been changed by application of load.