Regulation of Cardiac Contraction and Relaxation
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Fifty years ago, end-diastolic volume (Starling’s law of the heart) was generally believed to be the major determinant of cardiac performance. Although length-independent changes in the work of the heart had been observed by many investigators, including Starling, the significance of changing myocardial contractility was not appreciated in 1950, when Circulation was first published. Three articles published that year illustrate this lack of understanding. The first, which described patients with cor pulmonale, noted that digitalis increased the output of the failing right ventricle while right-sided filling pressures were decreased.1 Although cardiac glycosides were concluded to improve the “function of the failing ventricle,” a diagram in this article shows the failing heart operating on the descending limb of a Starling curve, with digitalis bringing the heart back to the apex of this curve. A second article examined digitalis toxicity in patients with heart failure and, citing work on isolated cardiac muscle published in the 1930s, concluded that “increased cardiac output following digitalis administration . . . is presumably largely due to an enhanced contractility.”2 The third article described reflexes that “depress the strength of cardiac contraction,” and concluded that autonomic stimulation could “modify the manifestations of Starling’s Law.”3 However, because there was no foundation of knowledge that could explain “enhanced contractility,” these observations could not be reconciled with the dominant view that end-diastolic volume is the key determinant of cardiac work.

Discovery of the Interplay Between Length-Dependent Changes in Cardiac Function (Starling’s “Law of the Heart”) and Changing Myocardial Contractility: The “Family of Starling Curves”
The interplay between regulation by changing end-diastolic volume and changing contractility was clarified by Sarnoff,4 who in 1955 described the “family of Starling curves” (Table 1). Although this demonstrated that length-independent changes in the contractile properties of cardiac muscle play an important role in regulating the work of the heart, almost 10 years were to pass before these changes, which Sarnoff called myocardial contractility, were explained by discoveries in biochemistry and biophysics.

Discoveries in Skeletal Muscle: The Sliding Filament Hypothesis and Role of Calcium
In 1953, H.E. Huxley and Jean Hanson, using x-ray diffraction5 and electron microscopic6 data, showed that the length of the macromolecules responsible for muscular contraction does not change when muscle shortens. This was a heretical view, as theories dating back to the 19th century had assumed that muscular contraction depends on the folding of asymmetrical molecules. These new observations indicated instead that muscle shortens and generates tension when myofilaments slide by one another and that the contractile process depends on interactions between cross-bridges made up of the heads of myosin in the thick filaments and actin in the thin filaments. Extension of these studies to cardiac muscle7 led to the discovery that Starling’s law is not due primarily to changes in the overlap between the thick and thin filaments but instead occurs because changing sarcomere length modifies the intensity of excitation-contraction coupling.8 The key to understanding contractility came in the early 1960s, when calcium was found to be the physiological activator of the contractile proteins in skeletal muscle,9,10 and an internal membrane system called the sarcoplasmic reticulum (SR) was shown to be the major source of activator calcium.11,12

At the same time that calcium was discovered to mediate excitation-contraction coupling in skeletal muscle, efforts to understand myocardial contractility were moving in a different direction, toward the view that potassium is the key regulator. Evidence that many positive inotropic interventions are accompanied by increased potassium efflux from the myocardium,13 along with earlier observations that high potassium concentrations inhibit the interactions between actin and myosin in vitro, were interpreted as evidence that potassium efflux plays a central role in increasing myocardial contractility.14 This view found support in a generally overlooked observation of Ringer, who of course is remembered today for his discovery that extracellular calcium is essential for cardiac contraction. However, Ringer had also found that increasing extracellular potassium weakens contraction of the frog heart,15 a phenomenon that is now explained by effects of this alkali metal ion on excitability rather than contractility.
Regulation of Cardiac Contraction and Relaxation by Calcium: Functional Signaling

**Troponin as the Calcium Receptor for Excitation-Contraction Coupling**

That calcium and not potassium is the major determinant of myocardial contractility became clear when Ebashi and Kodama\(^\text{16}\) described troponin, and regulatory proteins in the thin filament were found to be essential for micromolar calcium concentrations to activate the contractile proteins of skeletal muscle in vitro.\(^\text{17}\) In 1966, discovery of a similar calcium-sensitive regulatory mechanism in the heart\(^\text{18}\) opened a new area of discovery regarding cardiac regulation.

**SR as the Source of Calcium for Excitation-Contraction Coupling**

The pioneering work that had defined the role of the SR in skeletal muscle led to the next major advance in understanding myocardial contractility, which occurred in the late 1960s, when the cardiac SR was shown to have both the affinity and capacity to remove all of the calcium bound to troponin.\(^\text{19,20}\) The cardiac SR calcium pump was purified in 1970,\(^\text{21}\) and its structure was published in 1985.\(^\text{22}\) A related plasma membrane calcium pump ATPase that transports calcium out of the cell was described in the early 1980s.\(^\text{23}\) Characterization of the intracellular channel that releases calcium from these internal membranes, often called the ryanodine receptor, closed a major gap in understanding the role of the SR in excitation-contraction coupling.\(^\text{24}\)

Recognition that the contractile proteins are activated by downhill calcium fluxes and that relaxation requires the active, uphill transport of calcium into the SR and out of the cell answered a once “classic” question: “Does contraction or relaxation require energy?” The answer, of course, is both. The role of energy starvation in the living heart was clarified with the discovery that the normal cytosolic ATP concentration is 5 to 10 mmol/L, whereas the substrate-binding sites of most ATP-hydrolyzing systems are saturated at ATP concentrations of \(<1 \text{ mmol/L};\) these findings made it very unlikely that, except in the dying heart, ATP concentrations can fall to levels below those needed to saturate known ATPase enzymes. Observations that high ATP concentrations exert allosteric effects that accelerate ion pumps, ion exchangers, and passive ion fluxes through membrane channels suggested that reduction in these regulatory effects can reduce inotropy and lusitropy in the energy-starved heart. An even more important consequence was discovered to be a decrease in the energy made available by hydrolysis of the terminal phosphate of ATP, the free energy of ATP hydrolysis, or \(-\Delta G.\)\(^\text{25}\) Even a slight fall in the ATP-to-ADP ratio, which in the energy-starved heart is due mainly to an increase in ADP concentration, can slow both the calcium pump of the SR and cross-bridge cycling.\(^\text{26}\)

**The Sodium/Calcium Exchanger, Sodium Pump, and Mechanism of Action of Digitalis**

Despite Ringer’s early observation that cardiac contraction depends on extracellular calcium, in 1950 virtually nothing was known of the role of calcium in regulating myocardial contractility. A puzzling observation made in 1948 that contractility in the frog heart is proportional to the ratio between extracellular sodium and calcium\(^\text{27}\) led to the discovery of the sodium/calcium exchanger, an antiport that can carry either of these ions in either direction across the plasma membrane.\(^\text{28}\) The structure of this exchanger was published in 1990.\(^\text{29}\)

Competition between sodium and calcium for transport by the sodium/calcium exchanger made it possible to explain the inotropic effect of the cardiac glycosides. Although early reports described direct interactions of the cardiac glycosides with the contractile proteins, and after the discovery of the role of the SR with the calcium pump, these were never convincing. Instead, the mechanism became clear when cardiac glycosides were found to inhibit the sodium pump.\(^\text{30,31}\) In 1964, recognition that increased cytosolic sodium inhibits calcium efflux from the myocardium via the sodium/calcium exchanger explained how sodium pump inhibition could increase myocardial contractility.\(^\text{32}\) Many years were to pass, however, before this explanation for one of the oldest problems in cardiology came to be generally accepted.

**Calcium Influx, Slow Inward Current, and Calcium-Triggered Calcium Release**

The function of extracellular calcium in regulating myocardial contractility was discovered in the early 1960s, when stimulation was found to increase calcium influx across the plasma membrane.\(^\text{33,34}\) At that time, however, a physiological role for this calcium influx seemed doubtful, because action potentials in nerve and skeletal muscle could be explained almost entirely by sodium and potassium fluxes across the plasma membrane and because skeletal muscle can respond to electrical stimulation when extracellular calcium is very low. It was not until 1968 that myocardial contractility was found to be proportional to the magnitude of an inward
calcium current across the plasma membrane\textsuperscript{35}; this depolarizing calcium current was called the "slow inward current" because it activates and inactivates more slowly than the larger, sodium current responsible for the action potential upstroke. Increased calcium influx explains the inotropic effect of increased heart rate (the positive staircase described by Bowditch at the end of the 19th century) and, as described below, contributes to the inotropic effect of \( \beta \)-adrenergic stimulation.

The role of calcium entry in cardiac excitation-contraction coupling was subsequently explained by the finding that calcium release from the cardiac SR, unlike that of skeletal muscle, depends on a small calcium influx across the plasma membrane in a process called "calcium-triggered calcium release".\textsuperscript{36} Calcium release from the cardiac SR, which causes localized "calcium sparks" that can be visualized when cells are injected with calcium-sensitive dyes,\textsuperscript{37,38} is a critical determinant of myocardial contractility.

### Modification of Myofilament Responsiveness to Calcium and the Role of pH

Mines, at the beginning of the 20th century, found that acidosis reduces the strength of cardiac contraction. The mechanism was identified when protons were discovered to reduce the calcium sensitivity of purified contractile protein preparations\textsuperscript{39} and skinned cardiac fibers.\textsuperscript{40} Changes in the myofibrillar responsiveness to calcium caused by \( \beta \)-adrenergic agonists (see below) and \( \alpha \)-adrenergic agonists\textsuperscript{41} were subsequently found to modify both inotropy and lusitropy.

These discoveries were followed by observations that the inotropic responses of mammalian cardiac cells to angiotensin II and endothelin-1, as well as to \( \alpha \)-adrenergic agonists, occur when protein kinase C causes intracellular alkalization. The resulting changes in intracellular pH are regulated predominantly by a Na\(^+\)/H\(^+\) exchanger,\textsuperscript{42} which, along with the related Na\(^+\)/HCO\(_3\)\(^-\) symport and the sodium-dependent HCO\(_3\)/Cl\(^-\) antiport, allows changing intracellular pH to regulate contractility in both normal and failing hearts.\textsuperscript{43}

### Norepinephrine, cAMP, Protein Kinase A, and Phospholamban

Efforts to explain the heart’s response to sympathetic stimulation began with a search for direct interactions of catecholamines with the contractile proteins and the SR. As was the case for the cardiac glycosomes, positive results were published, but most could not be repeated. Discovery of the role of cAMP as an intracellular second messenger\textsuperscript{44} and the ability of cAMP-dependent protein kinases (protein kinase A) to catalyze phosphorylations that mediate responses to \( \beta \)-adrenergic agonists\textsuperscript{45,46} stimulated 4 groups to test the hypothesis that norepinephrine causes cAMP-activated phosphorylation of the SR.\textsuperscript{47-50} This led to the discovery of phospholamban, a regulatory protein that in its dephospho form inhibits the SR calcium ATPase.\textsuperscript{51} The ability of phospholamban phosphorylation to stimulate calcium uptake by the cardiac SR was immediately recognized to provide an explanation for the lusitropic effect of sympathetic activation.

Although phospholamban phosphorylation had been suggested in 1973 to increase contractility by enhancing calcium loading of the SR within the myocardium,\textsuperscript{52} this hypothesis was not confirmed until the 1990s, when studies were carried out in transgenic mice that lack\textsuperscript{53} and overexpress\textsuperscript{54} this regulatory protein.

The lusitropic effect of \( \beta \)-adrenergic stimulation was subsequently found to be mediated also when protein kinase A–catalyzed phosphorylation of troponin I desensitizes the contractile proteins to calcium.\textsuperscript{55,56} This effect not only facilitates relaxation but also increases the calcium requirement for contraction. However, the inotropic effect of \( \beta \)-adrenergic stimulation predominates because of another important response to sympathetic stimulation, an increase in the slow inward (calcium) current\textsuperscript{57} that overcomes the decreased calcium sensitivity of troponin. Together, these effects increase contractility and accelerate relaxation so as to provide an integrated response that is essential in allowing the inotropically stimulated heart to fill during sympathetic stimulation, when increased heart rate shortens diastole.

### Regulation of Contraction and Relaxation by Molecular Changes and Modification of Phenotype: Transcriptional Signaling

Fifty years ago, the failing heart was generally assumed to operate on the descending limb of the Starling curve (see Reference 1). Sarnoff’s demonstration that negative inotropic interventions shift the heart to a depressed Starling curve,\textsuperscript{4} along with the recognition that the heart cannot operate at a steady state on the descending limb,\textsuperscript{58} suggested instead that contractility is depressed in diseased hearts. Confirmation of this hypothesis in 1967\textsuperscript{59} had a major impact on concepts regarding heart failure, which came to be viewed largely as a pump disorder caused by depressed myocardial contractility. Although relaxation and filling abnormalities were subsequently recognized in failing hearts,\textsuperscript{60} a new paradigm, that of transcriptional regulation, has now emerged as the major cause of the chronic inotropic and lusitropic abnormalities in heart disease.

Changes in contractility and relaxation, such as those caused by altered pH, digitalis, and \( \beta \)-adrenergic stimulation, can be viewed as functional responses that develop rapidly, generally over a few seconds or minutes. These responses, which are effected by mechanisms like altered calcium fluxes and posttranslational phosphorylations, differ fundamentally from transcriptional (proliferative) responses that evolve over days, months, and often years. The latter are caused by activation of transcription factors that regulate gene expression, protein synthesis, cell growth and division, and programmed cell death (apoptosis). Because adult cardiac myocytes have little or no ability to divide, transcriptionally mediated changes increase cell size (hypertrophy) and modify molecular composition. The resulting changes in organ structure and function have profound effects on both ejection and filling that are central to the long-term adjustments of pump function when adult hearts are subjected to chronic stress.

The first evidence that transcriptional regulation modifies myocardial contractility was published in 1962, when...
ATPase activity was found to be depressed in myofibrils isolated from failing human hearts. This discovery, and subsequent observations that myosin ATPase activity is altered by hyperthyroidism, marked a paradigm shift, as it demonstrated that cardiac performance can be regulated by changes in the composition of the heart. It soon became clear that these transcriptional responses are at least as important as the functional responses that alter the behavior of preexisting structures in the heart.

Transcriptional responses play an important role in chronically overloaded hearts, where they not only promote cell growth and apoptosis but also reduce contractility and impair relaxation. Many of these changes, which are most marked in pressure overload, involve enzymes of energy metabolism, myofilaments, the cytoskeleton, membrane channels, ion exchangers and pumps, and proteins that mediate cell signaling.

The initial finding of a fall in myofibrillar ATPase activity in failing hearts (see above) was subsequently shown to be due to an isoform shift in which the adult, high-ATPase cardiac myosin α-heavy chain is replaced with the lower-activity fetal β-heavy chain. More recent work has identified additional shifts to fetal isoforms, including some that alter the calcium sensitivity of the contractile proteins. A second type of transcriptional response, which slows relaxation, is not caused by an isoform shift but instead is due to reduced expression of the SR calcium pump ATPase. This also represents a reversion to the fetal phenotype, as contraction and relaxation in embryonic hearts depend mainly on calcium fluxes between the cytosol and extracellular fluid, rather than between the cytosol and internal stores within the SR.

The plasticity of transcriptional regulation of myocardial contractility was demonstrated in the early 1970s, when physical training was found to increase both actomyosin ATPase activity and calcium uptake by the SR. These responses, which increase contractility and accelerate relaxation, represent enhanced expression of the adult phenotype and are opposite to the changes seen in chronically overloaded hearts.

The recent discovery that the sodium/calcium exchanger, which transports calcium out of the cell across the plasma membrane, is upregulated in failing hearts represents another example of reversion to the fetal phenotype; in this case, a greater reliance on calcium fluxes across the plasma membrane than on calcium fluxes into and out of the SR. Increased activity of the sodium/calcium exchanger helps relax the heart, but by reducing calcium loading of the SR, also decreases contractility.

Conclusions
The initial clinical promise of therapy based on the physiologically and biologically based discoveries regarding cardiac contraction and relaxation described in this article has not, unfortunately, been fulfilled. Although alleviation of the obvious hemodynamic consequences of depressed contractility and impaired relaxation is of short-term clinical benefit, efforts to “correct” maladaptive functional signaling often have adverse long-term effects. For example, powerful inotropic agents, such as phosphodiesterase inhibitors, transiently improve hemodynamics but shorten survival. More surprising, in the context of the history reviewed in this article, is evidence that β-adrenergic blockers, despite their initial negative inotropic (functional) effects, improve long-term prognosis and slow the progressive dilatation of the failing heart, called remodeling, that results from transcriptional signaling. The ability of converting-enzyme inhibitors, which also prolong survival in heart failure, to inhibit remodeling highlights the importance of maladaptive transcriptional signaling in this clinical syndrome.

Fifty years after publication of the first volumes of Circulation, therefore, explanations of heart disease appear once again to require a new paradigm. Much as the physiological explanations that dominated cardiology were being superseded by biochemical and biophysical explanations in the 1950s, emphasis today is moving from functional to transcriptional regulation. Clinical trials suggest that the current paradigm shift, which is changing efforts to treat heart failure from correcting functional abnormalities in contractility and relaxation to modifying inappropriate transcriptional signaling, will prove to be of considerable practical benefit.

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