Homogeneity Out of Heterogeneity

Arnold M. Katz, MD, and Phyllis B. Katz, PhD

Three different mechanisms are now recognized as participating in the regulation of cardiac function: by changing end-diastolic fiber length (Starling's law of the heart), by biochemical changes occurring within the myocardial cell (myocardial contractility), and by altered gene expression (molecular biology). Each plays a distinct role in allowing cardiac function to respond to the changing demands that the body places on the cardiovascular system. Starling's law of the heart, which operates at the organ level, regulates the output of the heart on a beat-to-beat basis by adjusting cardiac work capacity to changes in preload and afterload. Changing myocardial contractility regulates cardiac performance over a slower time course, largely by altering the Ca^{2+} fluxes involved in excitation-contraction coupling; this second mechanism allows individual myocardial cells to respond to humoral stimuli such as the sympathetic neurotransmitters released during exercise. Regulation by altered gene expression, the third mechanism, alters myocardial function over an even slower time course in that changing protein composition facilitates the cardiac response to sustained changes in cardiovascular function that occurs in endocrinopathies, aging, and chronic hemodynamic overloading.

We describe an additional role for regulation by altered gene expression in an effort to clarify the significance of the remarkable cellular and molecular heterogeneity in the heart. Using the ancient Greek trireme as a model, we illustrate the manner by which the cellular and molecular heterogeneity made possible by variable gene expression underlies the remarkable homogeneity of function of the heart as an organ.

Homogeneity Out of Heterogeneity in the Trireme

The ascendancy of Greece in the 5th century BC was based, in large part, on its naval power; the Greek naval victory over the Persians at Salamis ranks among the pivotal battles in the struggle between East and West. Most important of the Greek warships of the time was the trireme, a vessel approximately 37 m long and 6 m wide, whose main weapon was a bronze ram mounted in the bow. Although the trireme carried sails, the major source of power was provided by 170 oarsmen seated in three rows on either side of the ship (Figure 1). Effective use of the trireme required that the oarsmen row in synchrony, which allowed these vessels to travel long distances at high speed and, in battle, to generate sufficient forward momentum to drive the ram deep into an enemy vessel. The recent reconstruction of a classic trireme, which has demonstrated the engineering sophistication necessary to allow the three tiers of oars to function in concert, has shown that functional homogeneity in the rowing of the trireme depends on heterogeneity of structure (Figure 2). For example, the midship oars were made slightly longer than those at the bow and stern, and, to equalize the angles by which the oars of the different levels were raised and lowered, the oar blades and oarlocks of each level had different configurations. In addition, the upper-tier oars had to be slightly thinner and more heavily counterweighted than those of the lower tiers to equalize handle pressures and balance.

As in the trireme, the functionally homogeneous contraction of the muscular walls of the heart depends on heterogeneity in structure. Well-known morphologic, electrophysiologic, and metabolic specializations in the heart and a remarkable diversity in molecular structure ensure that all regions of the ventricles contract in a coherent manner so as to generate a forceful and efficient contraction.

Morphologic Heterogeneities

Almost a century ago, Woods recognized the importance of the law of Laplace, a simple physical law, in determining the shape of the ventricles. Woods's observation that the "thickness of the heart at any place bears a direct proportion to the relative tension at that place" led him to predict that left ventricular pressure in the human heart was about sixfold higher than right ventricular pressure. The complex architecture of the ventricles, which are made of overlapping spiral fiber bundles having different orientations and stresses, allows the normally vigorous contraction of the heart to expel blood in a manner that produces relatively little
turbulence. This remarkable adaptation of form to function becomes apparent when disease alters the patterns of blood flow through the heart. For example, a narrowed valve or a defect in the interventricular septum creates turbulence that dissipates the energy of cardiac contraction and is readily detected by the stethoscope as a murmur. Different hemodynamic overloads lead to distinct abnormalities in ventricular shape, and regional wall motion abnormalities that disturb the normal synchrony of contraction or relaxation impair pump function and reduce the mechanical efficiency of the heart.

The complex geometry of the heart is also reflected in differences between sarcomere lengths in the various layers of the ventricle and important heterogeneities in the mechanical conditions that govern contraction in different regions of the heart.

Among the most important of the latter are the higher stresses developed in the endocardial regions of the ventricle; because systolic stress is among the major determinants of myocardial energy demand, this aspect of the mechanical heterogeneity of the ventricle contributes to the susceptibility of the endocardium to ischemia. Regional differences in the sensitivity of the myocardium to an imbalance between energy production and energy use also reflect heterogeneities in the coronary circulation, especially the lower coronary vasodilator reserve in the endocardial rather than epicardial regions of the ventricle.

Electrophysiologic Heterogeneities

The wave of depolarization responsible for the orderly activation of the heart is conducted to the atria and ventricles through a complex pathway involving at least three specialized systems: the sinoatrial node, the atrioventricular node, and the His-Purkinje system. Pacemaker cells in the sinoatrial node initiate this wave of depolarization, which is then propagated to the working myocardial cells of the atria. The impulse reaches the ventricles via the atrioventricular node, which is made up of slowly conducting cells that, by delaying atrioventricular conduction, set the relative timing of atrial and ventricular systole to allow the atria to serve as a primer pump. The ventricles are depolarized via the His-Purkinje system, a network of rapidly conducting cardiac muscle cells that synchronizes activation of the more slowly conducting ventricular myocardial cells. Each of these regions of the heart is made up of special cardiac cell types containing specialized membrane channels that carry the ionic currents that determine conduction velocity and refractoriness in the different parts of this activation pathway.

While a review of this topic is beyond the scope of this editorial, two recent studies illustrate the remarkable electric heterogeneity of the heart. The first is a comparison of the action potentials in the epicardium and endocardium, which demonstrates how heterogeneities among the ion currents involved in repolarization give rise to regional variations in refractoriness that reduce the likelihood of reentry in the normal depolarization of the ventricles. The second study provides a dramatic illustration of the regulation made possible by these electrophysiologic heterogeneities; in this report, a model of the cardiac pacemaker was constructed by computer simulation of arrays of sinoatrial node cells that behaved as a large population of electrically coupled oscillators having different intrinsic periodicities. From the contributions of large numbers of these electronically coupled heterogeneous pacemaker cells, this model of cardiac pacemaker activity could explain many puzzling clinical and experimental observations regarding the behavior of the cardiac pacemaker.

The importance of the homogeneity that results from these electrophysiologic heterogeneities is well
known. The fatal consequences of disordered ventricular depolarization were noted more than 75 years ago by Sir Thomas Lewis, who wrote, "When the ventricles fibrillate, the co-ordinate beat of these chambers is lost; the muscle is divided up into small areas, which show independent activities; as a result the output of the heart ceases abruptly, the blood pressure falls to zero, the circulation is at a standstill. In other words, fibrillation of the ventricle, if it occurs in man, is responsible for unexpected and sudden death." Less drastic changes in this normal activation sequence (e.g., where ventricular depolarization is slowed and does not follow the normal conduction pathway) also impair the pumping of the heart. Thus, direct stimulation of the ventricle, which allows the wave of activation to bypass the rapidly conducting fibers of the His-Purkinje system, reduces the synchrony of ventricular depolarization, thereby prolonging systole and depressing ventricular function.

**Metabolic Heterogeneities**

Complex biochemical heterogeneities influence the adaptation of different regions of the ventricles to their nonuniform energy requirements. Most important of these is that the endocardial regions of the ventricles, which have higher wall stresses and yet are relatively underperfused (see above), have an approximately 20% greater oxygen consumption per unit mass than the epicardium. While our knowledge of these biochemical heterogeneities remains incomplete, it appears that the subendocardium has a greater capacity for anaerobic metabolism and a higher content of the enzymes and substrates of anaerobic metabolism (for review, see References 3, 17, and 23). These metabolic heterogeneities would favor the ability of the endocardium to generate adenosine triphosphate (ATP) under anaerobic conditions. During simulated ischemia, endocardium remains more excitable than endocardium of superfused right ventricles, perhaps in part because of the resistance of Purkinje fibers to hypoxia.

**Molecular Heterogeneities**

Yet another type of heterogeneity in the heart became apparent when different muscles were recognized to contain different myosins, and the ATPase activity of cardiac myosin was found to change in response to “tonic” pathophysiologic abnormalities such as chronic hemodynamic overloading, aging, and endocrinopathies (for review, see References 2 and 3). These functional differences in the myosin molecule, which determine the speed of muscle shortening and thus contribute to the regulation of myocardial contractility, are now under-
stood to reflect the encoding of a variety of myosin heavy and light chains by different gene families.

The highly regulated synthesis of the many possible isoforms of myosin in various muscle tissues results in the expression of different myosin genes at various stages in development within the same muscle and in different muscle types such as cardiac, slow twitch, and fast twitch muscle.\textsuperscript{26,27} The capability for alternate splicing of contractile protein genes\textsuperscript{28} further increases the potential for variability in the myosin isoforms synthesized by the heart and so can play an important role in regulating the mechanical performance of the heart. These and other mechanisms for molecular heterogeneity in the heart probably account for the recent demonstration\textsuperscript{29,30} of different myosin heavy-chain immunologic reactivities, light-chain composition, and ATPase activities in adjacent cells of the heart (Figure 3). While the functional significance of the heterogeneity is not clear, heterogeneity has been shown to modify the shape of the force-velocity curve in skeletal muscle fiber.\textsuperscript{31}

Although the precise role of this capacity to synthesize a large number of different myofibrillar proteins remains to be fully evaluated, the structural heterogeneities made possible by variable myosin gene expression could play a role in adjusting myocardial cell performance to the mechanical and metabolic heterogeneities in the heart. For example, because a slow ATPase myosin isoform increases the economy of tension development,\textsuperscript{4} preferential expression of slow ATPase myosin in the endocardial region of the ventricle\textsuperscript{32} could facilitate adaptation to the precarious balance between energy production and energy use in this region of the ventricle (see above). In this manner, the higher content of slow ATPase myosin in the endocardium might facilitate the ability of this relatively energy-starved region of the ventricle to develop tension.

Chronic hemodynamic overloading and heart failure are among the most important causes of changes in cardiac myosin gene expression.\textsuperscript{33–39} The ability of the resulting changes in myosin to facilitate the adaptation of the heart to a chronic increase in hemodynamic load is apparent in the rat ventricle, which can express several myosin isoforms, depending on the myosin heavy chain that is synthesized. Expression of the $V_1$ ($\alpha$) myosin heavy chain determines a high myosin ATPase activity and rapid shortening velocity, while the $V_3$ ($\beta$) myosin heavy chain determines slow myosin ATPase activity and slow shortening velocity. In response to chronic

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$^*$Expressed as percent cycling frequency of control hearts.

$^\dagger$Integral of tension developed during a single contraction.

$^\ddagger$Tension-time integral/tension-dependent initial heat, an index of "efficiency."

Modified from Hamrell and Alpert.\textsuperscript{4}

**Figure 3. Microphotographs of serial sections from the anterior trabeculated wall of the human right atrium processed for indirect immunofluorescence with two different antiventricular human myosin antibodies (Panels a and b) and stained histochemically for myosin ATPase activity (Panel c). A hybridoma that stained all atrial fibers uniformly is shown in Panel a, while a 2A hybridoma that preferentially stained certain fibers is shown in Panel b. Arrowhead, an atrial fiber highly reactive with 2A hybridoma antibody (Panel b) exhibits weak ATPase activity (Panel c). Arrow, an atrial fiber weakly reactive with the 2A hybridoma antibody (Panel b) exhibits high ATPase activity (Panel c). Bar, 20 μm. Reprinted from Bouvagnet et al\textsuperscript{30} by permission of the American Heart Association, Inc.**
pressure overloading, the gene that encodes the V\textsubscript{1} heavy chain is preferentially expressed, thereby increasing the proportion of the slow ATPase myosin isofrom. This replacement of fast myosin with slow myosin decreases the rate of cross-bridge cycling and so reduces contractility; however, this alteration in gene expression also increases mechanical efficiency\textsuperscript{4} (Table 1) and so may preserve myocardial cell viability in the overloaded heart.\textsuperscript{40,41}

Although major heterogeneities in myosin isofrom are not found in the human ventricle, a similar change in myosin gene expression has been observed in patients with left atrial enlargement, where a decreased proportion of fast (a) atrial myosin heavy chain was found to parallel the extent of left atrial enlargement\textsuperscript{42} (Figure 4). Expression of different isofoms of lactate dehydrogenase\textsuperscript{43} and creatine phosphokinase\textsuperscript{44,45} in the hypertrophied ventricle, and changes in membrane proteins (e.g., the sarclemmal sodium pump\textsuperscript{46}) may also participate in the response to altered physiologic state. In this way, the molecular heterogeneity made possible by the differential expression of myosin genes and by alternative gene splicing could contribute to the adaptation of structure to functional specialization in individual myocardial cells and the response of the myocardium to sustained changes in cardiovascular function.

**Conclusions**

Complex morphologic, electrophysiologic, metabolic, and molecular heterogeneities play important roles in the adaptation of form to function in the heart. Synchrony of contraction and relaxation in the walls of the ventricles, the orderly spread of the depolarization wave through the heart, and metabolic adaptation to regional differences in energetics are all facilitated by complex specializations in the individual cells of the heart. Variability in gene expression in the heart allows myocardial cells to adapt both their functional and metabolic environments to a number of long-term abnormalities. Thus, like the structural heterogeneities required for the orderly rowing of a 5th century BC Greek trireme, a remarkable variability of form makes possible the normal coordinated pumping action of the heart.

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