REMODELING OF CARDIAC MYOCYTES IN CHRONIC HEART DISEASE

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Summary. Congestive heart failure is generally characterized by a dilated, relatively thin-walled ventricle. Isolated myocyte data obtained from failing explanted human hearts with and without ischemic disease indicate that alterations in cell shape may be largely, if not exclusively, responsible for this anatomical change. Specifically, myocyte length and length:width ratio are significantly increased. The increase in myocyte length:width ratio, the cellular analogue of chamber diameter:wall thickness, is clearly maladaptive, since this parameter is normally maintained within a very narrow range. Though cell lengthening appears to be the cause of chamber dilation, stunted or arrested growth of the myocyte transverse area may be the underlying cellular defect. Data from humans and animal experiments suggest that transverse growth may be arrested at a relatively normal level in nonhypertensives with heart failure. In hypertensives, the maladaptive increase in myocyte length may begin after transverse growth reaches an upper limit of approximately 350–400 μm². Understanding the molecular basis of maladaptive myocyte growth may lead to newer and more effective therapies in the treatment and prevention of heart failure.

INTRODUCTION

Chronic cardiovascular diseases such as ischemia and hypertension may lead to congestive heart failure. Although there is not general agreement on a comprehensive definition of heart failure, this clinical syndrome is typically characterized anatomically by cardiac hypertrophy and a dilated, relatively thin-walled ventricle [1]. Data from humans and experimental animals with chronic congestive heart failure have demonstrated a clear and consistent alteration in cardiac myocyte shape that appears to be maladaptive [2–5]. Irrespective of the underlying disease process

Pathophysiologic Mechanisms of Ischemia–Reperfusion Injury

(e.g., chronic ischemia, hypertension, idiopathic dilated cardiomyopathy), ventricular dilation in heart failure is associated with a large increase in cardiac myocyte length due to series addition of sarcomeres [2–5]. The associated changes in myocyte cross-sectional area are not as obvious, though we believe that arrested or inadequate myocyte transverse growth may be an important early event leading to ventricular dilation and heart failure [6]. This chapter will review myocyte shape changes in cardiomegaly of various etiologies and compare myocyte remodeling in ischemic and nonischemic diseases leading to heart failure to determine if any specific alterations in cardiac myocyte shape can be attributed to ischemia. The discussion will focus largely on articles containing comprehensive data on myocyte shape (e.g., volume, length, cross-sectional area or width), since it is difficult to reach meaningful conclusions based on incomplete information (e.g., cell width or cross-sectional area only). This literature deals primarily with data collected from isolated cardiac myocytes, where cell boundaries and cardiac myocyte shape can be readily determined. The most consistent and best-documented approach to assess myocyte shape will be outlined briefly below.

DETERMINATION OF MYOCYTE SHAPE

It has been recognized for some time that myocyte length is difficult to measure from tissue sections due to the stair-step nature of the intercalated disc and the drawback of sampling from a finite plane of section [7,8]. Myocyte cross-sectional area, however, can be collected reliably from sections of whole tissue, provided that appropriate corrections are made for artifacts such as tissue compression, variation in sectioning angle, differences in contractile phase, and tissue processing artifacts [7]. In 1986, we demonstrated an excellent correlation between three methods for measuring myocyte size using whole-sectioned tissue and isolated myocytes [7]. These experiments were successful primarily because all known sources of error with the morphometric methods were eliminated or corrected for the first time. The most time-efficient and objective of these methods involves the measurement of isolated myocyte volume using a Coulter Channelizer, measurement of cell length using a microscope, and calculation of myocyte cross-sectional area from volume/length. Application of these methods in the assessment of myocyte dimensions has provided a clear and consistent understanding of myocyte remodeling in volume and pressure overload-induced cardiac hypertrophy, cardiac atrophy, and heart failure (reviewed in [6,9]). A major advantage of this approach is that all data can be directly compared. For instance, comparison of data from normal rats, cats, hamsters, guinea pigs, hamsters, ferrets, and humans reported in several studies published over the past ten years indicates that average dimensions of left ventricular myocytes from each of these mammalian species are virtually the same [3,7,10–13]. While other methods may provide useful information, valid comparisons are often limited to experimental groups from the same study. This is particularly true when one makes comparisons of data produced in different laboratories using different techniques.