Congestive heart failure: Role of cross-bridge cycle kinetics

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The fundamental role of the heart in the circulatory system is to pump an amount of blood that is precisely matched to the requirements of the body’s tissues for adequate perfusion. This task must be accomplished without interruption and under all conditions. Because of this, and under normal conditions, cardiac output is tightly controlled via a multitude of regulatory feedback systems that operate with different time constants that range from virtually instantaneous (heart rate, contractile state, venous capacitance), intermediate (fluid and salt retention) and long term (cardiac remodeling). Under pathological conditions when myocardial function is depressed, cardiac output is maintained by an increase in the regulatory feedback signals. However, if myocardial function continues to decline, a point is ultimately reached at which cardiac output no longer increases upon an increase in the feedback signals. At this point, all regulatory cardiovascular feedback control systems have been exhausted and the clinical syndrome of heart failure ensues [1].

The symptoms of heart failure are due to the responses of the peripheral cardiovascular system to reduced cardiac pump function, yet the underlying cause of the syndrome lies in the depression of intrinsic myocardial function [2]. There have been numerous studies in the last decade aimed at elucidating the mechanisms that underlie the cellular contractile dysfunction that is seen in human heart failure [3]. Collectively, these studies have shown, rather conclusively, that calcium homeostasis is altered in end-stage human heart failure. To determine whether myofilament function is affected, investigators have measured the relationship between isometric contractile force generation and calcium concentration in intact or skinned isolated human myocardium [4–6]. Unfortunately, the results of these studies have been inconsistent, showing either no change or an increase in the myofibrillar calcium responsiveness. In addition, these studies contrast with some of the animal studies that have shown depressed calcium responsiveness in experimental heart failure [7–10].

However, the ability to maintain contractile force at a given cytosolic calcium concentration is but one aspect of cardiac contractile function. In order to pump a volume of blood under pressure, a total amount of energy equivalent to stroke work must be generated by the cardiac myofilaments in a process termed ‘chemo-mechanical transduction’, in which ATP hydrolysis by active cycling cross-bridges is converted into mechanical energy. The rate at which energy is converted is reflected in the power-generating capacity of the heart [11]. Both of these parameters are fundamental properties of the sarcomere that are directly linked to the force–velocity relationship, as was demonstrated early in this century by the seminal work of A.V. Hill [12]. Although there is some debate as to the exact nature of the mechanical–energetic link in cardiac muscle [13], there is no doubt that cross-bridge cycling plays an integral role in determining the dynamic properties of the heart.

To date, however, only one study has been reported in which the dynamic mechanical properties of failing isolated human myocardium is compared to non-failing tissue. In work on skinned myocardium, Hajjar and Gwathmey [14] found 40% reductions in the maximum unloaded shortening velocity and minimum dynamic stiffness frequency. Both of these parameters are reflections of the intrinsic cross-bridge cycling rate. The report by Ruf et al. [15] from the group of Holubarsch in Freiburg, in this issue of *Cardiovascular Research*, both confirms and extends these observations to intact isolated myocardium during a barium contracture. As in the work of Hajjar and Gwathmey [14], these investigators find a 40% reduction in the cross-bridge cycling rate in failing human myocardium, which suggests that alterations in the dynamic properties of the cardiac sarcomere may play an important role in the development of human heart failure.

There are several cellular mechanisms that may underlie these results. Until recently, it was widely held that human
myocardium exclusively contains β-myosin heavy chain (β-MHC) [16,17], unlike the situation in small rodent hearts in which a prominent switch from the high cross-cycling rate α-MHC to the slower β-MHC occurs under pathological conditions and with aging [18]. However, a recent revisit of this issue by the group of Leinwand in Colorado has demonstrated a significant amount of α-MHC mRNA in the non-failing human heart, while virtually no α-MHC mRNA was detected in explanted failing human hearts [19]. Furthermore, recent preliminary results indicate that there is a measurable amount of α-MHC protein in the non-failing human heart, while none is detectable in the failing human heart (Leinwand, personal communication). Thus, the reduced myocardial cross-bridge cycling rate that is seen at end-stage human congestive heart failure (CHF) may be due to alterations in MHC isoform expression. Clearly, this issue can only be resolved when quantitative data are available as to the extent of MHC isoform composition, as well as accurate data on the impact of myosin isoform composition on the dynamics of contractile protein function [20,21]. Contractile protein isoform expression alterations may not be restricted to myosin. There have been reports of alterations in isoform expression of other contractile proteins in human heart disease, such as troponin-T (TnT) [22]. The functional consequence of altered TnT isoform expression is not clear, but it has been suggested to induce altered calcium responsiveness for steady state force generation [23]. Likewise, mutations in TnT and other contractile proteins have been identified in certain forms of familial hypertrophic cardiomyopathy [24,25]. Currently, intensive investigations are underway in several laboratories to unravel the functional consequences of these mutations on the steady state force of contraction as well as on twitch dynamics and the cross-bridge cycling rate. Most notably, there are indications that some mutations in the troponin complex or in tropomyosin may have a profound impact on the cross-bridge cycling rate [25]. These novel data are exciting because they may explain, at least in part, the origin of the idiopathic cardiomyopathy in patients that present with, until now, unexplained heart failure. Even more exciting, these mutations also provide for a ‘molecular tool’ that may allow investigators to solve the puzzle of the molecular mechanism of muscle contraction itself. That is, these data show that the role of the thin filament in muscle contraction goes far beyond a simple ‘on-off’ switching action for the actin-myosin interaction [26].

Another mechanism that may account for the reduction in cross-bridge cycling in human heart failure may be related to post-transcriptional modification of contractile proteins [27,28]. This is likely in light of recent reports that indicate alterations that occur in signal transduction processes in heart failure [29–31], in addition to the well documented down-regulation of β-adrenergic responsiveness [1,32]. It is well established that phosphorylation of troponin-I results in a reduction in calcium responsiveness for force generation [27,33]. In contrast, the impact of contractile protein phosphorylation on cross-bridge cycling is less clear. For example, conflicting reports have been published with regard to the impact of protein kinase A in isolated rat myocardium [34–37]. Likewise, it has been suggested that phosphorylation of contractile proteins by protein kinase C may have a profound impact on cross-bridge cycling [38,39] and, as such, this signal pathway may be of paramount significance in the depressed myocardial function that is seen at end-stage heart failure. One attractive aspect of this notion is that it may explain the apparent beneficial effect of angiotensin converting enzyme (ACE) inhibition [40] or angiotensin type 1 (AT-1) receptor antagonism, since the downstream signal pathway of angiotensin-II and endothelin involves protein kinase C [41]. A problem that remains, nevertheless, is whether contractile protein phosphorylation is indeed altered in vivo in heart failure and, if so, how precisely contractile protein phosphorylation is linked to alterations in contractile function.

Even though marked alterations have been found in contractile function in end-stage human heart failure, it should be remembered that such studies are only correlative. In particular, in human disease, one invariably deals with end-stage heart disease that is severe enough to warrant cardiac transplantation. Therefore, whether or not the changes in contractile function (or, for that matter, calcium homeostasis) that are seen at this stage play a causal role in the development of heart failure is not known at present. Hence, the development of reproducible experimental animal models of heart failure are of the utmost importance to allow longitudinal studies during the development of heart failure to contrast the results obtained from isolated human myocardium at end-stage failure to those obtained from animal studies under well defined experimental conditions.

Despite modern treatment of heart failure, the prognosis of this syndrome is dismal, with mortality rates approaching that of some malignancies. Nevertheless, the future perspectives for solving the problem of heart failure are encouraging. During the last decade, sophisticated techniques have become available for the study of isolated human and animal myocardium, ranging from multicellular preparations, single cells, down to single myosin motors. Each of these techniques address different and important aspects of cellular cardiac function, ranging from signal transduction, cross-bridge cycling dynamics and energetics, to structure–function relationships of the contractile proteins. At the same time, biochemical knowledge regarding cellular signaling pathways in health and disease is rapidly expanding. Molecular biology is now providing techniques to probe, for the first time, into the fine details of the contractile protein structure–function relation. Although gene therapy to alter contractile protein isoform composition or calcium handling proteins may be far in the future, agents to alter either cellular signaling pathways or
contractile protein function are certainly within reach in the near future. Clearly, accurate knowledge regarding the cellular processes that participate in the development of human heart failure is critical to the development of such novel treatment strategies.

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