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Review article

Myofilament length dependent activation

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ABSTRACT

The Frank–Starling law of the heart describes the interrelationship between end-diastolic volume and cardiac ejection volume, a regulatory system that operates on a beat-to-beat basis. The main cellular mechanism that underlies this phenomenon is an increase in the responsiveness of cardiac myofilaments to activating Ca^{2+} ions at a longer sarcomere length, commonly referred to as myofilament length-dependent activation. This review focuses on what molecular mechanisms may underlie myofilament length dependency. Specifically, the roles of inter-filament spacing, thick and thin filament based regulation, as well as sarcomeric regulatory proteins are discussed. Although the "Frank–Starling law of the heart" constitutes a fundamental cardiac property that has been appreciated for well over a century, it is still not known in muscle how the contractile apparatus transduces the information concerning sarcomere length to modulate ventricular pressure development.

Contents

1. Frank–Starling's Law of the Heart

Over a century ago, Otto Frank in Germany and Ernest Starling in England reported on the relationship between the extent of ventricular filling and pump function of the heart, a phenomenon collectively referred to as Frank–Starling's Law of the Heart. A modern view of this phenomenon [1] (illustrated in Fig. 1) holds that there is a unique relationship between end-systolic volume and end-systolic pressure in the heart that is solely determined by contractile state. As a consequence, for a given contractile state, ventricular stroke volume is (i) proportional to diastolic filling (i.e. preload), and (ii) stroke volume can be maintained in the face of increased aortic pressures (i.e. afterload) simply by increasing preload as illustrated by the two pressure-volume loops in Fig. 1. Contractile state, within this framework, can be viewed as any factor that alters end-systolic pressure *independently* of end-systolic volume and can conveniently be estimated semi-quantitatively by the slope of the end-systolic pressure–volume relationship (ESPVR; cf. solid line—control state and dashed blue line—enhanced contractile state in the right panel of Fig. 1). The ESPVR-slope is a very useful index of cardiac contractility that can be measured *in situ* by various methods; a convenient and popular approach is the use of the pressure-volume conductance catheter [2]. The cellular mechanisms that underlie the ESPVR are discussed in the following section.

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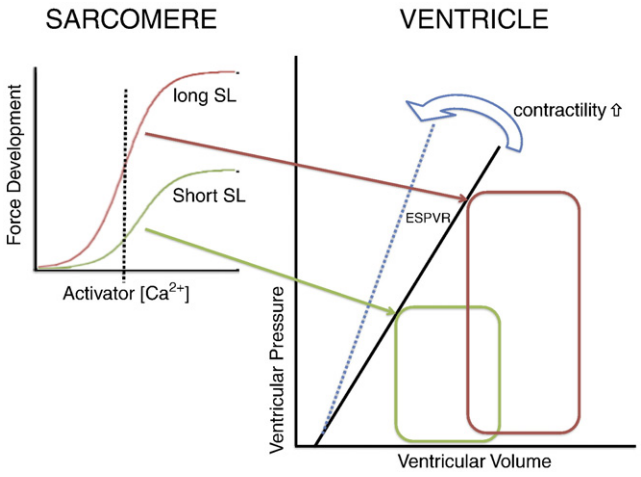

Fig. 1. The Frank–Starling mechanism and myofilament length dependent activation. The Frank–Starling Law of the Heart describes a fundamental property of the heart (figure on the right). That is, for a given contractile state there is a unique relationship between end-systolic pressure reached in the heart and end-systolic pressure (ESPVR); increased contractility results in an increased slope of the ESPVR (cf. blue arrow). Increased ventricular filling (pre-load; red PV loop) leads to an increase in ventricular pressure development at end-systole which allows for (i) increased stroke volume for a given systolic pressure (after-load) and (ii) sustained stroke volume at elevated systolic pressure. The Frank–Starling mechanism has, as its basis, a modulation of myofilament Ca^{2+} sensitivity upon a change in sarcomere length as illustrated in the left graphs. Myofilament force development is the result of activation by Ca^{2+} ions. The relationship between force development and activator [Ca^{2+}] is shifted up and to the left at longer sarcomere length (short SL, green; long SL, red). For a given contractile state (and, thus, cytosolic [Ca^{2+}]; dashed vertical line), more myofilament force is developed at the longer SL (red) leading to a higher ventricular pressure at higher end-systolic volume (red PV loop). Thus, the Frank–Starling Law of the heart is a direct consequence of the myofilament length-dependent activation properties of the cardiac sarcomere.

2. Relationship between whole heart property and myofilament length-dependent activation

Pump function of the heart is intimately related to force generation, active shortening, and regulation of cardiac sarcomere activation and relaxation [1,3]. The relationship between biomechanical properties of the cardiac sarcomere and mechanical behavior of the heart's chamber is complex [3]. It is determined not only by the orientation and density of the constituent cardiac muscle fibers (i.e. spatial parameters), but also by the timing of cardiac muscle fiber activation and relaxation (i.e. temporal parameters). Nevertheless, there is ample evidence to support the notion that the biochemical properties of the cardiac cell, and indeed the cardiac sarcomere itself, are directly responsible for many, if not most, of the mechanical properties of the heart [1,3–8]. Indeed, twitch force in isolated cardiac muscle is directly proportional to systolic sarcomere length; furthermore, the shape of the force-sarcomere length relationship is modulated by contractile state such that more force is generated at a given sarcomere length when contractile activation is elevated (e.g. by raising extracellular [Ca^{2+}]) [9]. At first sight, it may appear logical to suggest that variation of contractile filament overlap underlies the Frank–Starling Law of the Heart. However, the relationship between contractile twitch force and sarcomere length is too steep and too variable between contractile states to be solely explained by such a simple mechanism [8–12]. Activation of the contractile apparatus is initiated upon a transient increase in the cytosolic calcium concentration [13]. Under normal physiological conditions, calcium entry during the plateau phase of the cardiac action potential is not sufficient to directly activate the myofilaments, but instead serves as a trigger to release calcium from the sarcoplasmic reticulum [13]. The mechanisms that underlie this excitation-contraction coupling process are beyond the scope of this overview (for excellent reviews on this topic see [6,13]). Nevertheless, it is important to note here that, in general, there is a direct relationship between the magnitude of the calcium transient and the contractile state of the cardiac cell and, therefore, the ventricle [13–15]. However, the level of myofilament activation is by no means a simple proportional function of cytosolic calcium concentration. Rather, it constitutes a complex and dynamic signal transduction process that itself is also subject to regulation and modulation by both intrinsic (mechanical loading, sarcomere length) and extrinsic (neuro-hormonal) factors. Early experiments by Fabiato suggested that the released amount of this activator calcium varies with sarcomere length [16], but these results have not since been confirmed. Instead, more recent experiments [11,17,18] clearly demonstrated that it is the level of activation of the cardiac contractile apparatus itself that is sensitive to changes in sarcomere length [3,10]. These early experiments were performed on chemically permeabilized (skinned) isolated cardiac muscle, a preparation that allows direct access to the contractile apparatus such that steady state force can be measured as function of activator calcium concentration and sarcomere length; more recent experiments on intact twitching isolated myocardium employing fluorescent Ca^{2+} probes have confirmed these results [19]. Therefore, there is a direct proportionality between sarcomere length and the sensitivity of the cardiac sarcomere to Ca^{2+} ions, such that more force is generated at a given concentration of activator Ca^{2+} as sarcomere length is increased (the curves are both shifted to the left on the activator [Ca^{2+}] axis and up to higher forces at the higher sarcomere length. Hence, it can be said that the myofilaments possess a length dependency property that is termed “myofilament length-dependent activation”. This phenomenon is illustrated in the left panel of Fig. 1: because of the sarcomere length modulation of sarcomeric properties, myofilament force development for a given level of activator [Ca^{2+}] during the cardiac cycle (left panel; dashed vertical line) is also modulated and this, in turn, results in modulation of ventricular pressure development at end-systole (right panel; the two colored arrows indicate the connections between peak myofilament twitch force and end-systolic ventricular pressure). Thus, the whole heart Frank–Starling property has, as its basis, the myofilament length-dependent activation property of the cardiac sarcomere. Incidentally, intact twitching cardiac muscle responds to a change in length in two distinct phases: an immediate change in twitch force, and a slower phase that develops over the course of several minutes. Experimental evidence suggests that the latter phase is due to a change in sarcoplasmic reticulum calcium release secondary to altered calcium loading of the cell, while the immediate response is due to the change in calcium sensitivity of the cardiac sarcomere described above [12]; this review is focused on the immediate response to a change in sarcomere length. Despite the importance for the Frank–Starling mechanism, the molecular mechanisms that may underlie the immediate response of myofilament force generation upon a change in sarcomere length have not been entirely elucidated [3,8].

3. Myofilament length-dependent activation and the sarcomere

The change in myofilament force upon variation of sarcomere length is due to a change in the number of active cycling, force producing cross-bridges in the cardiac sarcomere [12,20,21]. The major proteins that make up the striated muscle sarcomere are: in the thin filament actin, troponin, and tropomyosin, and in the thick filament, myosin, myosin light chains, and myosin binding protein C (for a detailed review see [3,7,8,22–24]. Fig. 2 shows a schematic diagram illustrating the structure of the sarcomere as well as some of the possible molecular mechanisms that underlie myofilament length-dependent activation. Dimers of the asymmetric molecule myosin are located in the thick filament. Their tail portions form the backbone of this filament, while the globular heads protrude from