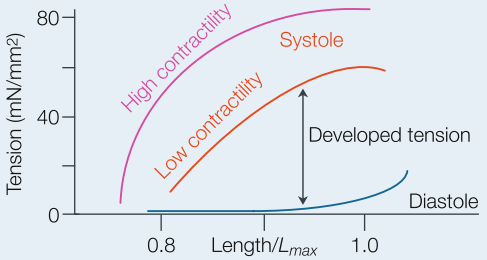
Chapter 12
Cardiac Muscle Mechanics



Relations between force and length in the relaxed state, diastole, and in two active states, systoles, of an isolated cardiac muscle. A low and high contractile state can be obtained by, for instance, changing the Calcium concentration in the extracellular medium and thus intracellular. During contraction a family of force-length relations is traversed, but here only the diastolic and the maximal or systolic relations are shown. The difference between the systolic and diastolic force is developed force. Force is expressed relative to cross-sectional area of the muscle and called tension (stress would be a better term). The length is normalized with respect to L_{max}, the length where developed force is maximal. The force-length relation forms the basis of the pressure-volume relation. Other important relations are:

- The force-velocity relation, showing that velocity of contraction decreases when force increases.
- The relation between intracellular calcium and force, showing that an increase in Calcium results in increased force.

Description

The cardiac muscle cells, also called fibers, branch and interdigitate. They are typically 40 μm long and about 10 μm in diameter; the fibers contain fibrils that are built up by the basic contractile units the sarcomeres (Fig. 12.1). Each sarcomere is bounded at the ends by Z-discs about 2 μm apart. The thin actin filaments about 1 μm long, are attached to the Z-discs, and extend towards the center of the sarcomere. They can

N. Westerhof et al., *Snapshots of Hemodynamics: An Aid for Clinical Research and Graduate Education*, DOI 10.1007/978-1-4419-6363-5_12,

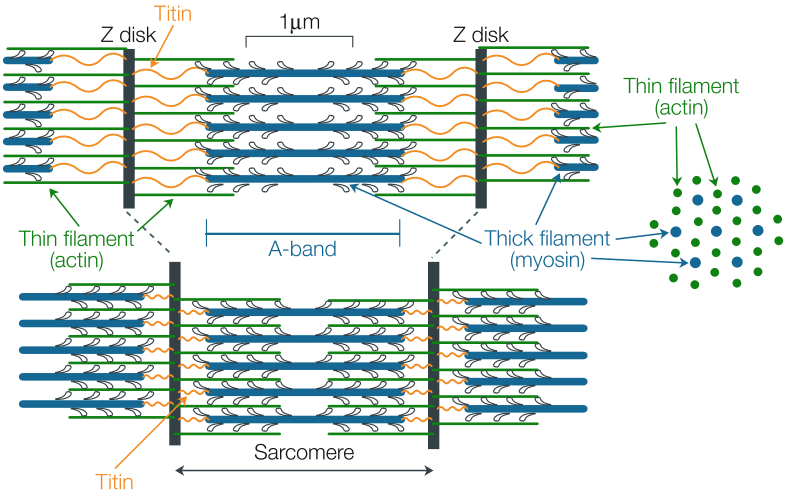


Fig. 12.1 The contractile unit of cardiac muscle is the sarcomere. The basic mechanical elements are presented here at two muscle lengths in the longitudinal direction. On the right hand side the cross section at overlap of thin and thick filaments is shown. Only one (instead of 6) titin molecule per half thick filament is shown for simplicity

either meet in the center, when sarcomere length is about 2.0 μm, overlap each other when sarcomere length is <2.0 μm, or not quite reach each other when sarcomere length >2.0 μm. Spanning the center of the sarcomere length are the thick myosin filaments, 1.6 μm long, which interdigitate with the thin filaments. They are connected to the Z-discs with a titin molecule, the third filament. The titin filament contains several spring sections, each with their own stiffness. The titin is the main determinant of muscle stiffness in diastole [1]. Changes in sarcomere length are achieved by sliding of thin between thick filaments; the sliding filament model. This sliding is caused by the action of the active, heavy meromyosin ATPase, i.e., ATP consuming unit, the 'cross-bridge'. The cross-bridges project sideways from the thick filaments, apart from a 'bare area' in the central zone of approximately 0.2 μm in length. The physiological range of sarcomere lengths (SL) is 1.6–2.3 μm, so that the number of cross-bridges in apposition to thin filaments is constant.

Calcium

Depolarization of the heart muscle cell membrane causes influx of calcium ions, Ca^{2+}, over the cell membrane. This increase in Ca causes a further and larger release of calcium ions from the Sarcoplasmatic Reticulum, SR, the so-called calcium-induced calcium release. Calcium reacts with myosin ATPase to produce a contraction.

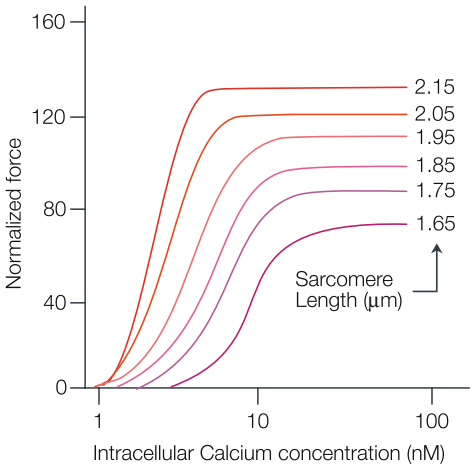


Fig. 12.2 Relation between intracellular calcium ion concentration and isometric force. Normalization is with respect to isometric force at a sarcomere length of 1.85 μm. Adapted from ref. [2], used by permission

The magnitude of the force of contraction produced when the sarcomere is prevented from shortening, i.e., isometric sarcomeres, is a function of sarcomere length and of intracellular calcium ion concentration, $[Ca]_i$.

The interrelationships between this isometric force, F_0, with sarcomere length, SL, and $[Ca]_i$ are sigmoidal (Fig. 12.2). On the up-sloping part of this curve, an increase in $[Ca]_i$ resulting from increased Ca^{2+} release, causes an increase in F_0, called an increase in contractility, or positive inotropic effect. This must be distinguished from an increase of F_0 due to increase in sarcomere length, which is due to increased sensitivity of the contractile filaments to Ca^{2+}. Increased sensitivity implies an upward and leftward shift of the F_0 – $[Ca]_i$ curve. This effect forms the basis of the Frank-Starling Law that states that 'the energy of contraction is a function of initial fiber length'. This effect is brought about by the presence of regulatory proteins on the thin filaments, namely the tropomyosin and the troponin complex. Other proteins and factors also play a role, e.g., Titin and lattice spacing.

The curvilinear shapes of the F_0 versus SL (or length) vary with the level of $[Ca]_i$, as shown in the Figure in the box.

The Force-Length Relation

The force-length relation of cardiac muscle (see Figure in box) forms the basis of the ventricular pressure-volume relation. The relation between pressure and (local) tension can in principle be obtained by Laplace's law, but more sophisticated

approaches are advised. Many models have been proposed with varying success. The main problems are:

- *(Local) wall stress* can not be measured in the intact heart, so that verification of models is not yet possible [3]. Subendocardial shortening is larger than subepicardial shortening, but forces may or may not be different.
- *Cardiac geometry is complex*. Cylindrical or ellipsoidal heart models are only rough approximations of reality.
- *Relations between ventricular volume and (local) fiber length*, as well as between volume changes and changes in fiber length also suffer from heterogeneity and geometric complexity. The simplest approach is to assume that the heart is a cylinder, with the volume proportional to fiber length squared, or a sphere, with volume proportional to fiber length to the third power.
- *The force-length relation* of the muscle therefore only qualitatively relates to the pressure-volume relation of the heart.

The Force-Velocity Relation

Another basic property of cardiac muscle is that for larger force the velocity of shortening is smaller (Fig. 12.3). This inverse relation between force and velocity is called the force-velocity relation (*F-v* relation). *In vivo*, heart muscle shortens against a force F that is less than the isometric force, F_0; these forces (stresses) are also called 'loads'. The *F-v* relation can be described by a hyperbola with the Hill equation:

$$\left(F_0 - F\right)\cdot \mathrm{b} = \left(\mathrm{F} + \mathrm{a}\right)\cdot v$$

The maximal velocity, v_0, depends on the maximum velocity of ATP splitting by the myosin ATPase.

In Fig. 12.4, two sets of Force-velocity (*F-v*) relations are given. The *F-v* curves are hyperbolic except near F_0. The left hand side presents *F-v* relations for two

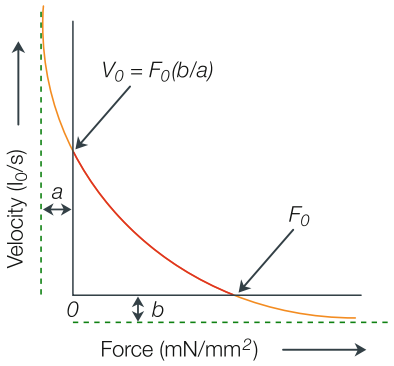


Fig. 12.3 Force-velocity relation of cardiac muscle. The hyperbola can be described by the Hill equation

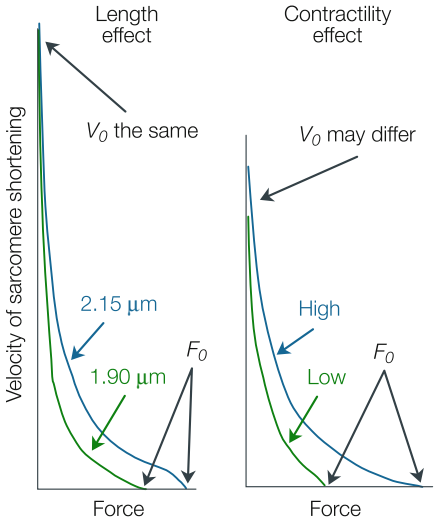


Fig. 12.4 Force-sarcomere shortening velocity relations are influenced by muscle length and contractility. Two lengths and two levels of contractility are depicted. Adapted from ref. [4], used by permission

sarcomere lengths, 1.90 and 2.15 μm. It shows that the increase in F_0 is not accompanied by an increase in the maximum velocity of sarcomere shortening, v_0, at zero force. This phenomenon depends on muscle length and disappears at short lengths. The right hand part of Fig. 12.4 shows the *F-v* relation for two contractility levels, or two levels of intracellular Calcium, $[Ca]_i$. With an increasing level of $[Ca]_i$ the v_0 increases until a saturation level is reached. In the rat this level is below the physiological $[Ca]_i$ so that v_0 will then not increase with increased contractility of increased intracellular Calcium. In the human there exists a range of Calcium concentrations where v_0 will increase.

The F-v *Relation and Pump Function*

F and *v* relate, through geometric transformations (Laplace) with pressure, e.g., pressure in the left ventricle, and (velocity to volume change) to flow. The *F-v* curves above refer to an instant in time within a contraction, whereas *CO* is a time-integrated quantity and not directly related. In other words, during the cardiac cycle the *F-v* relation is not constant but rises from one at the end of diastole, to one in systole and subsequently wanes down to the diastolic one again. This waxing and waning is not simply a 'parallel' shift because the time course of v_0 is more rapid

than that of F_0. A greater duration of contraction results in a higher Stroke Volume, *SV*, which is related to the average velocity. It is considered by some that the relevant *F*-*v* curve for the intact heart is the relationship between average *F* and average *v*, which is equivalent to the pump function graph relating mean ventricular pressure *LVP* to *CO* (see Chap. 14).

Experimental Problems

Studies on cardiac muscle are usually performed on isolated muscle strips, papillary muscle or trabeculae. These preparations are generally not perfused and therefore conditions have to be chosen such that a so-called anoxic core is avoided. These conditions are low temperature, low frequency, high P_{O2} of the superfusion fluid, etc. If *in vivo* conditions are desired, such as 37°C and physiological rate of contraction, a perfused preparation is required. Single skinned (permeable outer membrane) myocytes have been studied in terms of length and tension and calcium sensitivity, and very recently data on intact single myocytes have been reported [5].

Isolated cardiac muscle allows for studies of basic phenomena, such as tension development, calcium handling, effects of drugs, disease, etc. The advantage is that the muscle can be studied without the confounding effects of changes in cardiac loading. The disadvantage is that conditions are not physiological.

Determination of maximal isometric force requires that one stretches the preparation during contraction to prevent the sarcomeres from shortening because of compliant attachments of the preparation to the apparatus. This requires feedback control of the stretching apparatus keeping sarcomere length constant. The, average, sarcomere length can be derived from light diffraction provided the preparation is sufficiently thin. The method is used successfully in trabeculae, which are fine muscle bundles from the inside of the heart cavity, usually taken from the right ventricle.

In most cell cultures cell shortening is used as a measure of function. Unfortunately the shortening depends on the adherence of the cells to the substrate, and this adherence is not known. Also the amount of shortening cannot be related to the force.

Nomenclature Problems

Another term for v_0, used in the past was v_{max}, but this is now avoided because of erroneous attempts to calculate it in intact hearts. Traditionally, isolated muscle experiments were arranged so that the force was constant during systole and early relaxation, whereas in life, force decreases during systole and falls to about zero in early relaxation (before diastolic lengthening). This constant force during systole

and early relaxation was called ‘afterload’, a term which is clearly inappropriate to use in the intact heart. Before it was possible to measure sarcomere length throughout an experiment, the muscle was hung vertically and its initial length was set with variable weights; these weights were called ‘preloads’. This term is no longer appropriate because the fundamental independent variable, sarcomere length, can now be measured. It is unwise to apply terms derived from cardiac muscle mechanical studies, which are one-dimensional, to the intact heart, which is three-dimensional.

Limitations of the Sliding Filament Model

Students of cardiac muscle have traditionally tried to relate their findings to thinking arising from skeletal muscle studies, and the latter has been dominated by the idea that the cross-bridges attach mechanically to the thin filaments. Herzog et al. review one of the phenomena that are not compatible with the theory that the cross-bridges attach mechanically to the thin filaments [6]. Liu and Pollack provide evidence that filaments slide in steps of integers of 2.7 nm [7], and Kishino and Yanagida [8] show myosin heads alone, attached to glass can exert full ATP-dependent force. Finally Holohan and Marston [9] show that immobilized myosin in a motility assay can induce full bead-tailed actin filament force-velocity characteristics, when an electromagnetic field is applied in the presence of ATP.

Currently there is no sign of such critiques in the cardiac muscle literature, although it was shown in cardiac muscle that myosin binding can switch on actin filaments in rigor conditions but it does not contribute significantly under physiological conditions. The physiological mechanism of co-operative Ca^{2+} regulation of cardiac contractility must therefore be intrinsic to the thin filaments [10].

Rigor is a pathological condition characterized by cross-bridge attachment to filaments caused by ATP depletion. Physiological contraction takes place in the presence of ATP, which ensures absence of cross-bridge attachment to thin filaments and catalyses contraction through an electromagnetic or electrostatic mechanism.

Physiological and Clinical Relevance

The maintenance of the circulation requires that the heart muscles have a sufficiently high *F-v* relation and duration of active state. Failure of these, as for example due to reduced contractility, will lead to clinical heart failure. Clinical heart failure can also occur due to damage of part of the heart, e.g. myocardial infarction. Stimulation of contractility may be necessary in the treatment of acute heart failure, using positively inotropic drugs. Unfortunately, this seemingly logical treatment is contra-indicated in chronic heart failure because it causes earlier death, presumably because increased oxygen is required by the cardiac muscle sometimes

in excess of possible supply rate; positively inotropic drugs mostly work by increasing $[Ca]_i$ which can also cause (possibly fatal) arrhythmia. However, an increase of Ca-sensitivity seems an option [11].

References

1. Fukuda N, Granzier HL. Titin/connectin-based modulation of the Frank-Starling mechanism of the heart. *J Muscle Res Cell Motil* 2005;26:319–323. Review
2. Kentish JC, ter Keurs HEDJ, Ricciardi L, Bucx JJJ, Noble MIM. Cardiac muscle mechanics: comparison between the sarcomere length-force relations of intact and skinned trabeculae from rat right ventricle. *Circ Res* 1986;58:755–768.
3. Huisman RM, Elzinga G, Westerhof N, Sipkema P. Comparison of models used to calculate left ventricular wall force. *Cardiovasc Res* 1980;14:142–153.
4. Daniels M, Noble MIM, ter Keurs HEDJ, Wohlfart B. Force and velocity of sarcomere shortening in rat cardiac muscle: relationship of force, sarcomere length, Ca^{++} and time. *J Physiol* 1984;355:367–381.
5. van der Velden J, Klein LJ, van der Bijl M, Huybregts MA, Stooker W, Witkop J, Eijsman L, Visser CA, Visser FC, Stienen GJ. Isometric tension development and its calcium sensitivity in skinned myocyte-sized preparations from different regions of the human heart. *Cardiovasc Res* 1999;42:706–719.
6. Herzog W, Lee EJ, Rassier DE. Residual force enhancement in skeletal muscle. *J Physiol* 2007;578:613–615.
7. Liu X, Pollack GH. Stepwise sliding of single actin and Myosin filaments. *Biophys J* 2004;86:353–358.
8. Kishino A, Yanagida T. Force measurements by micromanipulation of a single actin filament by glass needles. *Nature* 1988;334(6177):74–76.
9. Holohan SJ, Marston SB. Force-velocity relationship of single actin filament interacting with immobilised myosin measured by electromagnetic technique. *IEEE Proc Nanobiotechnol* 2005;152:113–120.
10. Sun YB, Lou F, Irving M. Calcium- and myosin-dependent changes in troponin structure during activation of heart muscle. *J Physiol* 2009;587(Pt 1):155–163.
11. Drake-Holland AJ, Lee JA, Hynd J, Clarke SB, Noble MI. Beneficial effect of the calcium-sensitizing drug EMD 57033 in a canine model of dilated heart failure. *Clin Sci (Lond)* 1997;93:213–218.