CARDIAC MUSCLE MECHANICS

EFFECTS OF EXERCISE AND CONCENTRIC OR ECCENTRIC HYPERTROPHY

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DESCRIPTION

The cardiac muscle cells, or fibers, branch and interdigitate. They are typically 40 ì m long and about 10 ì m in diameter. The fibers contain fibrils that are built up by the basic contractile unit the sarcomere. Each sarcomere (Fig. 1) is bounded at the ends by Z-discs about 2 ì m apart. The thin actin filaments are about 1 ì m long, are attached to the Z-discs, and extend towards the center of the sarcomere. They can either meet in the center, when sarcomere length (SL) is short, i.e., about 2 ì m, overlap each other when SL < 2 ì m, or not quite reach each other when SL > 2 ì m. Spanning the center of the sarcomere length are the thick myosin filaments, 1.6 ì m long, which interdigitate with the thin filaments. They are connected to the Z-discs with a titin molecule. Changes in sarcomere length are achieved by sliding of thin between thick filaments. This sliding is caused by the action of the active, heavy meromyosin ATPase, i.e., ATP consuming unit, the 'cross-bridges'. The cross bridges project sideways from the thick filaments, apart from a 'bare area' in the central zone of approximately 0.2 ì m length. The physiological range of sarcomere lengths is 1.6 - 2.3 ì m.

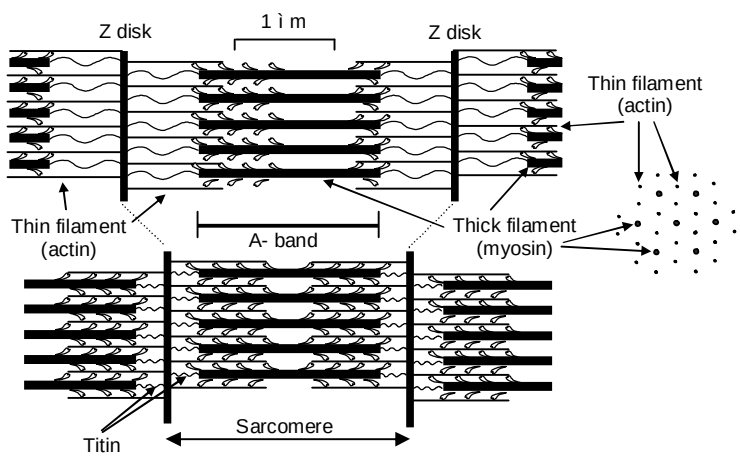

Figure 1. The sarcomere and the basic mechanical elements.

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 Sarcoplasmic Reticulum, SR, the so called calcium induced calcium release. Calcium reacts with myosin ATPase to produce a contraction. 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 the $[Ca]_i$ are shown in Fig. 2.

The relationship between F_0 and $[Ca]_i$ at any one sarcomere length is sigmoid. On the upsloping 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.

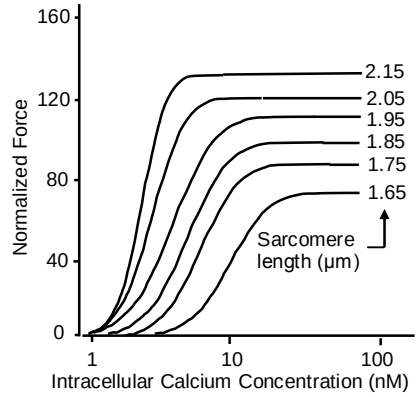

Figure 2. Isometric force as a function of intracellular calcium ion concentration for various sarcomere lengths.

The curvilinear shapes of the F_0 versus SL curves for one $[Ca]_i$ vary with the given level of $[Ca]_i$, as shown in Fig. 3.

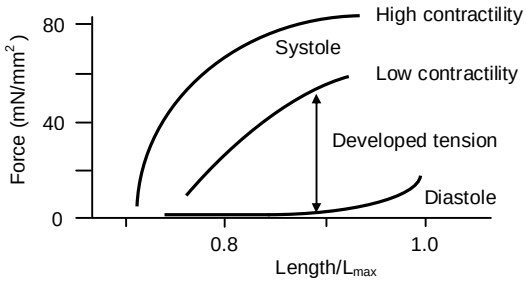

Figure 3. Isometric force as a function of sarcomere length for various levels of intracellular calcium ion concentration.

THE FORCE - LENGTH RELATION

The force-length relation of cardiac muscle (Fig. 3) 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 cannot be measured in the intact heart, so that verification of models is not yet possible (Huisman et al., 1980). Subendocardial shortening is larger than subepicardial shortening, but forces may or may not be different.
- cardiac geometry is complex. Cylindrical or ellipsoidal models are only approximations.
- 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 the volume proportional to fiber length to the third

power. So, qualitatively, the force-length relation of the muscle relates to the pressure-volume relation of the heart.

THE VARYING ELASTANCE MODEL

Pressure-volume loops (Fig. 4) can be analyzed by marking time points on the loop. When different loops are obtained and the times indicated, we can connect points with the same times, and construct isochrones (Fig. 4 right). The slopes of the isochrones can be determined, and the slope of an isochrone is the elastance at that moment in time. The fact that the elastance varies with time, leads to the concept of time-varying elastance, E(t). This means that during each cardiac cycle the elastance increases from its diastolic value E_{min} to its systolic value E_{max} and then returns to its diastolic value again.

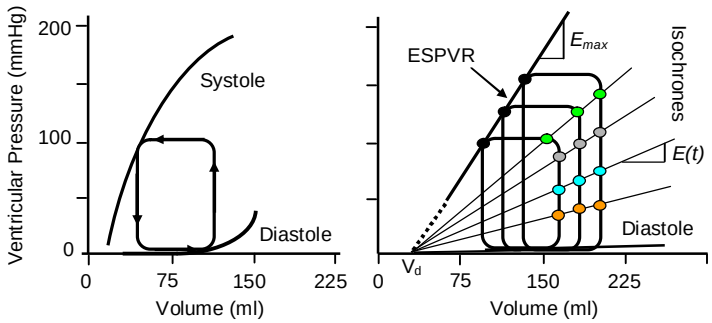

Figure 4. Pressure - volume loops and time - varying elastance E(t).

CONCENTRIC AND ECCENTRIC HYPERTROPHY

Concentric hypertrophy implies an increased wall thickness with similar lumen volume. This means a stiffer ventricle in diastole and in systole, i.e., both E_{max} and E_{min} are increased (Fig. 5 left). The increase in elastance E_{max} does not necessarily imply increased contractility of the contractile apparatus of the muscle but is mainly a result of more sarcomeres connected in parallel, a thicker fiber and increased wall thickness. Concentric hypertrophy leads to increased diastolic filling pressure and higher systolic pressure but similar Stroke Volume (blood volume ejected in every cardiac cycle).

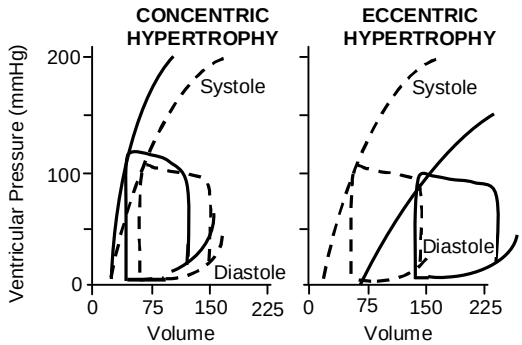

Figure 5. Pressure - volume loops in concentric (left) and eccentric (right) hypertrophy.

In eccentric hypertrophy the ventricular lumen volume is greatly increased, with more sarcomeres connected in series, and longer cells, while the wall thickness may

be unchanged or somewhat increased. The shift of the pressure-volume relation to larger volumes (Fig. 5 right) in eccentric hypertrophy implies, by virtue of the law of Laplace, that wall forces are increased.

THE PUMP FUNCTION GRAPH AND EXERCISE

The pump function graph (Fig. 6) describes the pump function of the heart for constant diastolic filling, heart rate and contractility. The pump function graph teaches us that the heart is neither a flow source nor a pressure source. The flow source was the assumed heart model used up until the 1960's. Contractility at constant loading pressure does not seem to affect significantly the Cardiac Output. Heart rate and diastolic filling contribute importantly to Cardiac Output.

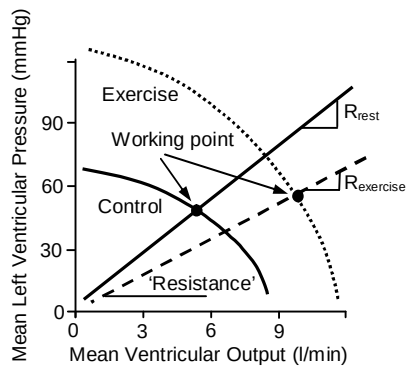

Figure 6. The pump function graph in moderate exercise.

Figure 6 shows what happens in moderate exercise. Due to the increase in heart rate, and the (small) increase in filling and the increase in contractility, the pump function graph shifts outward, with a small rotation as well. The increase in heart rate forms the major contribution to the outward shift of the pump function graph. The systemic vascular resistance is decreased. The overall result is an increase in Cardiac Output with only a small increase in pressure.

CONCENTRIC HYPERTROPHY AND HEART FAILURE

Figure 7 shows the pump function graph in concentric hypertrophy and failure. In hypertrophy a flow source is approached while in failure the heart acts more like a pressure source (Elzinga and Westerhof, 1985). These changes in pump function have an effect on reflected waves of pressure and flow returning from the periphery.

A flow source means that the flow is not affected by the reflected waves of flow but pressure is completely reflected and thus augmented, 'closed end reflection'. Inversely, a pressure source implies that pressure is not affected by the reflected waves of pressure but the flow is fully reflected and thus is decreased by the reflection.

Therefore in hypertrophy, the backward pressure wave is reflected at the heart (flow source) and is added to the forward pressure wave resulting in augmentation of the wave. The reflection and extra augmentation of pressure in hypertrophy shows the contribution of the hypertrophied heart to hypertension. In failure, when the heart approaches a pressure source the reflected flow wave affects the forward flow wave negatively resulting in a decrease in Cardiac Output.

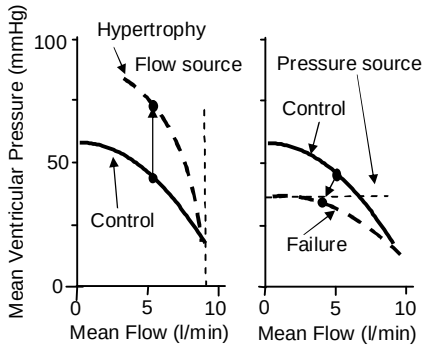

Figure 7. The pump function graph in concentric hypertrophy (left) and failure (right).

Understanding of the contribution of the heart to reflected pressure and flow waves may assist in giving suggestions for possible therapy in heart failure (Westerhof and O'Rourke, 1995).

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