Heart failure and diastolic dysfunction

The heart and a balloon have more in common than meets the eye. Like the heart, a balloon is a flexible bag that can be inflated and emptied. Using this example one can readily understand basic heart function and several reasons for failure. Consider a balloon that is filled with air for 10 seconds and then emptied over 5 seconds. The total time of balloon function or “balloon cycle” (filling and ejection) is 20 seconds. Now let us imagine that the balloon cycle time of filling (“balloon filling”) is reduced to 5 seconds; we have less time available to fill the balloon with air and hence the balloon will only be partially inflated. Thus a “balloon failure” condition appears. The ability to fill a balloon with air is also dependent on the properties of the material that it is made of. The thicker and more inflexible the material (“stiffer”), the harder it will be to inflate (“balloon stiffness”), and a greater force or “stress”\(^2\) must be applied to achieve the same results. This is analogous to a condition where the walls of the heart become thicker and/or increase in stiffness (“heart stiffness”) and it gets harder for the heart to fill. Again the “failure” condition ensues. Importantly these processes can occur without changing the balloon filling time. Since both types of balloon failure described (balloon filling time and balloon stiffness) occur during the filling of the balloon we term it “balloon filling dysfunction”\(^3\).

The heart is not that different from a balloon, and a chronic perturbation of the heart cycle—“cardiac cycle”—is clinically classified as a cardiac disease or heart failure (HF) condition. Just in Europe over 15 million people are diagnosed with HF and the number continues to rapidly increase, representing a major cause of hospitalization and death. About half of the HF patient population have a heart that is unable to properly relax and distend (“heart failure”). Classically, a “systolic failure” condition appears. The ability to fill the heart relaxes will it be able to fill and distend. During the filling phase alterations to the macro- (e.g. wall thickness, chamber geometry) or micro-properties (e.g. sarcomere stiffness and collagen deposition) of the tissue will change the heart’s diastolic stiffness, stress and “elasticity”\(^4\). It takes a healthy heart ~0.1 seconds to completely relax (isovolumetric relaxation); and another ~0.4 seconds to fill and distend to a total of 120 ml of blood (filling phase) before “isometric contraction”\(^5\) takes place. Together these processes of relaxation and filling are known as the diastolic phase of heart function. Hence, perturbations or disruption to these processes lead to “DIASTOLIC DYSFUNCTION”\(^6\).

In this thesis, I have studied the mechanisms that affect myocardial relaxation and contribute to “DIASTOLIC DYSFUNCTION” of the heart. These include changes of “SARCOTREM LENGTH”\(^7\), “Ca\(^{2+}\)”\(^8\), and “MYOCARDIAL ENERGETICS”\(^9\). A heart completely filled with blood is able to generate more pressure during contraction than a half full heart. This is because more of the heart muscle is engaged to contract and eject blood. This provides the basic framework work for what is known as the “FRANK-STARLING LAW”\(^10\). This Law relates the extent of heart filling (known as “length-dependency”) with the amount of pressure generated during contraction. From these findings comes the universal principle that the amount of blood ejected from the heart must equal the amount of blood acquired during filling. The force for heart contraction is generated by the unitary building blocks of the heart muscle, which are known as “sarcomeres”. Sarcomeres increase in length during filling which increases contractility of the heart cells. The term “SARCOMERE LENGTH-DEPENDENT ACTIVATION” describes the FRANK-STARLING LAW at the single cell level. Disruption of sarcomere lengthening function can result in improper filling of the heart (DIASTOLIC DYSFUNCTION) which affects the heart’s ability to generate force and limits the amount of blood pumped to the body. If it takes the healthy heart ~0.5 second to entirely fill to a total of 120 ml blood during the diastolic phase, it will take another ~0.3 seconds to contract and eject ~70 ml of that blood to maintain a steady flow to the body. The heart never completely empties as residual volume is present at all times. In HF patients the FRANK-STARLING RESERVE is limited, which is detrimental to maintaining a steady blood perfusion to the body (cardiac output). Exploring deeper into the sarcomere reveals the myofilament proteins. These come in two types: thin- (actin-containing) and thick- (myosin-containing). Molecular interactions between the actin and myosin proteins (“cross-bridges”) generates the contraction of the sarcomere. Cross-bridges activation is regulated by Ca\(^{2+}\) and the MYOCARDIAL ENERGY RESERVE that generates ATP from ADP. As it will be seen, it is the interplay of SARCOTREM LENGTH, Ca\(^{2+}\), and MYOCARDIAL ENERGETICS that regulate the diastolic function of the heart. When any, or several, of these mechanisms fail DIASTOLIC DYSFUNCTION follows.

Cross-bridging the gap between energetics, Ca\(^{2+}\), sarcomere length and diastolic dysfunction