1 Anatomy and Physiology of the Heart

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1.1 Introduction

1.1.1 *Overview*

This chapter outlines the anatomy, physiology, and pathophysiology of the heart, linking the micro- and macroscopic structure of cardiac muscle fiber to its function during contraction and relaxation. The properties of cardiac muscle cells and the process of contraction at a cellular level are also described. The macroscopic structure of the myocardium is explained as one muscle band wound into a double twist. We then present the intrinsic anatomy of the heart in terms of the intrinsically optimum ellipsoidal shape of the left ventricle that maximizes its contractility, i.e., the development of the myocardial wall stress, which in turn generates the intraventricular pressure during the isovolumic contraction phase leading to left ventricle (LV) ejection.

We then describe ventricular dynamics in terms of the twisting and untwisting of the myocardial fibers. This constitutes an important mechanism

of LV contraction. We have elaborated on this mechanism by presenting the analysis of a thick-walled cylindrical model of the LV during the isovolumic contraction phase. We have shown how the LV contraction is caused by LV twisting due to the contractile stresses developed in its helically wound myocardial fibers, which become less helical as contraction proceeds.

Coronary artery disease and its effect on left ventricular contractility are described. Myocardial perfusion and causes of disease are then discussed. We have shown how myocardial infarcted segments can be detected by means of echocardiographic texture analysis as highly reflectile segments compared to normal myocardial segments. The end result of myocardial infarction is remodeling of the heart and left ventricle. We have presented a quantitative measure of this remodeling phenomenon in terms of the change in the sphericity index from end-diastole to end-systole.

Together, all of this presents quantifiable and clinically applicable measures of heart anatomy and physiology.

1.1.2 *Heart anatomy and physiology*

Anatomy of the heart: The heart and blood vessels are part of the cardiovascular system. The heart is a four-chambered muscular pump with four valves. Studies on the structure of heart are at different levels: cellular level or histological studies, and muscle level. The cellular level explores the myocyte structure, alignment and ionic pathways or overall fiber architecture. The muscle level gives clues on how the heart functions, and hence is an indication of where and how things go wrong in heart diseases or disorders. Physiology of the heart: The heart is a muscular pump that supplies blood to the body. This goal is achieved by the electrical excitation process, caused by electrical signals generated by the sinoatrial node. The signals then travel through the electrical conduction system of the heart, through the right atrium to the atrioventricular node, along the Bundle of His and through bundle branches to cause contraction of the heart muscle. This signal first stimulates contraction the right and left atria, and then the right and left ventricles, producing sequential ventricular emptying and filling.

The physiological sequence of ventricular function: The isovolumic contraction phase develops pre-ejection tension; and slow periods for

filling. The LV volume decreases rapidly early in systole and slowly thereafter, corresponding to the rapid early acceleration in the flow curve. The LV volume then increases rapidly in early filling and more slowly during late filling. This process relates LV function to the underlying functional muscular anatomy that causes the ventricular directional motions of (i) narrowing, shortening, and twisting, during contraction and (ii) lengthening, widening, and untwisting during filling. Pathophysiology of the heart: Heart (or cardiac) failure is the pathophysiological state in which the heart is unable to pump blood at a rate commensurate with the requirements of the metabolizing tissues, or can do so only from an evaluated filling pressure. Heart failure may be caused by myocardial ischemia, myocardial infarction, myocardial remodeling, or some combination of these. All these topics will be discussed in this chapter.

1.2 Anatomy of the Heart

The structure of the heart and its relation to myocardial function is still a challenging problem. The heart is the prime mover of blood into the circulatory system. By periodic stimulation of its muscles, it contracts periodically and pumps blood throughout the body.

The heart is located in the left center of the chest. The structure of the heart and course of blood through the heart chambers are shown in Figure 1.

Deoxygenated blood returning from the body enters the heart from the superior and inferior vena cava. The superior vena cava (SVC) carries blood from the head and other parts of the body above the heart, while the inferior vena cava (IVC) carries blood from the lower parts of the body. They merge as they enter the right atrium (RA).

Blood in the right atrium (RA) flows into the right ventricle (RV) through the tricuspid valve, whose function is to allow blood to flow into the right ventricle but prevent its return when the right ventricle contracts. Then, the right ventricular contraction pumps blood out through the pulmonary valve into the pulmonary artery, which carries blood to the lungs. The blood pumped to the lungs returns to the upper chamber on the left side of the heart, namely the left atrium, through the pulmonary veins.

From the left atrium, blood flows into the left ventricle through the mitral valve. Then, the left atrium also contracts to pump more blood into

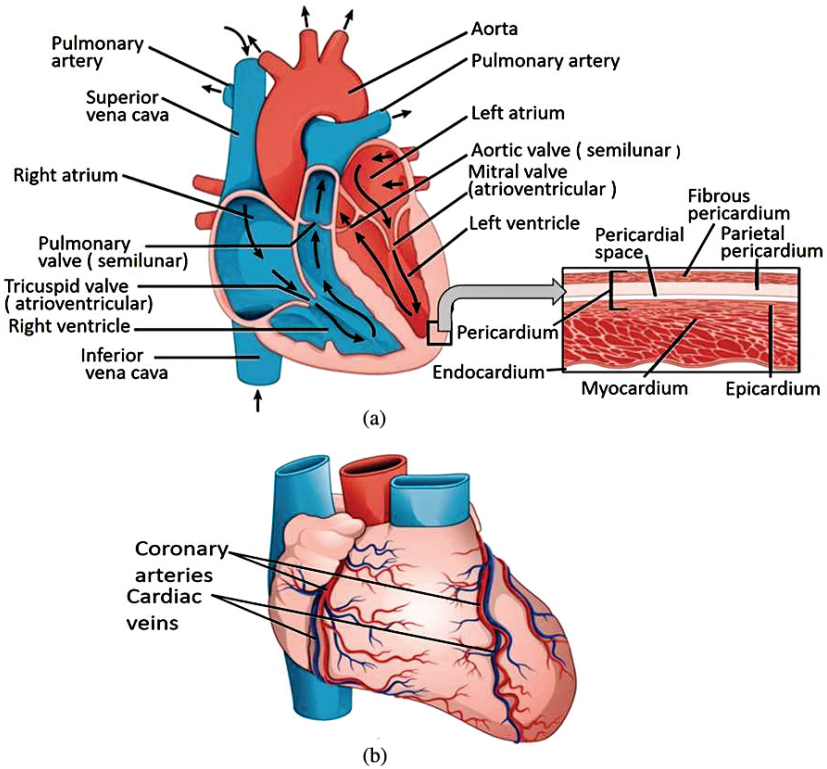


Figure 1. Human heart (a) The heart is primarily made up of a thick muscle layer, called myocardium, surrounded by membranes. One-way valves separate the four chambers. (b) Blood vessels of the coronary system, including the coronary arteries and veins, keep the heart muscles oxygenated [1].
Source: Download free at https://cnx.org/contents/GFy_h8cu@10.120:ZdC2EWuz@5/Mammalian-Heart-and-Blood-Vess.

the left ventricle. The mitral valve prevents blood from reentering the left atrium when the left ventricle contracts. Contraction of the left ventricle pumps blood out of the heart through the aortic valve into the aorta, and then into the upper circulatory system of the head, arms, and upper thorax. The aorta descends through the lower part of the thorax and abdomen, where the arteries branch off carrying blood to the liver, spleen, intestine, kidneys, gonads, and legs. After passing through the smaller arteries and then through the capillaries, the blood returns to the heart through the veins.

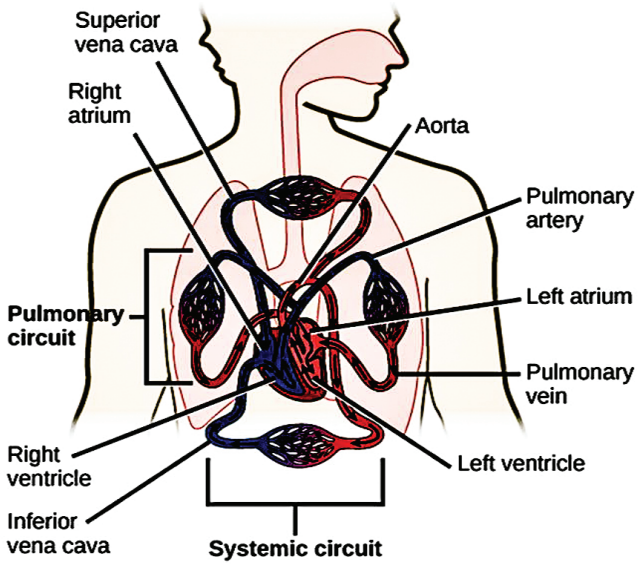


Figure 2. Circulatory System. The mammalian circulatory system is divided into three circuits: the systemic circuit, the pulmonary circuit, and the coronary circuit. Blood is pumped from veins of the systemic circuit into the right atrium of the heart, then into the right ventricle. Blood then enters the pulmonary circuit and is oxygenated by the lungs. From the pulmonary circuit, blood re-enters the heart through the left atrium. From the left ventricle, blood re-enters the systemic circuit through the aorta and is distributed to the rest of the body [1].
Source: Download free at https://cnx.org/contents/GFy_h8cu@10.120:ZdC2EWuz@5/Mammalian-Heart-and-Blood-Vess.

Figure 2 illustrates the circulatory system. Branching off the aorta as it leaves the heart is a pair of coronary arteries: Left main and Right coronary artery (RCA); the former bifurcates in the Left anterior descending (LAD) and the Left circumflex (LCX). The coronary arteries supply blood to the heart and are considered part of the systemic circulation. After passing through capillaries in the heart, the blood in the coronary circuit returns to the right side of the heart through veins that empty directly into the right atrium. Heart attacks are caused by clots in the coronary arteries, depriving the heart muscle of oxygen. The function of the heart chambers is summarized in Table 1.

Table 1. Functions of the heart chambers.

Chamber	Function
Right atrium	Receives deoxygenated blood from the superior and inferior vena cava and passes the blood through the tricuspid valve to the right ventricle
Right ventricle	Receives deoxygenated blood from the right atrium and pumps the blood through the pulmonary valve into the pulmonary trunk
Left atrium	Receives oxygenated blood from the pulmonary veins and passes the blood through mitral valve into the left ventricle
Left ventricle	Receives oxygenated blood from the left atrium and pumps this blood through the aortic valve into the aorta

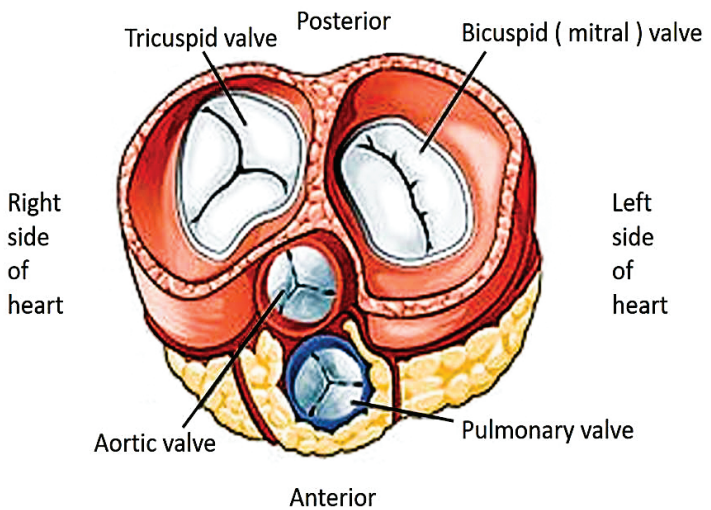


Figure 3. Anatomy of the heart valves [2].
Source: Download free from Anatomy & Physiology, Connexions Web site. http://cnx.org/content/col11496/1.6

The heart valves play an important role in directing blood flow through the heart chambers. Figure 1(a) illustrates the function of the heart valves and Figure 3 illustrates their anatomy.

The mitral and tricuspid valves are opened in order to fill the ventricles with blood, when the blood pressure is low and velocity is small. The mitral and tricuspid valves are attached to the papillary muscles, which contract in systole, pulling down the valves to generate systolic pressure rapidly, and preventing the valves from danger of inversion into the

atrium. The relatively smaller aortic and pulmonary valves (as seen in Figure 3) open in ventricular systole to pump blood out of the ventricles at high velocity. These valves do not have chordae tendineae to hold them in place. Instead, the cusps of the semilunar valves are cup shaped to use the blood's pressure to snap shut, and prevent blood regurgitating through them into the ventricles. Their intrinsic anatomy facilitates their efficient function, and contributes to the heart's physiological function. It may be worthwhile to mention that mechanical heart valves lack this anatomy, and hence cannot function as efficiently as tissue heart valves.

1.2.1 *Function and anatomy of the coronary arteries*

Coronary arteries supply blood to the heart muscle (namely, the myocardium), which needs oxygen-rich blood for its function. Myocardial contraction enables the blood to move inside the heart chambers, and the left ventricle to provide cardiac output. The coronary arteries wrap around the outside of the heart, and their small branches penetrate into the myocardium to bring it blood and carry away the oxygen-depleted blood (Figure 4).

There are three coronary arteries — LAD, LCX, and RCA. The LAD and LCX are branches of the left main coronary artery. The RCA and left

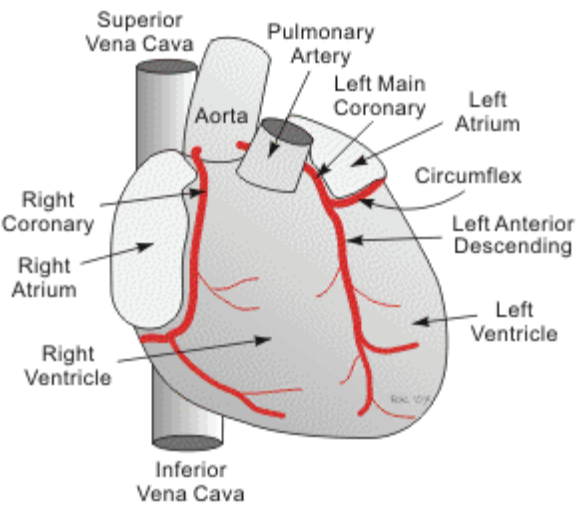


Figure 4. Coronary Vasculature. Adopted from Anatomy and Function of the Coronary Arteries, Johns Hopkins Health Library (http://www.hopkinsmedicine.org/healthlibrary/conditions/cardiovascular_diseases/anatomy and function of the coronary arteries 85,P0019).

main coronary artery arise from small bulbous dilatations of the aorta called sinuses of Valsalva or coronary cusps. The coronary arteries run on the outside of the heart (epicardially) and combine to supply the heart myocardium.

When an artery is blocked, a myocardial infarct (heart attack) can occur, where the myocardium that was supplied by that artery becomes ischemic and subsequently infarcted and is unable to contract. Sometimes, when the blockage is long-standing, collateral arteries can arise from the other coronary arteries to supply the myocardium that is ischemic. This is the heart's own attempt to save itself from a potential myocardial infarct. In general, the myocardium of the left ventricle is the muscle that is of utmost importance, because it is the left ventricle that pumps blood to most of the body. The right ventricle only pumps blood to the lungs, and is considered less important in the pathogenesis of ischemic heart disease.

Simplistically (and with several exceptions), the top of the left ventricle is supplied by the LAD, its side by the LCX and its bottom by the RCA. The coronary arteries are themselves subdivided into proximal, mid, and distal portions. Hence, one would refer to, say, the proximal LAD or the mid LCX or the distal RCA. Branches of the LAD are called diagonal branches; branches of the LCX, obtuse marginal (OM) branches; and branches of the RCA, posterior descending (PDA) and posterior lateral arteries (PLA).

1.2.2 *Myocardial histology and cellular structure*

To understand how the myocardium functions, we first need to understand the muscle structure at a basic level.

Each myocyte is bounded by a complex cell membrane, the sarcolemma (sarco = flesh, lemma = thick husk), and is filled with rod-like bundles of myofibrils (Figure 5), which are the contractile elements. The sarcolemma of the myocyte invaginates to form an extensive tubular network (the T tubules). The nucleus contains almost all of the cell's genetic information, and is often centrally located. Interspersed between the myofibrils and immediately beneath the sarcolemma are many mitochondria, the main function of which is to generate energy in the form of adenosine triphosphate (ATP) needed to maintain the heart's contractile

function and the associated transmembrane ion gradients. Of the other organelles, the sarcoplasmic reticulum (SR) is the most important.

The major function of myocardial muscle cells is to execute the cardiac contraction–relaxation cycle. The contractile proteins of the heart lie within these myocytes. About half of each ventricular cell is occupied by myofibers and about 25–33% by mitochondria (Table 2).

The contractile myocytes constitute more than half of the heart's weight. They are approximately cylindrical in shape. In the atrium they are quite small, being less than 10 μm in diameter and about 20 μm in length. In the ventricle, they are large, about 17–25 μm in diameter and 60–140 μm in length.

A myofiber is a group of myocytes (Figure 5) held together by the surrounding collagen connective tissue, the latter being the major component of the extracellular matrix. Further, strands of collagen connect myofibers to each other.

Cardiac fibers (myofiber) consist of elongated cells with central nuclei and branching attachments. About 75% of the total volume of the myocardium is composed of cardiac myocytes, representing about one-third of all cells in the myocardium. They are smaller than skeletal muscle fibers, measuring around 110 μm long and 15 μm wide.

When examined under the light microscope, the atrial and ventricular myocytes have cross-striations and are branched. Each myocyte is bounded by a complex cell membrane, the sarcolemma, and is filled with rod-like bundles of myofibrils. The myofibrils are the contractile elements; the sarcolemma forms an extensive tubular network; the nucleus contains almost all of the cell's genetic information.

Proper function of the myocardium requires highly controlled regulation of the calcium concentration within the cardiac myocytes. Contractions are initiated by calcium ions, discharged by the sarcoplasmic reticulum in response to electrical stimulation. The major molecules involved in contraction are the proteins actin and myosin (Figure 6). The thin actin filaments and the thick myosin filament contract by sliding over each other. This is commonly called "cross-bridge cycling". The relationship between electrical stimulation and intracellular calcium release is called excitation–contraction coupling. The calcium cycle is integral to the regulation of contractility of the myocardium.

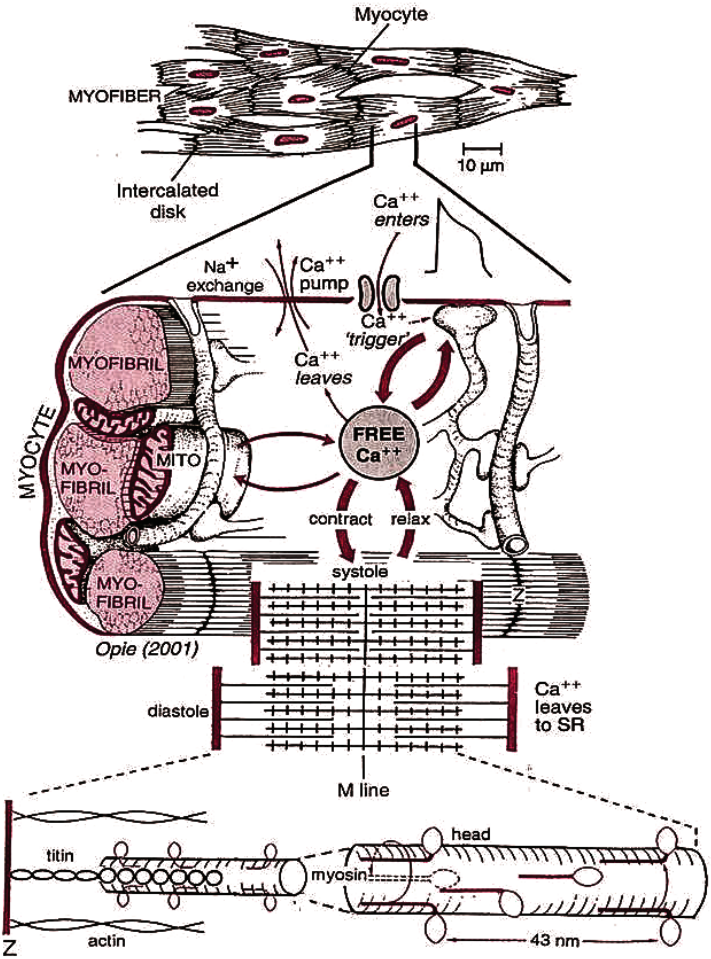


Figure 5. The crux of the contractile process lies in the changing concentration of Ca^{2+} ions in the myocardial cytosol. Ca^{2+} ions are schematically shown as entering through the calcium channel that opens in response to the wave of depolarization that travels along the sarcolemma. These Ca^{2+} ions trigger the release of more calcium from the sarcomplasmic reticulum (SR) and thereby initiate a contraction–relaxation cycle. Eventually, the small amount of calcium that has entered the cell leaves predominatly through an Na^{+}/Ca^{2+} exchanger with a lesser role for the sarcolemma calcium pump. The varying actin–myosin overlap is shown for (i) systole, when calcium ions arrive, and (ii) diastole, when calcium ions leave. The myosin heads, attached to the thick filaments, interact with the thin actin filaments. The upper panel shows the difference between the myocardial cell or myocyte and the myofiber, composed of many myocytes. MITO = mitochondria [4].

Table 2. Characteristics of cardiac cells, organelles, and contractile proteins.

	Microanatomy of heart cells		
Characteristics	Ventricular myocyte	Atrial myocyte	Purkinje cells
Shape	Long and narrow	Elliptical	Long and broad
Length, μm	60–140	About 20	150–200
Diameter, μm	About 20	5–6	35–40
Volume, μm^3	15,000–45,000	About 500	135,000–250,000
T-tubules	Plentiful	Rare or none	Absent
Intercalated disc	Prominent end-to-end transmission	Side-to-side, as well as end-to-end transmission	Very prominent abundant gap junctions. Fast; end-to-end transmission
General appearance	Mitochondria and sarcomere very abundant. Rectangular branching bundles with little interstitial collagen	Bundles of atrial tissue separated by wide areas of collagen	Fewer sarcomeres, paler

The electrically induced mechanical contraction response in the cardiac muscle occurs via the sliding filament model of contraction. In the sliding filament model, myosin filaments slide along actin filaments to shorten or lengthen the muscle fiber for contraction and relaxation. The pathway of contraction can be described in the following steps: (1) An action potential, induced by the pacemaker cells in the sinoatrial (SA) and atrioventricular (AV) nodes, is conducted to the contractile cardiomyocytes through the gap junctions. (2) As the action potential travels between the sarcomeres, it activates the calcium channels in the T-tubules, resulting in an influx of calcium ions into the cardiomyocyte. (3) Calcium in the cytoplasm then binds to cardiac troponin-C, which moves the troponin complex away from the actin binding site. This removal of the troponin complex frees the actin to be bound by myosin and initiates contraction. (4) The myosin head binds to ATP and pulls the actin filaments toward the center of the sarcomere, contracting the muscle. (5) Intracellular calcium is then removed by

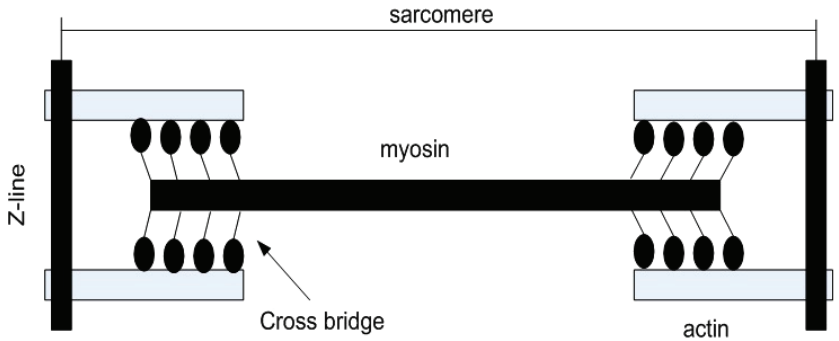


Figure 6. The actin and myosin filaments constituting the contractile components of the myocardial fibril [5].

the sarcoplasmic reticulum, dropping intracellular calcium concentration, returning the troponin complex to its inhibiting position on the active site of actin, and effectively ending contraction as the actin filaments return to their initial position, relaxing the muscle. The composition and function of each component of the ventricular cell are tabulated in Table 3.

1.2.3 *Macroscopic muscle structure*

A picture of the muscle structure on the macroscopic scale can be obtained by dissecting the heart. The established method used consists of (i) boiling the heart in water to soften the connective tissue, (ii) performing a blunt dissection of it, using figures, with the help of nontoothed forceps, scalpel, and scissors after removing the atrial, aorta, and pulmonary artery. This is the best way to identify the direction of the laminar pathways followed by the muscle bands.

1.2.3.1 *Helix phenomenon*

The cardiac helix form was described in the 1660s by Lower as having an apical vortex, in which the muscle fibers go from outside in, with a clockwise, and from inside out, in a counterclockwise, direction (as shown in

Table 3. Composition and function of ventricular cell.

Organelle	% of cell volume	Function
Myofibril	About 50–60	Interaction of thick and thin filaments during contraction cycle
Mitochondria	16 in neonate 33 in adult rat 23 in adult human	Provide adenosine triphosphate chiefly for contraction
T system	About 1	Transmission of electrical signal from sarcolemma to cell interior
Sarcoplasmic reticulum (SR)	33 in neonate 2 in adult	Takes up and releases Ca^{2+} during contraction cycle
Terminal cisternae of SR	0.33 in adult	Site of calcium storage and release
Rest of network of SR	Rest of volume	Site of calcium uptake en route to cisternae
Sarcolemma	Very low	Control of ionic gradients; channels for ions (action potential); maintenance of cell integrity; receptors for drugs and hormones
Nucleus	About 5	Protein synthesis
Lysosomes	Very low	Intracellular digestion and proteolysis
Sarcoplasm	About 12 in adult rat 18 in humans	Provides cytosol in which rise and fall of ionized calcium occur; contains other ions and small molecules

Figure 7). In fact, nature contains many pathways of clockwise and counterclockwise spirals that are called reciprocal spirals, as seen in flower bud, sea shell, horns, phosphate ions, and DNA.

The external inspection of the heart apex, proceeding toward the base, shows a clockwise and counterclockwise spiral formation with loops going from without to within and from within to without (Figure 8). This constitutes an intrinsically optimal design of the heart's helically wound myocardial fibers structure that facilitates its efficient contraction and rise in left ventricular pressure during isovolumic contractile phase, as explained in the following section.

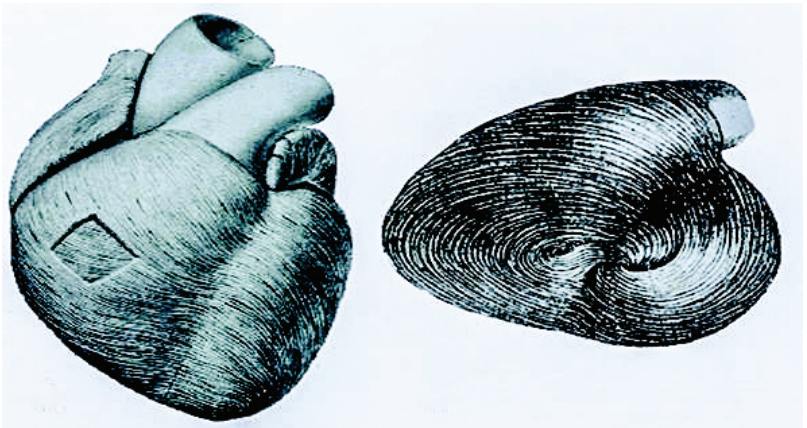


Figure 7. The helical heart is seen in (a), and the apical view in (b) defines the clockwise and counterclockwise spirals [6].

1.2.4 *Optimal ellipsoidal shape of the left ventricle*

We have been talking about the heart anatomy. A characteristic anatomy of the heart is its ellipsoidal shape. In particular, the optimal ellipsoidal shape of the left ventricle (LV) can be deemed to be that which provides to it the optimal contractile capacity to pump out blood into the aorta. The analysis presented here is based on our paper on LV Shape-based Contractility Indices [7]. For this purpose, the LV is configured as a prolate spheroid (or ellipsoid) truncated at 50% of the distance from equator to base, and its geometry is defined in terms of the LV chamber volume (V) and the LV myocardial wall volume (VM), which in turn are expressed in terms of the endocardial major and minor radii (SA and LA) and the wall thickness (h), as portrayed by Figure 9.

In a LV, the myocardial fibers are structured helically, which also imparts an ellipsoidal shape to it. Hence, when these helical myocardial fibers contract, the LV twists, contracts efficiently, and decreases in volume in systole. Based on Figure 9, we can define the LV Shape Factor S = SA/LA. Now for developing the LV contractility index, our rationale is that in systole, the LV pressure is developed by the LV wall stress σ, which we can normalize with respect to the LV pressure as $\sigma^* = \sigma/P$,

Figure 8. Cardiac muscle structure [6].

which makes it noninvasively determinable. This enables σ^* to be expressed as a function of the shape factor S and $V^* = V_M / V$. The LV Contractility Index is then based on maximizing σ^* with respect to the shape factor S, which yields:

$$S^{op} = 0.053V^* + 0.39 \tag{1}$$

Another way to define LV contractility can be in a nondimensional form at the start of ejection (se), in the form of the Shape Factor Index given by:

$$\text{SFI2} = (S_{se} - S_{se}^{op}) / S_{se}^{op} \tag{2}$$

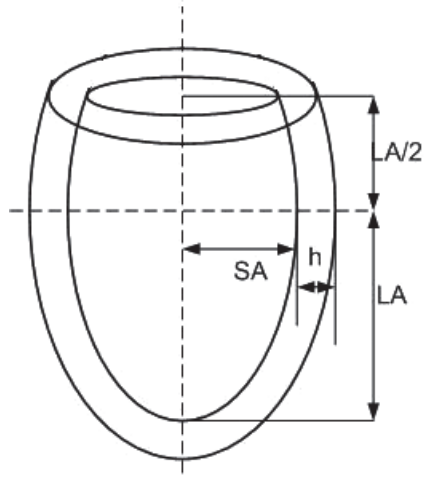


Figure 9. LV model geometry, showing the major and minor radii of the inner surface of the LV (LA and SA) and the wall thickness (*h*) [7].

where S_{se} is the measured shape factor value, S_{se}^{op} is the corresponding optimal value at the start of ejection. So, as SFI2 value increases, the LV contractility becomes poorer.

1.2.4.1 *Clinical application based on our study*

Measurements: All subjects included in this study were in resting recumbent state, after premedication. The LV chamber pressure was measured with a pigtail catheter and Statham P23Eb pressure transducer; the pressure was recorded immediately before or during the angiocardiography in all cases. Single-plane cineangiocardiograms were recorded in a posterior–anterior projection from an image intensifier at 50 fames/s using INTEGRIS Allura 9 with Dynamic Flat Detector (Philips Inc.).

Subjects: Group 1 consisted of ten normal subjects, with EF = 0.63 ± 0.05 and dP/dt_{max} = 1406 ± 51 mmHg/s. They did not use nicotine, caffeine, or

alcohol. The age profiles were similar and their anthropometric data, blood pressure, heart rate, and ejection fraction (EF) were within the expected range.

Group 2 consisted ten patients with coronary and/or valvular disease with EF = 0.49 ± 0.13 and $dP/dt_{\max}$ =1183 ± 62 mmHg/s, having a mean age of 57.4 years. Group 3 comprised of hospitalized patients, having EF = 0.38 ± 0.12 and $dP/dt_{\max}$ = 948 ± 78 mmHg/s, with poor (clinically assessed) contractility. The characteristics of these subjects are listed in Table 4.

Results: For each subject, the chamber pressure and dimensions were monitored at 20 ms intervals during the cardiac cycle. In Figure 10, we take the average values of V(se) and S(se) for each group, and then show how the corresponding LV shape looks like, for these three groups. The S^{op} was calculated using Eq. (1), and the SFI2 was calculated using Eq. (2). The average LV in Group 1 has an optimal value of SFI2, and hence the best contractility compared with the LVs of the other two Groups. The optimally shaped LV is that of Group 1. The average LVs of Groups 2 and 3 are more enlarged and less ellipsoidal compared with the LV of Group 1. So, it can be seen that the optimal LV shape is ellipsoidal, with S(se) value close to S^{op} and SFI2 close to zero.

Table 4. Clinically monitored data and computed parameters for three groups: Group 1 (normal contractility), Group 2 (inadequate contractility), and Group 3 (poor contractility). *$p < 0.05$ compared with normal contractility group [12].

	Group 1	Group 2	Group 3
Age (years)	58.70 ± 6.65	57.40 ± 5.85	58.20 ± 9.11
$dP/dt_{\max}$	1406.00 ± 51.00	1183.00 ± 62.00*	948.00 ± 78.00*
HR (beats/min)	72.69 ± 9.20	67.70 ± 10.04	74.02 ± 10.09
V_M (ml)	146.00 ± 43.00	189.00 ± 78.00	216.00 ± 80.00*
V(se) (ml)	119.26 ± 31.75	148.70 ± 68.32	177.41 ± 90.00
V(ee) (ml)	43.64 ± 9.87	79.45 ± 53.75*	116.73 ± 54.01*
EF	0.63 ± 0.05	0.49 ± 0.13*	0.38 ± 0.12.00*

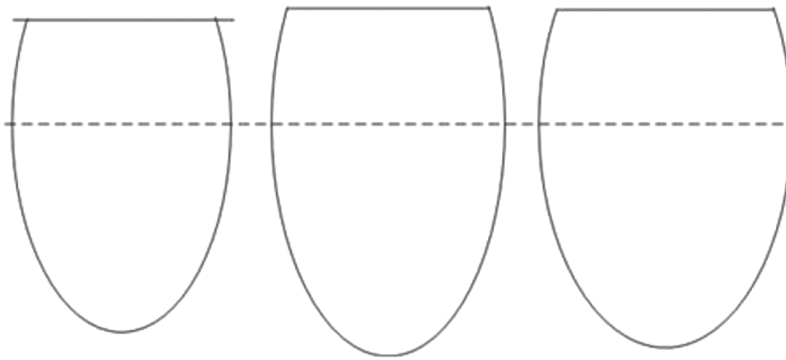


Figure 10. Shapes of the average LVs of Groups 1, 2, and 3 in Table 4, showing the mean values of V(se), S(se), S^{op}, and SFI2. The S^{op} was calculated using Eq. (1), and the SFI2 was calculated using Eq. (2) [7].

1.3 Physiology of the Heart

The heart is a muscular pump that supplies blood to the body. This goal is achieved by electrical excitation that produces myocardial contraction, resulting in cyclic ventricular emptying and filling. The physiological sequence of ventricular function is as follows: an isovolumic contraction phase to develop pre-ejection tension; and slow periods for filling. LV volume decreases rapidly early in systole and slowly thereafter, corresponding to the rapid early acceleration in the flow curve. The volume then increases rapidly in early filling and more slowly during late filling. This section relates function to the underlying precisely described functional muscular anatomy that causes the ventricular directional motions of narrowing, shortening, lengthening, widening, and twisting, thereby providing structure explanations for each of these contractile sequences.

1.3.1 *The cardiac cycle and ventricular dynamics*

Generally, the cardiac cycle consists of diastole (LV relaxation and LV filling) and systole (LV contraction and ejection). One cardiac cycle

can also be classified into several events (1, isovolumic contraction; 2, ejection; 3, isovolumic relaxation; 4, filling), as shown in Figure 11, by using the pressure curve.

1.3.1.1 *Isovolumic contraction phase*

This phase of the cardiac cycle begins with the appearance of the QRS complex of the ECG, which represents ventricular depolarization. This triggers excitation–contraction coupling, myocyte contraction, and a rapid increase in intraventricular pressure. Toward the end of this phase, the rate of pressure development becomes maximal, referred to as maximal *dP/dt*. This maximal *dP/dt* in the ventricles is determined by the rate of contraction of the myocardial fibers, which is determined by mechanisms governing excitation–contraction coupling.

The atrium–ventricular (AV) valves close as intraventricular pressure exceeds atrial pressure. Ventricular contraction also triggers contraction of

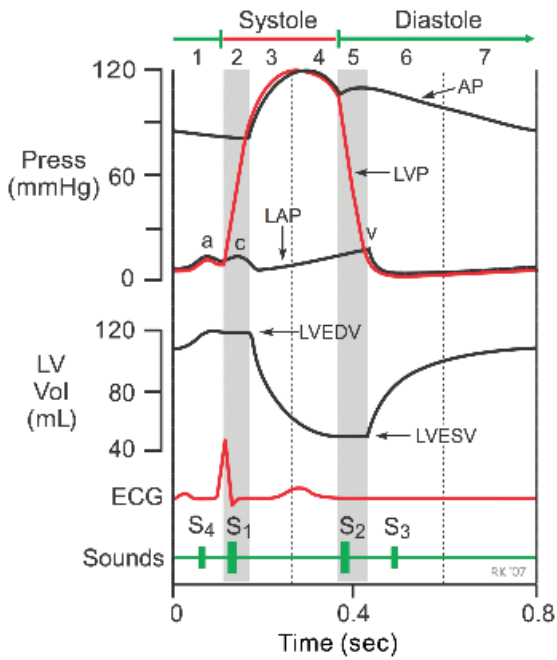


Figure 11. Typical cardiac cycle of left ventricle. LAP: left atrial pressure; LVP: left ventricular pressure; AP: aortic pressure; LVEDV: left ventricular end-diastolic volume; LVESV: left ventricular end-systolic volume [8].

the papillary muscles that prevent the AV valve leaflets from bulging back into the atria and becoming incompetent (i.e., "leaky"). Closure of the AV valves results in the first heart sound (S1).

Ventricular pressure rises rapidly without a change in ventricular volume (i.e., no ejection occurs). Ventricular volume does not change because all the valves are closed during this phase. Contraction, therefore, is said to be "isovolumic" or "isovolumetric". Individual myocyte contraction, however, is not necessarily isometric because individual myocyte are undergoing length changes. Individual fibers contract isotonically (i.e., concentric, shortening contraction), while others contract isometrically (i.e., no change in length) or eccentrically (i.e., lengthening contraction). Therefore, ventricular chamber geometry changes considerably as the heart becomes more ellipsoidal in shape.

1.3.1.2 *Ejection phase*

Ventricular ejection includes rapid and reduced ejection. Ejection begins when the intraventricular pressures exceed the pressures within the aorta and pulmonary artery, which causes the aortic and pulmonary valves to open due to energy gradients from LV to aorta or from RV to pulmonary vein. This pressure gradient across the valve is ordinarily low because of the relatively large valve opening (i.e., low resistance). Maximal outflow velocity is reached early in the ejection phase, and maximal (systolic) aortic and pulmonary artery pressures are achieved.

Atrial pressure initially decreases as the atrial base is pulled downward, expanding the atrial chamber. Blood continues to flow into the atria from their respective venous inflow tracts and the atrial pressures begin to rise, and continue to rise until the AV valves open at the end of the phase.

In late ejection, ventricular repolarization leads to a decline in ventricular active tension, and therefore the rate of ejection (ventricular emptying) falls, as shown by the T-wave of the electrocardiogram. Repolarization Ventricular pressure falls slightly below the outflow tract pressure; however, outward flow still occurs due to kinetic (or inertial) energy of the blood.

Left atrial and right atrial pressures gradually rise due to continued venous return from the lungs and from the systemic circulation, respectively.

1.3.1.3 *Isovolumic relaxation phase*

When the intraventricular pressures fall sufficiently at the end of ejection phase, the aortic and pulmonary valves abruptly close (aortic pulmonary) causing the second heart sound (S2) and the beginning of isovolumetric relaxation. Valve closure is associated with a small backflow of blood into the ventricles and a characteristic notch (incisura or dicrotic notch) in the aortic and pulmonary artery pressure tracings.

The rate of pressure decline $dP/dt_{\min}$ in the ventricles is determined by the rate of relaxation of the muscle fibers. Although ventricular pressures decrease during this phase, the volumes remain constant because all the valves are closed.

1.3.1.4 *Filling phase*

Filling includes rapid and reduced filling associated with atrial contraction. As the ventricles continue to relax at the end of isovolumic relaxation phase, the intraventricular pressures falls below their respective atrial pressures. When this occurs, the AV valves rapidly open and ventricular filling begins. Despite the inflow of blood from the atria, intraventricular pressure continues to fall because the ventricles are still undergoing relaxation. Once the ventricles are completely relaxed, their pressures will slowly rise as they fill with blood from the atria due to the decreased compliance of myocardium.

As the ventricles continue to fill with blood and expand, they become less compliant and the intraventricular pressures rise. This reduces the pressure gradient across the AV valves, so that the rate of filling falls.

In normal, resting hearts, the ventricle is about 90% filled by the end of this phase. In other words, about 90% of ventricular filling occurs before atrial contraction.

Atrial contraction phase is initiated by the P wave of the ECG, which represents electrical depolarization of the atria. Atrial depolarization then causes contraction of the atrial musculature. As the atria contract, the pressure within the atrial chambers increases, which forces more blood flow across the open mitral valve, leading to a rapid flow of blood into the ventricles.

Left atrial contraction normally accounts for about 10% of ventricular filling when a person is at rest, because most of left ventricular filling occurs prior to left atrial contraction, as blood passively flows from the left atrium into the left ventricle through the open mitral valve.

After left atrial contraction is complete, the atrial pressure begins to fall, causing a pressure gradient reversal across the mitral valve. At this time, the left ventricular volume is maximal, which is termed as end-diastolic volume (EDV).

1.3.2 *Myocardial fibers' helical orientation contributing to LV contractile twist and isovolumic pressure increase*

Let us now provide some quantification of heart physiology in terms of how the left ventricle is able to raise its pressure during isovolumic contraction and systole to deliver cardiac output. The left ventricle starts contracting due to the activation of the excitation–contraction coupling mechanism of the myocardial sarcomere, which results in contraction and stress development in the myocardial fibers. This contractile stress development in the helically wound myocardial fibers causes twisting of the LV and reduction of its chamber volume due to the compressibility of the blood. Then, because of the high value of the bulk modulus of blood, this causes a sharp increase in LV pressure during the isovolumic contraction phase. Now let us figure out how we can get some idea of the *in vivo* stresses and orientation of the myocardial fibers to cause this sharp pressure increase, based on a thick-walled cylindrical (large deformation) model of the LV [5], shown in Figure 12. For this purpose, we start with the monitored values of the LV pressure (P), LV volume (V), LV wall thickness (h), and LV myocardial volume (V_M). We then calculate the volume changes (ΔV) due to the instantaneous pressure changes (Δp) and the bulk modulus (K) of the blood. This enables us to express the instantaneous radial and length deformations of the LV model in terms of the incremental pressure Δp and K. These changes in the LV cylindrical length and radius along with the LV twist angle (whose reasonable values are assumed in this analysis) constitute LV deformations.

By employing finite elasticity and large-deformation analysis, we then express (1) the stretches and strains within the LV cylinder wall in

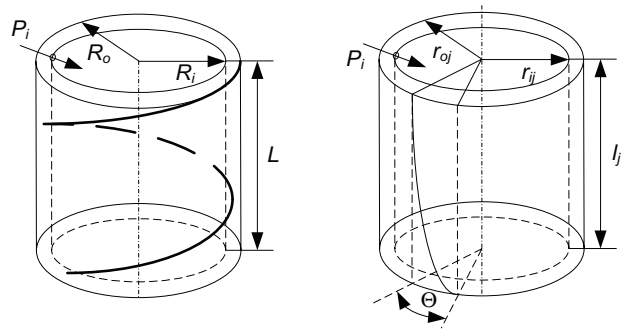


Figure 12. Left ventricular thick-walled cylindrical model, in undeformed and deformed states, showing (i) the inner and outer radii, length, and pressure in the undeformed state, (ii) the instantaneous inner and outer radii, length, twist angle, and pressure in the deformed state, and (iii) schematics of myocardial helical fiber orientation and twisting of the LV cylindrical model, to simulate LV contraction and account for LV pressure rise during the isovolumic contraction phase [9].

terms of these deformations and (2) the LV wall stresses in terms of these stretches and strains, by means of the strain energy density function and its material parameters. We then carry out the equilibrium analysis of this LV model's wall stress in terms of the monitored chamber pressure. By solving these equilibrium equations, we determine the values of (1) the myocardial material parameters of the strain energy density function, (2) the stretches and strains, and (3) the stresses.

We then proceed to determine and compute the principal stresses and the principal angle. We then associate (1) the principal compressive stress with that of the contractile stress in the myocardial fibers, and (2) the principal angle with the myocardial fiber angle. Thus, by means of this inverse analysis, we determine the *in vivo* stresses and the orientation of the activated and contracted myocardial fibers, which cause LV deformation (shortening and twisting) and rapid chamber pressure rise during the (0.04–0.06 s of) isovolumic contraction phase.

Finally, we determine the torque and the axial compressive force induced in the LV model due to its contraction and the activation of the helically wound myocardial fibers. This induced torque, causing the twisting of the LV and the resulting chamber pressure increase, is an important aspect of the LV contraction process.

We have displayed the time variations of the principal stress and the corresponding angle during the isovolumic phase in Figure 13. The notable result from Figure 13 is that both the principal stresses and their orientation angle keep changing during the isovolumic phase. It is seen from Figure 13 that the equivalent myocardial fiber orientation is 38° at the start of isovolumic contraction, and as the LV twists it becomes 33° at the end of the isovolumic phase — which is natural. In other words, the monitored internal pressure increase during isovolumic phase from 25 to 45 and then to 63 mmHg is attributed to the active contraction of the helically woven myocardial fibers from 38° to 33°, which causes increasing torque in the LV.

Let us now provide a fitting conclusion to this ground-breaking study. By determining the compressive principal stress (or the fiber stress) from the LV pressure and deformations data, we have indirectly demonstrated that the LV pressure build-up is due to the contraction of the LV spiral-wound myocardial fibers. This work also enables us to provide a measure of the equivalent LV myocardial fiber orientation (taken to be equal to the compressive principal stress angle). In other words, what is implied is that for known LV pressure-rise and twist-angle, we can determine the LV myocardial fiber orientations and stresses that cause this LV deformed state. We can now postulate that this equivalent myocardial fiber orientation of the LV constitutes an intrinsic property of the LV, which governs its contractility. Taking into consideration that it is not possible to measure the *in vivo* wall fiber orientation, the indirect determination of this equivalent fiber orientation is an important outcome of this work, because it can help us to provide an important clue to why some LVs are not able to effectively raise their LV pressure and are more prone to impaired LV contractility, and hence reduced cardiac output and stroke volume.

1.3.3 *Coronary circulation and myocardial mechanics*

The energy used by the heart is provided by the nutrients supplied by the coronary circulation. The blood supply to the myocardium is via large epicardial coronary arteries including left main coronary artery, RCA, LAD, LCX, and posterior descending (PDA) coronary artery. The left main then divides into the LAD and LCX, and the RCA, LAD, and LCX form three clinically significant vessels (Figure 14).

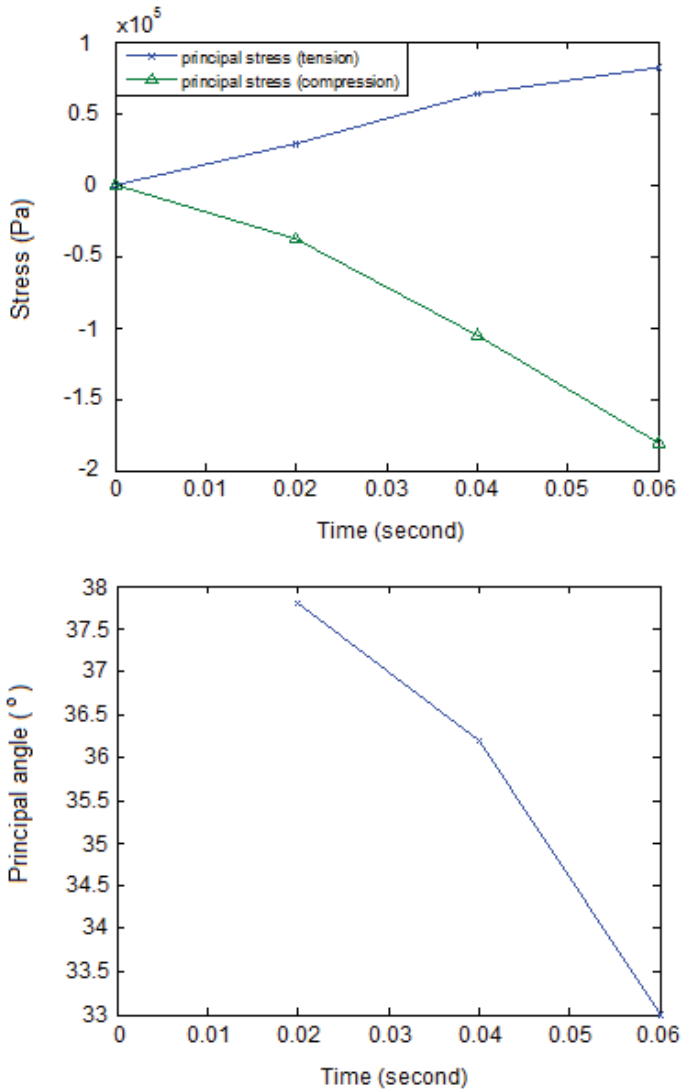
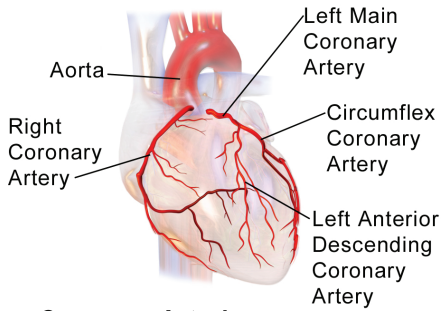
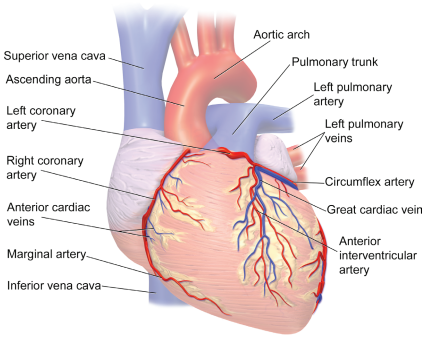


Figure 13. Variations of the principal stresses and the corresponding angle as functions of time during the isovolumic contraction phase [9].

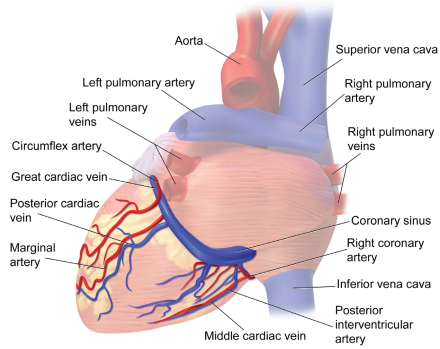
Coronary arteries arborize into a network of fine arterioles. The walls of these arterioles contain smooth muscle cells that contract in the basal state, contributing to coronary tone and resistance. When a proximal epicardial coronary artery develops stenosis, the corresponding distal



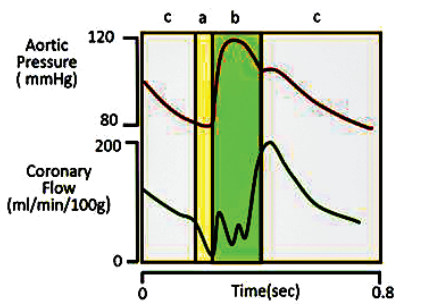
Coronary Arteries



Coronary Circulation (Anterior)



Coronary Circulation (Posterior)



Pulsatile nature of left coronary artery blood flow. Flow is lower during phases of isovolumetric contraction (a) and ejection (b) than during diastole (c)

Figure 14. The major coronary arteries supplying blood to the myocardium and their location anatomically [3][10][11].

arterioles dilate in response, thus lowering coronary resistance and effectively maintaining unchanged coronary blood flow (CBF). With exercise stress, tissue accumulation of metabolites occurs that relaxes arteriolar wall smooth muscle cell contraction. Arterioles further dilate (coronary hyperemia) by varying amounts depending on the basal coronary tone. Normal (nonstenosed) arteries dilate in response to stress more than stenosed arteries, because arterioles supplied by the latter are already semidilated even before exercise begins. Hence, the coronary flow reserve (CFR), defined as the ratio of stress CBF to rest CBF, is lower in stenosed arteries compared to normal arteries. Occlusion of the coronary arteries can lead to "one-vessel", "two-vessel" or "three-vessel" disease, depending on which major arteries are occluded.

Resting coronary blood flow is about 225 ml/min, which constitutes 4–5% of the total cardiac output. Coronary circulation provides oxygenated blood to the heart through myocardial perfusion. The delivery of the blood to the myocardium is determined by the intramyocardial pressure (which is a function of intraventricular pressure), i.e., when the intraventricular pressure is low the blood can flow into the myocardium. Extravascular compression (as depicted in the bottom picture of Figure 14) during systole markedly affects coronary flow. Hence, almost all the nutrient coronary flow takes place during diastole. Figure 15 illustrates the variation of coronary arterial flow with respect to LV pressure during a cardiac cycle. When the heart contracts in systole, the coronary arterial flow velocity is minimal, while the major contribution to coronary flow is during diastole. It can be noted that the mean coronary systolic flow is lower than the mean diastolic flow despite the higher input pressure during systole.

Coronary flow is tightly coupled to oxygen demand. This is because the heart has a very high basal oxygen consumption (8–10 ml O_2/min/100/g) and the highest A–VO_2 difference of a major organ (10–13 ml/100 ml). Because of extravascular compression, the endocardium is more susceptible to ischemia, especially at lower perfusion pressures. In nondiseased coronary vessels, whenever cardiac activity and oxygen consumption increases, there is an increase in coronary blood flow (active hyperemia) that is nearly proportionate to the increase in oxygen consumption. Good autoregulation between 60 and 200 mmHg perfusion pressure helps to maintain normal coronary blood flow whenever coronary perfusion pressure changes due

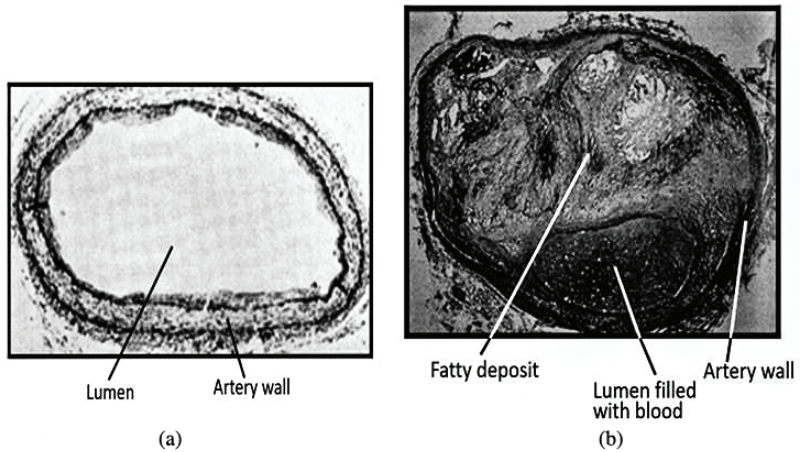


Figure 15. Cross-sections of (a) a normal artery and (b) an atherosclerotic artery whose lumen is diminished by fatty deposits. Atherosclerosis promotes the formation of a blood clot within the artery [12].

to changes in aortic pressure. In this regard, adenosine is an important mediator of active hyperemia and autoregulation. It serves as a metabolic coupler between oxygen consumption and coronary blood flow.

1.4 Pathophysiology of the Heart

Heart failure is the pathophysiological state in which the heart is unable to pump blood with the requirements of the metabolizing tissues. This is a complex clinical syndrome that can result from any structural or functional cardiac disorder that impairs the ability of the ventricles to fill with or eject blood. Heart failure may be caused by myocardial ischemia, infarction, and remodeling, or some combination of all of the above.

1.4.1 *Perfusion and atherosclerosis*

Atherosclerosis disease is the leading cause of death. This complex process includes the development of plaque composed of variable amount of connective tissue matrix, vascular smooth muscle cells, lipoproteins, calcium, inflammatory cells, and new blood vessels.

Figure 15 illustrates the morphology and the formation of an arteriosclerotic plaque. The emerging theories state that atherosclerosis may reflect a chronic inflammatory response to vascular injury caused by a variety of agents that activate or injury endothelium. Vascular remodeling can occur in atherosclerotic disease leading to enlargement of the vessel, termed positive remodeling, to try and restore blood flow. Once this process stops, the lumen will start to narrow as the plaque grows. Luminal narrowing can also occur as a result of adventitial restriction or contraction, termed negative remodeling.

1.4.2 *Myocardial ischemia: causes and effects*

The coronary arteries transport oxygen- and nutrient-rich blood to the myocardium (heart muscle) to sustain the heart's normal contractile pumping function. The pumping heart in turn generates pressure and flow within the coronary circulation to supply blood and oxygen to the heart.

Causes of myocardial ischemia: Myocardial ischemia occurs (i) when coronary blood flow (CBF) or perfusion is insufficient for myocardial metabolic needs. This can occur (i) when there is a reduction in blood flow due to a severe obstruction of the coronary arteries, such as in coronary artery disease (CAD), where atherosclerotic fatty deposits in the coronary artery wall narrow the lumen of the arteries, compromising blood flow and oxygen delivery to the heart; or (ii) when increased metabolic demands are not met by an increased supply of oxygen, such as during physical exercise.

During exercise, the workload of the heart increases so as to increase cardiac output to meet the increased requirements of the skeletal muscle. This increased workload requires an increase in coronary blood supply, which is met by vasodilatation of the arteriolar bed. However, in patients with coronary artery disease, this normal increase in coronary blood flow with exercise may be limited due to narrowing (stenosis) of one or more coronary arteries. Thus in a patient with a coronary stenosis, ischemia may arise when myocardial metabolic requirements and oxygen demand increase, but supply is limited by coronary disease, such as when the heart is stressed during exercise. Hence, a decrease in myocardial perfusion and/or an increase in myocardial metabolism impose an imbalance in supply–demand that results in ischemia (Figure 16).

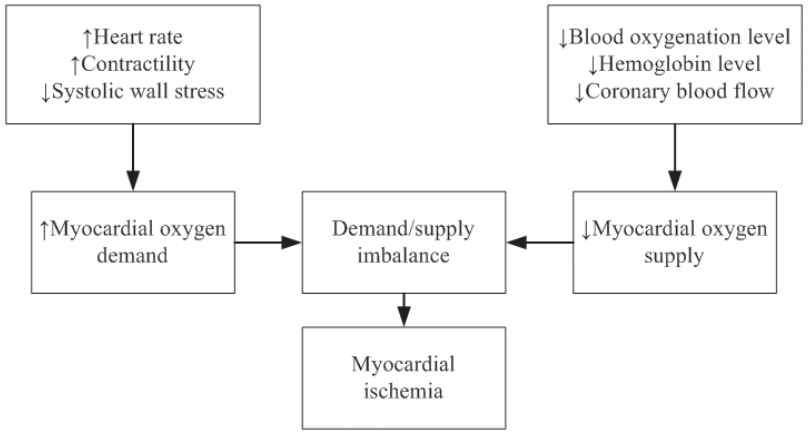


Figure 16. Factors influencing myocardial ischemia [13].

The onset and manifestations of myocardial ischemia usually occur in a step-wise sequence, which has been termed the ischemic cascade. The initial abnormality is that of insufficient coronary blood flow, either a reduction in coronary flow blood flow or an increase in metabolic demand that is not matched by an increase in blood supply. There is heterogeneity of coronary blood flow with lower blood flow in ischemic territories (supplied by diseased coronary arteries) compared to nonischemic territories, and also from the subendocardium to the subepicardium. Impairment of myocardial myofiber active relaxation and contraction ensue, resulting in diastolic (relaxation) and systolic (contraction) dysfunction, respectively. Depending on the extent of myocardial involvement and adequacy of compensatory hyperfunction of nonischemic myocardium, the global myocardial function, left ventricular ejection fraction, and stroke volume deteriorate variably. Ischemic changes on surface electrocardiograms (ECG) appear late often heralding the onset of anginal symptoms. The evaluation of ischaemia relies on the detection and measurement of these event parameters.

1.4.3 *Myocardial infarction*

Myocardial infarction is the necrosis of a portion of the myocardium secondary to prolonged lack of oxygen supply, due to an obstruction in a coronary artery. The obstruction is usually a blood clot that has formed as a result of atherosclerosis. This event is commonly called a heart attack, and

it may be fatal if a large portion of the myocardium is deprived of blood. It is thought that there is a continuum of events, from stable plaque to plaque rupture and thrombus formation, leading to myocardial infarction.

The process of myocardial infarction can be summarized as follows. Subendocardium is most vulnerable to ischemia, and hence necrosis usually begins there. During the first hour of occlusion, patches of irreversibly injured myocytes develop in the subendocardium. At three to 4 h, fingers of the necrotic wave front extend into the middle third of the myocardium. At twelve to 24 h, the entire wall thickness is involved in the necrosis. The schematics of myocardial remodeling after MI are shown in Figure 17.

It may be noted that myocardial stunning can also take place and that tissue that may look damaged on preliminary examination may actually be functioning at a later stage. Hence, revascularization therapy, i.e., surgery, is the best option for treatment in such a situation.

Infarcted myocardial segments can be detected as highly reflectile echo zones (HREZs) in 2D B-scan echocardiograms. In this context, we have shown how infarcted myocardial segments can be detected (in shape

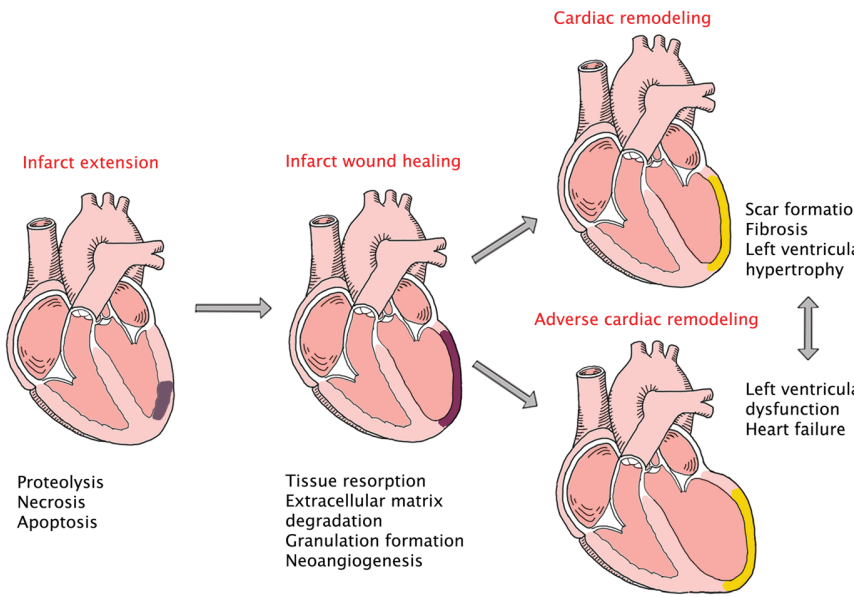


Figure 17. Schematics of myocardial infarction [14].

and size), by echo-texture analysis, as highly reflectile echo zones or HREZs. Each myocardial tissue component of the heart generates a grey-scale pattern or texture related to the tissue density and fibrous content. In diseased states (such as myocardial ischemia, myocardial fibrosis, and infiltrative diseases), changes in myocardial tissue density have been recognized by employing echo intensity and mean grey level of pixel as the basis for recognition of such myocardial disorders. It is found that hyperreflectile echoes (HREs) correlated well with diseased cardiac muscle and that myocardial tissue containing HREs corresponded with foci of subendocardial necrosis and even calcification [9].

1.4.4 *Left ventricular (myocardial) remodeling*

Heart disease causes structural (macroscopic and microscopic levels) and functional changes, called myocardial remodeling. Left ventricular remodeling may be defined as a change in shape, size, and function of the left ventricle due to physiological or pathological conditions. Physiological change is a compensatory change in the dimensions and function of the heart in response to physiological stimuli induced by exercise such as an athlete's heart. Pathological changes can be seen in disorders of the ventricles due to ischemic cardiomyopathy, hypertension, hypertrophy, and dilated cardiomyopathy.

The earlier described myocardial helical fibers concept is directly related to the altered cardiac anatomy in patients with heart failure (Figure 18). The ischemic heart dilates because the apex is lost from anterior infarction; apical dilatation also occurs from valvular insufficiency with ventricular stretching caused by volume overload. In the nonischemic failing heart, the muscle itself becomes damaged and a spherical shape replaces the apical contour.

1.4.4.1 *LV remodeling quantification in terms of remodeling index*

Herein, we are presenting a new remodelling index for clinical management of patients, based on measurements of LV short-axis and long-axis from MRI images of subjects. For patients with HF after MI, the LV shape

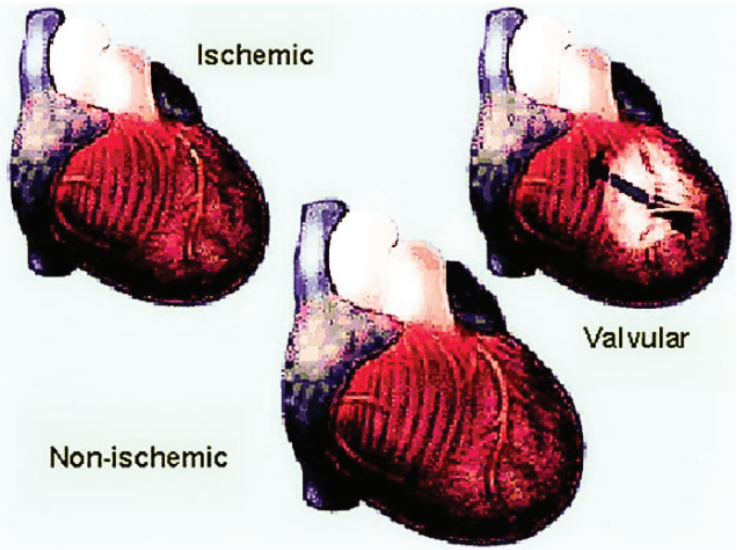


Figure 18. The spherical shape of the dilated heart in cardiac failure is shown for ischemic, valvular, and non-ischemic cardiomyopathy [6].

becomes more spherical, which can be defined in terms of the Sphericity index. For this purpose, let us refer to Figure 9, showing the LV model geometry, wherein the LV is modeled as a prolate spheroid, truncated 50% of the distance from equator to base, in terms of the major and minor radii of the inner surface of the LV (LA & SA) and the wall-thickness (h).

The endocardial minor axis dimension (SA) and major axis dimension (LA), shape factor (S), eccentricity (E) and Sphericity index (SI) can then be calculated as follows [15].

$$\mathrm{SA} = \mathrm{AP}/2; \quad \mathrm{LA} = \mathrm{BA}/1.5;$$

$$S = \mathrm{SA}/\mathrm{LA}; \quad E = \left(\frac{\mathrm{BA}^2 - \mathrm{AP}^2}{\mathrm{BA}^2}\right)^{0.5}; \quad \mathrm{SI} = \mathrm{AP}/\mathrm{BA} \tag{3}$$

where BA (the LV long axis) is defined as the longest distance from the apex to the base of the LV (defined as the mitral annular plane), as measured on the four-chamber cine MRI view of the heart; AP is defined as the widest LV minor axis.

A small value of SI implies an ellipsoidal LV, whereas values approaching "1" suggest a more spherical LV. The SI at end-diastole (SI_{ED}) and end-systole (SI_{ES}), and the % shortening of the long and minor axes can also be calculated. Then the difference between end-diastolic and end-systolic SI values, $SID = (SI_{ED} - SI_{ES})$, can be calculated, and referred to as LV Remodeling Index, which can be clinically employed.

1.5 Summary

Let us recapitulate the organization and contents of this chapter. We started with the anatomy of heart and identified the parts of the heart and described their functions. To understand how the myocardium functions, we then described the muscle structure at a basic level. A notable feature of the heart anatomy is the intrinsically optimal ellipsoidal shape of the left ventricle, that which affords it maximum contractility.

We then proceeded to describe the physiology of the heart, including the events of the cardiac cycle and traced the blood flow through the heart. We provided a significant aspect of left ventricular by determining the *in vivo* myocardial fibers stress and angle (of the order of 38°). When the left ventricle contracts, the fiber angle decreases as the LV twists; this is how LV anatomy and physiology come together to contribute to its optimal functional performance.

Thereafter, we discussed coronary circulation and its mechanics, and developed the basis of how atherosclerosis, myocardial ischemia, and myocardial infarction are caused in terms of coronary circulatory obstruction leading to inadequate myocardial perfusion.

We finally discussed LV remodeling due to myocardial infarction and dilated cardiomyopathy. There again, we provided a quantification of LV remodeling in terms of the sphericity index, and its difference between end-diastole and end-systole. The normal ventricle becomes more ellipsoidal from end-diastole to end-systole as the helical fibers contract and make the LV twist. What happens in infarcted LVs is a loss of contractile stress in some segments of the myocardial fibers, which in turn decreases the twist capacity of the LV and makes it less ellipsoidal or more spherical. Through it all, we have lent a useful quantification to heart anatomy and physiology, which in turn can lead to computational cardiology served by the remaining book chapters.

References

[1] Boundless. *Structures of the Heart*. Boundless Biology Boundless, 26 May, 2016.

[2] Betts, J.G., Desaix, P., Johnson, J.E., Johnson, E.W., Korl, O., Kruse, D., Poe, B., Wise, J., Womble, M.D., Young, K.A. (2013). *Anatomy and Physiology.* 787–846. OpenStax: Houston, TX, USA. *ISBN 1-938168-13-5.*

[3] Richard E.K. (2017). Anatomy and Function of the Coronary Arteries, Johns Hopkins Health Library. Available at. http://www.cvphysiology.com/Blood%20Flow/ BF001.

[4] Zipes, D.P., Libby, P., Bonow, R.O., Braunwald, E. (2001). *Braunwald's Heart disease: a Textbook of Cardiovascular Medicine*. Elsevier, pp. 459.

[5] Ghista, D.N., Zhong, L., Ng, E.Y.K., Lim, S.T., Tan, R.S., Chua, T. (2005). Systolic modeling of the left ventricle as a mechatronic system: determination of myocardial fiber's sarcomere contractile characteristics and new performance indices. *Mol. Cell. Biomech*. 2(4), 217–233.

[6] Gerald, D.B. (2002). Basic science review: The helix and the heart. *J. Thorac Cardiovasc. Surg*. 124(5), 863–883.

[7] Zhong L, Ghista DN, Ng EYK, Lim ST, Chua T, Lee CN. (2006). LV shape-based contractility Indices, *J. Biomech.* 39, 2397–2409.

[8] Richard E.K.. Available at. https://www.cvphysiology.com/Heart%20Disease/HD002

[9] Ghista, D.N., Liu Li, Leok Poh Chua, Ru San Tan, Yong San Tan (2009). Mechanism of left ventricular pressure increase during isovolumic contraction, and determination of its equivalent myocardial fibres orientation, *J. Mech. Med. Biol*. 9(2), 177–198.

[10] Blausen Medical. Available at : https://en.wikipedia.org/wiki/Blausen_Medical

[11] BruceBlaus. Available at: http://www.pathologyoutlines.com/topic/heartcoronary.html

[12] Gunstream, S.E. (2004). *Anatomy and Physiology with Integrated Study Guide*, McGraw Hill Learning Solutions.

[13] Gunstream, S.E. (2006). Anatomy and Physiology. pp. 262.

[14] Aleksandra Gombozhapova, Yuliya Rogovskaya, Vladimir Shurupov, Mariya Rebenkova, Julia Kzhyshkowska, Sergey V. Popov, Rostislav S. Karpov and Vyacheslav Ryabov (2017). Macrophage activation and polarization in post-infarction cardiac remodeling, *J. Biomed. Sci.* 24, 13 [16]

[15] Yeo, S.Y., Zhong, L., Su, Y., Tan, R.S., Ghista, D.N. (2009). A Curvature based approach for left ventricular shape analysis from cardiac magnetic resonance imaging, *Med. Biol. Eng. Comput.* 47, 313–322.

[16] Ghista, D.N., Ng, E.Y.K. (2008). *Cardiac Perfusion and Pumping Engineering, pp.* 58.

[17] Zhong, L., Ghista, D.N., Ng, E.Y.K., Lim, S.T., Chua, T., Lee, C.N. (2006). Left ventricular shape-based contractility index, *J Biomech.* 39, 2397–2409.