

Ali Dabbagh

Contents

1.1	Introduction to Cardiac Physiology	2
1.1.1	The Physiologic Anatomy of the Heart	2
1.1.2	Anatomy of the Coronary Arteries	8
1.2	Cellular Physiology	10
1.2.1	Action Potential	11
1.2.2	Excitation-Contraction Coupling (ECC)	13
1.2.3	Contractile Mechanisms and Their Related Processes	18
1.3	Cardiac Cycle and Cardiac Work	24
1.3.1	Normal Cardiac Cycle	24
1.3.2	Cardiac Work	25
1.3.3	Frank-Starling Relationship	26
1.4	Cardiac Reflexes	28
1.4.1	Bainbridge Reflex	28
1.4.2	Baroreceptors Reflex (or Carotid Sinus Reflex)	28
1.4.3	Bezold-Jarisch Reflex	29
1.4.4	Valsalva Maneuver	30
1.4.5	Cushing Reflex	30
1.4.6	Oculocardiac Reflex	31
1.4.7	Chemoreceptor Reflex	31
	References	31

Abstract

Cardiac physiology is one of the most interesting discussions both in physiology and cardiac-related clinical sciences. Anatomy and physiology of the heart are directly related to the clinical presentations of disease states. The heart is composed of pericardium, endocardium, and myocardium, the last being more

A. Dabbagh, MD

Department of Anesthesiology and Anesthesiology Research Center, Faculty of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran

e-mail: alidabbagh@sbmu.ac.ir

discussed here and consists of cardiac connective tissue cells, cardiomyocytes (which have contractile function), and cardiac electrical system cells (consisting of “impulse-generating cells” and “specialized conductive cells”). The main cardiac cells are cardiomyocytes with their unique structure having some shared features with both skeletal muscles and smooth muscles, though not completely similar with any of the two.

Cardiac cells have three different but “highly interrelated” aspects: action potential, excitation-contraction coupling (ECC), and contractile mechanisms, each of the three being a complex of many different physiologic chains to create together and as a final outcome a main goal: cardiac contraction leading to cardiac output.

A number of physiologic reflexes are involved in cardiac physiology discussed in the final part of the chapter.

1.1 Introduction to Cardiac Physiology

1.1.1 The Physiologic Anatomy of the Heart

The normal heart is a physiologic pump composed of two adjacent, parallel pumps (i.e., left and right); each of these separate pumps is composed of two chambers (i.e., atrium and ventricle); each atrium conducts the blood to its related ventricle; the ventricle would in turn pump the blood to the main artery connected to the related outflow tract, i.e., from left ventricle outflow tract to aorta and from right ventricle outflow tract to pulmonary artery. Afterwards, blood is sent forward, to the arterial tree in a propulsive manner. This is known as the cardiac contractile system composed of the cardiac muscle, which in turn is composed of two muscle masses known as “cardiac muscle syncytium”: the atrial syncytium and the ventricular syncytium which are separated by a fine part of the cardiac conductive system (see following pages).

Grossly speaking, both right atrium (RA) and left atrium (LA) have a delicate structure mainly composed of two muscle layers and are located above the related ventricle. Meanwhile, right ventricle (RV) and left ventricle (LV) are composed of three gross muscular layers, much thicker than atria. The two atria are separated anatomically by the interatrial septum, while the two ventricles are separated by the interventricular septum. However, the two atria are connected as an electrical unit through the atrial electrical conduction system discussed later. The same is also correct for the ventricles, and they have a common electrical system with its divisions and branches spread throughout the ventricles.

The great veins are attached to the upper chambers of the heart, i.e., atria; in other words, the superior and inferior venae cavae are attached to the right atrium and bring the deoxygenated blood from the upper and lower organs to the right heart, respectively. However, the right and left pulmonary veins bring oxygenated blood from the right and left lung to the left atrium. On the other hand, the deoxygenated blood is sent from the right atrium through the right ventricle to the right ventricular outflow tract (RVOT) to enter the pulmonary artery to go to the lungs to be oxygenated. The oxygenated blood traverses the left atrium to the left ventricle and is

pumped through the left ventricular outflow tract (LVOT) to the ascending aorta, aortic arch, and descending aorta to perfuse the whole body by oxygenated blood.

Each atrium is separated anatomically from its ventricle by an atrioventricular valve; on the right side, the tricuspid valve does this and on the left side; the mitral valve separates the left atrium from the left ventricle; the tricuspid valve has three leaflets (or three cusps), while the mitral (bicuspid) valve has two leaflets (cusps). The leaflets of the atrioventricular valves are strengthened by the chordae tendineae, which are fibrous connective bundles anchoring the ventricular wall to the inferior surface of the same side atrioventricular valve cusps; muscular extensions, named papillary muscles, are located between the ventricular wall and the chordae tendineae. The structure composed of chordae tendineae and papillary muscles prevents prolapse of the atrioventricular valve from the ventricular cavity back to the atrial chamber during ventricular systole.

Also, each ventricle is separated from the related artery by a semilunar 3-leaflet valve; the right ventricle is separated from the pulmonary artery by the pulmonary valve, while the aortic valve separates the left ventricle from aorta (Fig. 1.1).

The heart is a muscular organ; its location is posterior to the sternal bone in the anterior mediastinum, a bit deviated to the left. Anatomically speaking, the heart is composed of three layers:

- “Pericardium”: the outermost layer, covers the heart as a tissue sac, and has itself three layers:
 1. Fibrous pericardium (firm, outermost layer).
 2. Parietal pericardium (between fibrous pericardium and visceral pericardium).

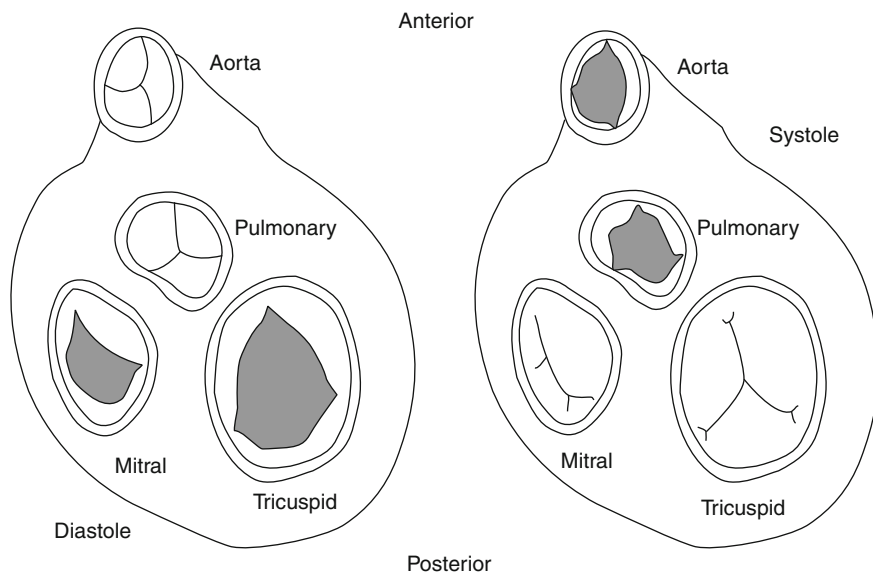


Fig. 1.1 The apex of the heart when viewed from above in systole and diastole; note the position of the valves and their relationships

3. Visceral pericardium (innermost layer of pericardium) which is attached directly to the outer border of myocardial tissue; normally, a potential space exists between visceral and parietal pericardial layers which are filled with a few milliliters of serous tissue, functioning as a lubricant between the two layers while there is continuous heart rhythm and myocardial contractions.
- “Myocardium”: the middle layer, has the main role of contraction, and is composed mainly of:
 1. Myocardial muscle tissue
 2. Coronary vascular system
 - “Endocardium”: the innermost layer, covers the inner space of the cardiac chambers
(Silver et al. 1971; Anwar et al. 2007; Tops et al. 2007; Haddad et al. 2009; Silbiger and Bazaz 2009; Ho and McCarthy 2010; Rogers and Bolling 2010; Atkinson et al. 2011; Dell’Italia 2012; Silbiger 2012)

Here we discuss more about the myocardial muscle tissue and its ingredients. The cardiac muscle (myocardium) is mainly composed of three cell types:

1. Cardiac *connective* tissue cells
2. *Cardiomyocytes* (which have contractile function)
3. Cardiac *electrical system cells* (consisting of “*impulse-generating cells*” and “*specialized conductive cells*”)

1.1.1.1 Cardiac Connective Tissue Cells

The cardiomyocytes are arranged in a cellular bed of protective system and supporting structure known as the cardiac *connective tissue cells*; these cells have the following main functions:

1. Supporting the cardiac muscle fibers as a physical protective structure
2. Transmission of the cardiomyocyte-produced mechanical force to cardiac chambers
3. Adding “tensile strength and stiffness” to the structure of the heart
4. Preventing excessive dilation and overexpansion of the heart
5. Keeping the heart within its original framework, returning the heart to its original shape after each contraction through the elastic fibers

The cardiac connective tissue would be modified according to the function of the related cardiac region; for example, “the amount of collagen in atria is different than in the ventricles” which shows the diversities and dissimilarities of anatomy that are the result of difference in function, both regarding “pressure and volume” work of different cardiac regions (Borg et al. 1982; Robinson et al. 1986, 1988; Rossi et al. 1998; Distefano and Sciacca 2012; Watson et al. 2012).

1.1.1.2 Cardiac Contractile Tissue Cells (i.e., Cardiac Muscle Cells or Cardiomyocytes)

The following hierarchy could lead us to overall order seen in the fine and specialized structure of the myocardial histology:

- The myocardium is composed of myocardial cells called *heart muscle cell*, *cardiac myocytes*, or, briefly, *cardiomyocytes*.

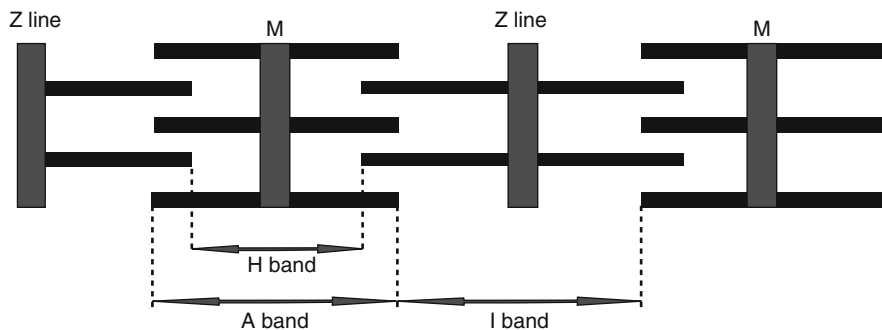


Fig. 1.2 Microscopic structure of a sarcomere; thin and thick filaments are presented as *thin* and *thick* interspersed horizontal rods; a sarcomere is defined as the part of sarcomere between two *Z lines*

- These cells have contractile function similar to striated muscle cells, with the especial difference that their contraction is involuntary.
- Also, instead of having many nuclei in each cell (like the cellular structure seen in skeletal muscle cells), each cardiomyocyte has only 1–2 nuclei and is 100 μ in length and 25 μ in width.
- The internal structure of each cardiomyocytes is in turn composed of a wealth of cardiac myofibrils.
- And finally, each cardiac myofibril is composed of a vast number of sarcomeres; each sarcomere is located anatomically between two Z lines; thin filaments are attached perpendicularly to Z lines on each side, while thick filaments are in between them in a parallel fashion (Fig. 1.2).

Now let's discuss the above lines in more detail.

The cardiomyocytes are specialized muscle cells, ranging from 25 μ m length in atria up to about 140 μ m in ventricular cardiomyocytes. About half of a cardiomyocyte is composed of contractile parts (called myofibrils) arranged as contractile units called *sarcomere* (each cardiomyocyte contains a number of sarcomeres); sarcomere is the basic unit of contraction or better to say *contractile quantum of the heart*.

The other half is composed of other cellular structures including nucleus, mitochondria, sarcoplasmic reticulum, and cytosol.

Sarcolemma, T tubules, and sarcoplasmic reticulum: each cardiomyocyte is enveloped by a especial membrane called sarcolemma, which not only covers the cardiomyocyte but also has a large network “invaginating” between the cells creating transverse tubules (*T tubules*) having a central role in Ca^{2+} transfer in sarcoplasmic reticulum of the cardiomyocytes. Ca^{2+} has a pivotal role in all the main three cardiac physiologic functions, known among them is *excitation-contraction coupling* which is discussed later; however, in summary, excitation-contraction coupling could be assumed as the “hinge” between the *electrical* and *mechanical* functions of the cardiomyocyte.

The sarcoplasmic reticulum (SR) has a dual function for Ca^{2+} homeostasis; first, SR releases Ca^{2+} after Ca^{2+} influx during depolarization, causing contractility

through junctional SR (JSR), and after that, SR reuptakes Ca^{2+} causing cardiac muscle relaxation through longitudinal SR (LSR).

Intercalated discs: *intercalated discs* are among the basic cellular structures found in cardiomyocytes, which are “cardiac-specific structures”; these cardiomyocytes structures are the main communication port between adjacent cardiomyocytes.

The main functions of intercalated discs could be categorized as:

1. *Mechanical* connection between adjacent cardiomyocytes
2. *Electrical transport* between adjacent cardiomyocytes (i.e., rapid transduction and transmission of action potential)
3. *Synchronization* of cell contraction

The above main functions of the intercalated discs have an integral role in creating a “physiologic” syncytium. Intercalated discs are special to cardiac muscle cells; adult skeletal muscle cells are devoid of these specialized cellular structures. *Intercalated discs* perform their roles through three types of intercellular junctions:

1. Spot desmosomes
2. Sheet desmosomes
3. Gap junction

Spot desmosomes are intercellular connections which “anchor the intermediate-filament cytoskeleton” in the adjacent cells.

Sheet desmosomes are the place for contractile structures that connect two neighboring cells; it means that sheet desmosomes fasten and fix the contractile apparatus between the neighboring cells.

Gap junctions are primarily responsible for electrical transmission between adjacent cells causing rapid electrical wave progression in “cardiac syncytium” having two roles:

- *Anchorage* which is an integral part of cardiac morphogenesis
- *Communication* which is essential for cardiac conduction and cardiac action potential propagation

Gap junctions are composed of connexins (mainly connexin 43) as one of their main subunits, so the cellular pathologies in gap junctions of cardiomyocytes (especially those related to connexin 43) can have a major role in ischemia and some lethal arrhythmias. In human, connexin 43 is the most common and important type of cardiac connexins. Usually, the Purkinje cells have a high amount of gap junctions, while they do not have considerable amounts of contractile elements.

Each cardiomyocyte is composed of a number of contractile units: let’s say *contractile quantum* or as we are more familiar it is called *cardiac sarcomere*. So, sarcomere is the basic unit of contraction (i.e., the *contractile quantum* of the heart). The primary function of cardiomyocyte is produced in each sarcomere.

As mentioned above, the cardiomyocytes are ranging from 25 to 140 μm in diameter; meanwhile, cardiac sarcomeres are “contractile quantum” of the heart and are about 1.6–2.2 μm in length.

Nearly about half of each sarcomere is composed of contractile elements, arranged as contractile fibers, while the other half is composed of all other cellular structures like mitochondria, nucleus, cytosolic structures, and other intracellular organelles.

The contractile fibers are classically divided as thick filaments and thin filaments; however, if the microscopic anatomy of sarcomere is viewed, each sarcomere is defined as the contractile part of the sarcomere located between two Z lines and consists of the following parts:

- Z lines: when seen with a microscope present as thick lines, the margins of each sarcomere is defined by Z line in each side; Z stands for “Zuckung,” a German name meaning “contraction” or “twitch”; so, each sarcomere is the region of myofilaments between two Z lines; the Z line is like an “anchor” to which the thin filaments are attached.
- Thin filaments are attached perpendicularly to Z lines on each side; thin filaments are composed of actin, tropomyosin, and troponin.
- Thick filaments are in between them in a parallel fashion; these filaments are composed of myosin and are located in the center of the sarcomere; the two ends of thick filaments are interspersed with thin filaments.
- “I” band is the area of sarcomere adjacent to Z line; during myocardial contraction, “I” band shortens.
- “A” band is the central part of each sarcomere; each “A” band, while located in center, takes two “I” bands (each I band in one side of the single A band) plus two Z lines (each Z line attached to the other side of “I” band); this complex composes a sarcomere (as presented in figure).
- “H” band is the central part of “A” band, composed mainly of thick filaments.

A full description of contractile proteins, thick filament and thin filament, is described in this chapter in later sections and also in Figs. 1.2 and 1.6.

Histological differences between cardiac muscle and skeletal muscle: one could find the following differences between cardiac muscle cell and striated muscle cell.

Cardiac muscle tissue is a complex of united and combined contractile cells, totally named as a syncytium; this syncytium is:

- Composed of branched cells with the myofibers usually being fused at their ends.
- Connected together through a *relatively unique cardiac cellular structure* called intercalated discs.
- Electrical current is transmitted by an especial electrical link “gap junctions.”
- Cardiomyocytes usually have 1 or 2 (rarely 3–4) central nuclei.
- Accompanied with *many mitochondria* having an essential role in *energy production and metabolism regulation*, the energy is delivered as ATP through oxidative phosphorylation for many processes including “excitation-contraction coupling” and the “sarcomere activity” and the relationship between contractile filaments in systole and diastole.
- One of the most important functions of mitochondria is Ca^{2+} homeostasis (see below); this is why in cardiomyocytes, the mitochondria are located near the sarcoplasmic reticulum (SR).
- Both mitochondria and Ca^{2+} have a central role in cardiomyocyte necrosis; the role of mitochondria changes from an “ATP-producing engine” to “producers of excessive reactive oxygen species” which would release “pro-death proteins.”
- The high rate of metabolism in these cells necessitates high vasculature with all the cells having aerobic metabolism.

- The special Ca^{2+} metabolism of these cells is the main result for having fewer T tubules, while these T tubules are wider (cardiac T tubules are about 5 times more than skeletal muscles in diameter).
- Thin filaments in cardiac muscles do not have a constant length.
Skeletal muscle cells have the following features due to their pattern of contraction; which is a pattern of neuromuscular junction unit:
 - Longer, multinucleated, and cylindrical shape.
 - Usually not arranged as syncytium; instead, they are located side by side with no tight binding or gap junctions.
 - Lower metabolism needs necessitating medium vasculature, with lower amounts of mitochondria (about 2–3 % of the cell).
 - Both aerobic and anaerobic metabolism.
 - Thick and thin filaments in skeletal muscles have a constant length (Severs 1985; Peters 1996; Gordon et al. 2000; Kirchoff et al. 2000; Lo 2000; Alberts 2002, 4th edition, *New York: Garland Science*; Burgoyne et al. 2008; Kobayashi et al. 2008; Meyer et al. 2010; Shaw and Rudy 2010; Workman et al. 2011; Anderson et al. 2012; Balse et al. 2012; Bingen et al. 2013; Delmar and Makita 2012; Eisner et al. 2013; Khan et al. 2012; Kubli and Gustafsson 2012; Miragoli et al. 2013; Orellana et al. 2012; Scriven and Moore 2013; Wang et al. 2012; Zhou and O'Rourke 2012).

1.1.1.3 Cardiac Conductive Tissue Cells

The synchronized *mechanical system* needs a delicate *electrical control* known as *cardiac electrical network* or *cardiac electrical system*. Cardiac electrical system is composed of two main cells:

- Excitatory cells known as “impulse-generating cells” consisting mainly of the sinoatrial (SA) node
- Specialized conduction system known as “conductive cells” composed of the atrioventricular conduction pathways, AV node, the His bundle and its right and left branches, and finally, the Purkinje fiber cells or the Purkinje fiber network distributed all over ventricles to conduct the electrical impulse all over the ventricles effectively and rapidly

This hierarchical pattern is the mainstay for effective mechanical contraction of ventricles leading to an effective cardiac output (Desplantez et al. 2007; Dun and Boyden 2008; Atkinson et al. 2011) (Fig. 1.3).

1.1.2 Anatomy of the Coronary Arteries

The coronary arterial system has four main elements (Fig. 1.4):

- Left main coronary artery (LMCA)
- Left anterior descending coronary artery (LAD)
- Left circumflex coronary artery (LCX)
- Right coronary artery (RCA)

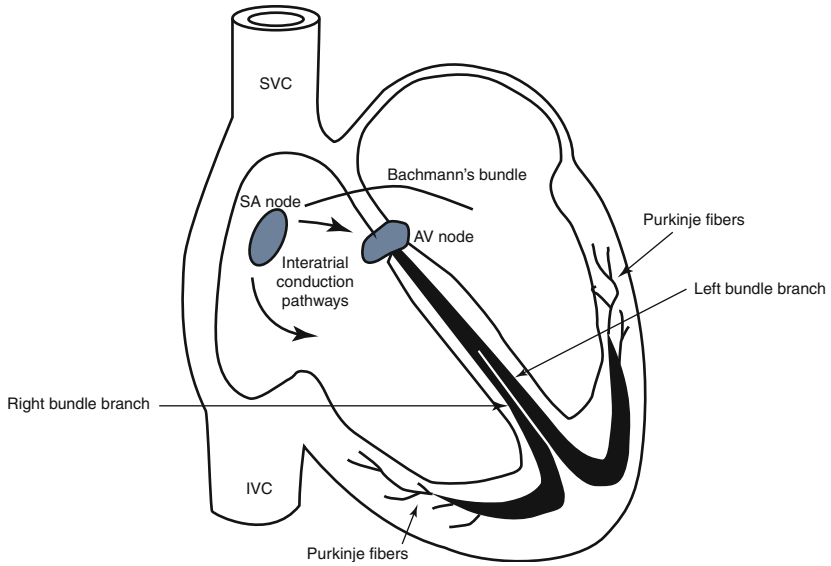


Fig. 1.3 Cardiac conductive system: different elements of the conduction system

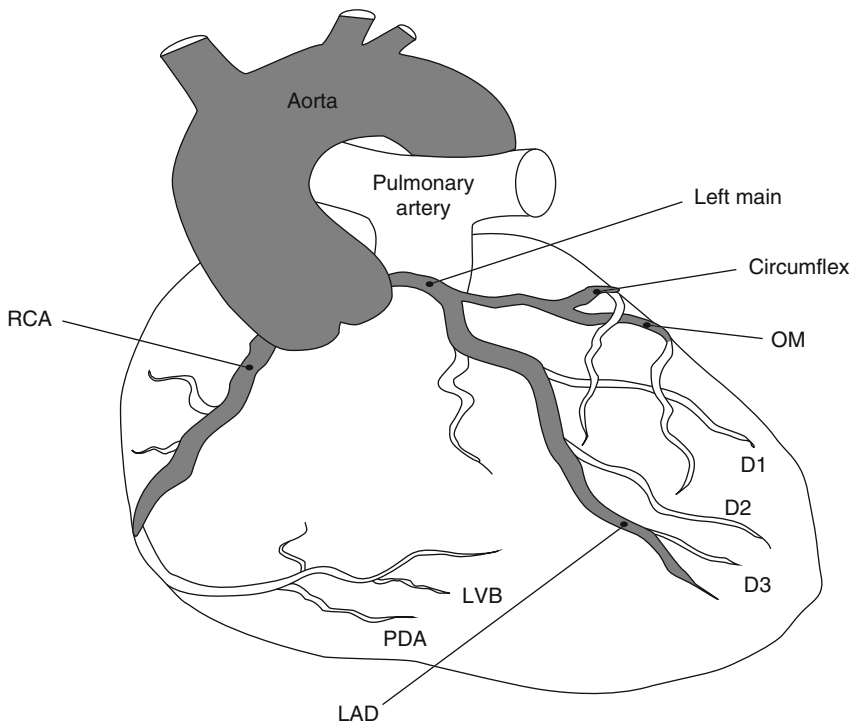


Fig. 1.4 Anatomy of normal epicardial coronary arteries

1.1.2.1 Left Main Coronary Artery (LMCA)

LMCA starts from the left coronary ostium in left Valsalva sinus and after passing a length (between 0 and 40 mm) is divided to two branches: LAD and LCX. At times, an extra branch is divided from the LMCA and passes parallel to the diagonal arterial system; this arterial branch is called the “ramus” branch.

1.1.2.2 Left Anterior Descending (LAD) Artery

After LCX is separated from LMCA, the remainder of LMCA continues its path as left main coronary artery; LAD goes down the interventricular septum and reaches the apex:

- The *diagonal branches* run as oblique derivations between LAD and LCX; the main role of diagonal branches is to perfuse the lateral wall of the left ventricle; these are demonstrated in Fig. 1.4 as D1 to D3.
- Besides the diagonal branches, there are *septal branches* of LAD which perfuse the anterior two-thirds (2/3) of the interventricular septum.

1.1.2.3 Left Circumflex Coronary Artery (LCX)

LMCA is divided to LAD and LCX often at a 90° angle at the separation point; LCX has a number of ventricular branches which perfuse the lateral and posterior walls of the left ventricle (LV); these branches are called *obtuse marginal* or simply OM; in 40 % of the patients, LCX perfuses the SA node; the other 60 % are perfused by RCA.

1.1.2.4 Right Coronary Artery (RCA)

Right coronary artery (RCA) originates from the right coronary ostium of the Valsalva sinus; so, its origin is from a different coronary ostium compared with the abovementioned coronary arteries; RCA then goes through the right atrioventricular groove (i.e., the groove located between the atria and ventricles) towards right to reach the posterior part of interventricular septum where it gives a branch called acute marginal artery; as mentioned, 60 % are perfused by RCA. Finally, RCA is divided to two main branches:

- *Posterior descending artery* (PDA): to perfuse the posterior 1/3 of the interventricular septum and the inferior wall of LV and also the posteromedial papillary muscle; in the majority of the people (85 %), PDA originates from RCA; these are called *right dominant*; however, in the other 15 %, called *left dominant*, PDA originates from LCX.
- *Posterolateral branch*: to perfuse the posterior part of LV wall.

1.2 Cellular Physiology

Among the main characteristic features of cardiomyocytes are their *very specialized* functional and histological features; these subspecialized anatomical and physiological features have a key role in production, propagation, and transmission of “electrical and mechanical” functions of cardiomyocytes. Physiologically speaking, these electrical and mechanical functions are translated to three main domains:

1. Action potential
2. Excitation-contraction coupling (ECC)
3. Contractile mechanisms and their related processes

As mentioned above, the heart muscle is composed of two main syncytia: the atrial syncytium and the ventricular syncytium. It means that in each syncytium, all the cells are interrelated with many widespread intercellular connections. The cardiomyocytes resemble the skeletal muscles, being composed of actin and myosin filaments, contracting and relaxing in a well-cooperated and organized manner in order to produce the cardiac contractile force. The intercellular connections between cardiac muscles are through the “intercalated discs” which are delicate pores located at the proximal and distal parts of each cardiomyocyte; these discs are able to transport great amounts of ions between the cardiomyocytes, transferring the ions from each cell to the next cell through the gap junctions. Hence, the term “syncytium” is not just an anatomical term but also a physiologic term. However, the two syncytia (atrial and ventricular) are separated physiologically by the AV node and AV bundle to act independently.

1.2.1 Action Potential

The normal cardiomyocytes have different electrical potentials known as action potentials. However, the resting potential and the action potential of all cells are not the same. Though, the production mechanism is similar and is the result of ion currents across the cellular membrane, the final result is consecutive depolarization and repolarization which produces the cardiac electrical impulse. The impulse is generated and conducted over the cardiac “electrical” and “conduction” system.

Action potential of cardiomyocytes is composed of five phases which are produced due to the influx and efflux of ions; especially Na^+ , Ca^{2+} , and K^+ ions, across the cell membrane.

This action potential is about 105 millivolts (mV) starting from about -80 to -90 mV reaching up to $+15$ to $+20$ mV, then experiencing a plateau for about 0.2 milliseconds, and finally turning down to the baseline which is -80 to -90 mV (Eisner et al. 2013).

The cardiomyocyte action potential is much similar to the action potential of skeletal muscle; however, it has two main features:

- First of all, the fast Na^+ channels are present, both in the skeletal muscles and the cardiomyocyte.
- Second, the slow (L)-type Ca^{2+} channels are present in the cardiomyocytes, but not in the skeletal muscle cells; however, after the start of action potential mainly by the fast Na^+ channels, L-type Ca^{2+} channels would open late and also would remain open for a few milliseconds to create the plateau of action potential. These channels have two main effects: first to decrease the heart rate in the physiologically defined range and second to augment cardiomyocyte contractions.

Besides Na^+ and Ca^{2+} , the third important ion in cardiomyocyte action potential is K^+ . Just after cardiomyocyte depolarization, due to Ca^{2+} entry to the cell, there is abrupt and considerable decreases in K^+ outflux from the cell to the external milieu. This is also an important reason for delayed plateau of the action potential, mainly

created by the slow (L)-type Ca^{2+} channels but also enforced by K^+ efflux. The permeability of the cardiomyocyte cell membrane to K^+ will return to normal after cessation of Ca^{2+} and Na^+ channels to normal potential (about 0.2–0.3 milliseconds) which causes the return of K^+ outside the cell and ending action potential.

The phases of action potential in ventricular and atrial cardiomyocytes and also His bundle and Purkinje cells are:

- Phase 0: early rapid upstroke of action potential caused by huge Na^+ influx.
- Phase 1: short-term and incomplete repolarization due to K^+ efflux.
- Phase 2: slow (L)-type Ca^{2+} channels open and there is Ca^{2+} influx; initiation of the contractions starts immediately afterwards; this phase is also called plateau.
- Phase 3: large amounts of K^+ efflux which overcome the Ca^{2+} influx; again the action potential moves to negative levels to reach the resting potential; this phase, named resting potential phase, equals diastole.
- Phase 4: influx of very negligible amounts of K^+ ; however, the “ Na^+ - Ca^{2+} exchanger” also known as “NCX” has a very important role in relaxation phase, since it sends Ca^{2+} against its gradient into the exterior of myocardial cell and sends K^+ against its gradient to interior of myocardial cell; the failure of this pump to function properly has been implicated as one of the mechanisms involved in heart failure (Table 1.1, Fig. 1.5).

Table 1.1 A summary of action potential events in ventricular and atrial cardiomyocytes and also His bundle and Purkinje system

Phase	Term	Involved ion(s)
0	Rapid upstroke	Na^+ influx
1	Short-term and incomplete repolarization	K^+ efflux
2	Plateau	Ca^{2+} influx and K^+ efflux
3	Repolarization (main part)	Large K^+ efflux
4	Diastole (resting potential)	K^+ influx (very negligible amounts)

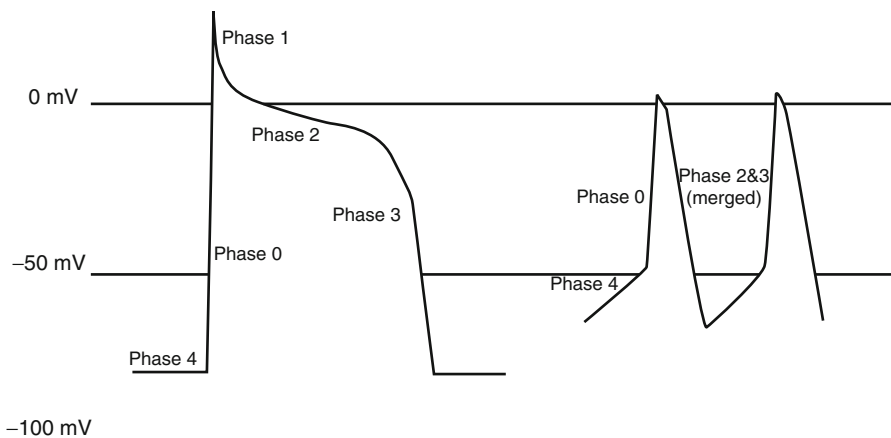


Fig. 1.5 Action potential in a normal cardiac cell (*left*) and a conducting cell (*right*)

There are a number of differences between “sinoatrial (SA) node and atrioventricular (AV) node cells” on one side with “ventricular and atrial cardiomyocytes and also His bundle and Purkinje cells” on the other side regarding the phases of action potential; these differences are mainly due to increased “Na⁺ influx” during phase 4 and increased “Ca²⁺ influx” and decreased “K⁺ influx” during phase 4 which causes:

- Resting potential of pacemaker cells is less negative than the other cardiac cells; it means that if resting potential in majority of cardiac cells is -80 to -90 mV, it would be just -50 to -60 mV in pacemaker cells; the reason for the change is that the flux of Na⁺ from outside to inside of pacemaker cells (i.e., Na⁺ influx) continues during repolarization, changing the resting potential level from about -90 mV to upper levels in such a way that it reaches the needed voltage for threshold of repolarization (i.e., about -50 to -60 mV); this Na⁺ current is called pacemaker *funny current of heart*, i.e., I(f) of the heart; this funny current is responsible for rhythmic, spontaneous, pacemaker activity of the pacemaker cells, especially SA node.
- Phase 4 (diastole) of action potential is more abrupt and head up, i.e., not as much flat of the cardiac muscles’ action potential, again due to the same Na⁺ current in repolarization period.
- Phase 1 of action potential is nearly eliminated.
- Phases 2 and 3 are nearly merged together.

Refractory period of cardiomyocytes: refractory period in cardiac action potential is the time interval after termination of each action potential in which no new impulse could be generated after any stimulus; the role of refractory period is to prevent premature contractions during a definite time interval and also could have a protective role for the heart against “reentrant arrhythmias.” However, *the time interval for refractory period* is not constant all over the cardiac cells, being shorter in the atrial cells (0.15 s) than the ventricular cells (0.3 s). Physiologically speaking, the phase 2 (plateau) of action potential is the *main determinant factor* for duration of refractory period.

(Boyden et al. 1988; Szigligeti et al. 1996; Reuter et al. 2005; DiFrancesco 2006, 2010; Bucchi et al. 2007; DiFrancesco and Borer 2007; Zhang and Hancox 2009; Chen et al. 2010; Neco et al. 2010; Pott et al. 2011; Coronel et al. 2012; DiFrancesco and Noble 2012; Ednie and Bennett 2012; Shy et al. 2013; Strega et al. 2012; Torres-Jacome et al. 2013; Brunello et al. 2013; Goldhaber and Philipson 2013; Kim et al. 2013; Ottolia et al. 2013; Papaioannou et al. 2013; Sipido et al. 2013; Weisbrod et al. 2013)

1.2.2 Excitation-Contraction Coupling (ECC)

Excitation-contraction coupling (ECC): this term, used in 1952 for the first time, depicts a physiologic process which *transforms an electrical impulse to a mechanical contraction* which is seen in both skeletal and cardiac muscles. In cardiac muscles, ECC acts as a “joint” in cardiomyocytes between the *electrical function* and *mechanical function* of the heart. ECC is one of the most important mechanisms in

cardiac physiology. This very important mechanism is composed of three main delicate cellular and subcellular mechanisms, each having their individual elements; when these structures interact together in a regulated manner, the *electrical action potential* is changed to the *mechanical force* of the cardiomyocyte. These composing aspects are:

1. Functioning organelles of ECC
2. Calcium ion (Ca^{2+})
3. Controllers of ECC

A summary of these composing aspects and their related items are presented in the Table 1.2.

1.2.2.1 Which Parts of Cardiomyocyte Are the Functioning Organelles of ECC?

Which parts of cardiomyocyte are the main components of ECC? The following parts of cardiomyocyte involved in the ECC process are:

1. *Cell membrane* (which is responsible for electrical function, i.e., action potential; discussed before)
2. *Thick and thin filaments* (which are responsible for mechanical function, i.e., contractile function; discussed later in this chapter)
3. *Mitochondria* (ECC needs a great amount of energy; mitochondria are responsible for supporting ECC regarding its energy needs in the form of ATP through oxidative phosphorylation; discussed before)
4. *Sarcoplasmic reticulum* (known as SR; discussed here)
5. *Transverse tubules* of cardiomyocytes (known as T tubules; discussed here)

Sarcoplasmic reticulum: SR is divided into longitudinal SR (LSR) and junctional SR (JSR). LSR releases Ca^{2+} reserves into the cell as fast as possible in just a few milliseconds, which would activate cardiomyocyte contractile structures. Junctional SR contains huge “ Ca^{2+} -releasing channels” called “ryanodine receptors.” These receptors form a protein network which would enhance the release of Ca^{2+} in response to the Ca^{2+} influx. The role of “ryanodine receptors” is more recognized when considering this fact:

Table 1.2 A summary of the composing aspects of ECC and their related items

1	Functioning organelles of ECC	Cell membrane Thick and thin filaments T tubules Sarcoplasmic reticulum
2	Calcium ion (Ca^{2+})	Ca^{2+} influx to the cardiomyocytes (by L-type Ca^{2+} channels in <i>systole</i>) Ca^{2+} release inside the cell (by RyR in <i>systole</i>) Ca^{2+} efflux from the cardiomyocytes (by NCX in <i>diastole</i>) Ca^{2+} reuptake from the cell (by SERCA in <i>diastole</i>)
3	Controllers of ECC	Ryanodine receptor (RyR) family Dihydropyridine receptor (DHPR) Calmodulin

For *cardiac cell* contraction, nearly 75 % of Ca^{2+} in cardiac cell cytoplasm is released from SR.

T tubules: as mentioned before, T tubules are invaginations of the cardiomyocyte cell membrane into the interior space of the cardiac muscle cells and transmit the action potential of the cell membrane to the interior parts of the cardiomyocyte. The role of T tubules is conducting the depolarization phase of action potential, as rapidly as possible, from the cell membrane to the interior of the cell.

Then, the electrical current produced by action potential is transmitted through the T tubules to the interior of the cell, to the “longitudinal sarcoplasmic reticulum.” During some cardiac diseases like heart failure or ventricular hypertrophy, the “loss of integrity in transverse tubules” is one of the main etiologies for impaired availability of Ca^{2+} for sarcomere contractile mechanisms, which would impair Ca^{2+} movements and its availability for contraction of the sarcomere myofilaments.

T tubules of cardiomyocytes have some *unique features*:

1. Ca^{2+} is the main mediator playing the most important role in cardiomyocyte action potential, ECC, and finally, muscle contraction. Although the start of action potential in *cardiac muscles* is similar to skeletal muscle, its continuation is dependent on the role of Ca^{2+} , as mentioned above (see subtitle of *action potential*). As mentioned above, the role of Ca^{2+} is also important in the release of intracellular Ca^{2+} reservoirs: “the CICR phenomenon”; CICR is one of the mechanisms demonstrating why structural disintegration and disturbance of T tubules is an early happening in heart failure.
2. Although cardiac cell action potential is the main trigger for Ca^{2+} release, the first Ca^{2+} release is from the large Ca^{2+} reservoirs of T tubules, and T tubules would trigger the release of more Ca^{2+} from SR. As mentioned before, the influx of Ca^{2+} from ECF to interior of cardiac cells through slow (L)-type calcium channels located on the T tubule strengthens the depolarization of *cardiac muscle* cells and causes the plateau phase of depolarization; this feature is special to depolarization of cardiac cells, while in skeletal muscle depolarization, the influx of Ca^{2+} to skeletal cells, through T tubule’s slow (L)-type calcium channels, *does not* have any significant role.
3. T tubules are invagination of the cell membrane to the cells; it means that T tubules are in fact part of the extracellular fluid (ECF); so, they have continuous exchange of Ca^{2+} with ECF. Any decrease in Ca^{2+} concentration of blood would be associated with a decrease in Ca^{2+} concentration of ECF, which in turn would reduce Ca^{2+} concentration in the intracellular milieu; this is why any decrease in plasma levels of Ca^{2+} is associated with decreased cardiac contractility.

1.2.2.2 Ca^{2+} Homeostasis

Ca^{2+} homeostasis in cardiomyocytes is such an important issue that any perturbation in its equilibrium state would result in cardiac disturbances. Intracellular Ca^{2+} is

considered as a second messenger in cardiac sarcomeres, while its concentration and trends of change exert important effects on “mitochondrial energy,” “cell death or apoptosis,” and “the intracellular buffering capacity for controlling stress.”

To have this equilibrium in a continuous manner for a lifelong time, a delicate balance between Ca^{2+} influx and Ca^{2+} efflux in cardiomyocytes is an obligation: the Ca^{2+} balance has a central role in each cardiac cycle, composed of a systole (contraction) and a diastole (relaxation); although there are a number of states in which influx would exceed efflux or vice versa, a number of subcellular mechanisms work together to modify these fluxes and reach the final equilibrium in such a way to increase the efficacy of myocardial contractions as a result of control in Ca^{2+} homeostasis.

Ca^{2+} surge and Ca^{2+} reuptake are both located inside the cardiomyocytes and also, both are among the main features of systole and diastole, respectively. This dual phase is seen in all aspects of Ca^{2+} homeostasis, including cardiac contraction, Ca^{2+} flow direction, Ca^{2+} concentration inside each cell, and Ca^{2+} release and reuptake in all potential intracellular elements like mitochondria.

The *dual phase pattern of Ca^{2+}* with its widespread pattern of distribution and its extensive effects is controlled mainly by four mechanisms:

1. Ca^{2+} influx to the cardiomyocytes (mainly by L-type channels in *systole*: contraction phase)
2. Ca^{2+} release inside the cell (by ryanodine receptor or “RyR” in *systole*: contraction phase)
3. Ca^{2+} efflux from the cardiomyocytes (mainly by Na^+ - Ca^{2+} exchanger “NCX” in *diastole*: relaxation phase)
4. Ca^{2+} reuptake from the cell (by sarcoendoplasmic reticulum Ca^{2+} transport ATPase “SERCA” in *diastole*: relaxation phase)

One of the main etiologic mechanisms for heart failure is “reduced and sluggish Ca^{2+} release and slow removal of Ca^{2+} .” In these patients, reduced and delayed function of L-type Ca^{2+} channel, slowed release of Ca^{2+} from SR, and “delayed activation” of Na^+ - Ca^{2+} exchanger “NCX” are among the most important mechanisms involved in the pathogenesis of the disease state.

1.2.2.3 What Are the Controllers of ECC?

The exact mechanisms of ECC are delicately controlled and regulated *mainly* by these proteins:

1. Ryanodine receptor (RyR) family (a class of intracellular Ca^{2+} receptors)
2. Dihydropyridine receptor (DHPR)
3. Calmodulin

Let’s once more stress on the fact that Ca^{2+} cycling is the ultimate goal of ECC and the main mechanism responsible for its course, including commencement, continuation, and termination of ECC.

Ca^{2+} would enter the cardiomyocyte cytosol through L-type Ca^{2+} channels (also known as dihydropyridine, DHP) in cytosol. This primary Ca^{2+} influx would trigger Ca^{2+} release from subsarcolemma SR (i.e., the specific part of the SR which is under the sarcolemma):

Ca^{2+} cycling is the ultimate goal of ECC and the main managing mechanism.

The functional steps in ECC are as follows:

1. ECC is started by Ca^{2+} entry into cells through L-type Ca^{2+} channels (i.e., DHP).
2. These initial small amounts of Ca^{2+} trigger type 2 of ryanodine receptor (i.e., RyR2).
3. RyR2 is located on the JSR and the triggering RyR2 causes huge amounts of Ca^{2+} to be released from SR (the release of large Ca^{2+} amounts after the initial small Ca^{2+} influx is called Ca^{2+} -induced Ca^{2+} release “CICR,” a phenomenon first explained by Fabiato).
4. In turn, the necessary Ca^{2+} for contraction is released from SR reservoirs.
5. Immediately afterwards, interaction of Ca^{2+} with contractile proteins of sarcomere occurs.
6. The above interaction between Ca^{2+} and contractile proteins produces mechanical force of contraction.
7. The Ca^{2+} surge would be resolved by later Ca^{2+} reuptake.
8. Ca^{2+} reuptake is primarily done through a recycling mechanism in SR (SR acts as a very huge intracellular Ca^{2+} reservoir) which happens after occurrence of the contraction.
9. The rest of Ca^{2+} is effluxed outside the cell by a pump called $\text{Na}^+/\text{Ca}^{2+}$ exchanger (NCX).
10. Ca^{2+} reuptake by SR ends contraction and starts relaxation; Ca^{2+} reuptake is a primary function of a specific protein called sarcoendoplasmic reticulum Ca^{2+} transport ATPase “SERCA” which is an ATP-dependent Ca^{2+} pump in SR; SERCA is also the main protein component of SR.
11. The 2nd main protein of SR is phospholamban which inhibits the function of SERCA; in other words, “phospholamban is a major regulator of SERCA pump.”
12. SERCA activates Ca^{2+} reuptake and relaxation, while phospholamban ends the Ca^{2+} reuptake and, hence, ends the relaxation phase.

Besides SERCA, calmodulin, and phospholamban, there are a number of other main proteins involved in Ca^{2+} reserve and adjustment called calsequestrin, calreticulin, and calmodulin.

Calsequestrin is a Ca^{2+} -storing reservoir inside the sarcoplasmic reticulum containing large amounts of calcium which keeps calcium inside SR against its gradient; the release of calcium from calsequestrin is among the main triggering factors for contraction.

Calmodulin (CaM) is an abbreviation for *calcium-modulated protein*, a small-sized protein with the following characteristics:

- Each molecule of calmodulin binds to 4 Ca^{2+} ions.
- Calmodulin controls and modulates (i.e., excites or inhibits) two main Ca^{2+} ports which have essential role in ECC,
- Calmodulin controls both slow (L)-type Ca^{2+} channel (located in transverse tubules of the sarcolemma) and also RyR located at JSR.

- So, calmodulin is a multifunctional protein which does its functions through signal transduction and plays the role of the “boss” who controls all the Ca^{2+} bottlenecks in cardiomyocyte.

(Abbott and Ritchie 1951; Sandow 1952; Hamilton et al. 2000; Periasamy and Huke 2001; Tang et al. 2002; Scoote et al. 2003; Yang et al. 2003; Bickler and Fahlman 2004; Scoote and Williams 2004; Reuter et al. 2005; Vangheluwe et al. 2006; Periasamy et al. 2008; Currie 2009; Kerckhoffs et al. 2009; Koivumaki et al. 2009; Neco et al. 2010; Williams et al. 2010; Malik and Morgan 2011; McDonald 2011; Prosser et al. 2011; Rybakova et al. 2011; Tavi and Westerblad 2011; Eisner et al. 2013; Ibrahim et al. 2013; Jafri 2012; Lu et al. 2013; Nakada et al. 2012; Scriven and Moore 2013; ter Keurs 2012; Goldhaber and Philipson 2013; Shy et al. 2013; Sipido et al. 2013; Solaro et al. 2013)

1.2.3 Contractile Mechanisms and Their Related Processes

The contractile function of the heart is a unique function produced in each of the cardiomyocytes. As mentioned in the previous parts of this chapter (Sects. 1.1 and 1.2), the cardiac muscle is composed of two muscle masses: “atrial syncytium” and “ventricular syncytium.” We can assume each of the two syncytia as a separate “military band” with all the cardiomyocytes working and acting in a cooperated, regulated, and arranged manner, as each soldier acts in a military group during a “military march.” So, the physical outcome of cardiomyocyte function is force generation, and its physiological outcome is cardiac contraction which in turn would produce cardiac output. However, cardiac output (i.e., physiological role of the heart) is set in a widespread spectrum; so, the body demands are met well in severe exercise as well as deep sleep. Such an adaptive and cooperative capacity for fulfilling demands in a wide range of body physiologic needs is directly dependent on the contractile properties of sarcomere. Part of these mechanisms is discussed here; but, the full nature of these mechanisms, in health or in disease, is far beyond the scope of this book.

As described in the previous pages (Sect. 1.1), each cardiomyocyte is composed of a number of contractile units or let’s say *contractile quantum* which is called *cardiac sarcomere*. So, the main function of cardiomyocyte is produced in sarcomere. As mentioned, each sarcomere is margined by a line named “Z” line; so, each sarcomere is the region of myofilaments between two Z lines. Thin and thick filaments are the main contractile elements of sarcomere.

It would be worth to know that genetic disturbances (including mutations) are an important source for creating pathologies in sarcomere myofilaments; these pathologies would be the origin for a number of cardiac diseases (named sarcomere diseases with genetic origin); among them, a number of hypertrophic or dilated cardiomyopathies, rhythm disorders, and sudden cardiac death could be mentioned.

However, when considering the cellular mechanisms of contraction, the storey is much more complicated, containing the following steps:

- Contraction of the cardiomyocyte is composed of a repeated and continuous contraction-relaxation process, being the main function of the sarcomeres.
- We should know that the engine of this contractile process is started with an *ignition switch*: Ca^{2+} , which is the initiator of the contractile process.
- Cardiomyocyte action potential releases Ca^{2+} from sarcoplasmic reticulum (SR) and T tubules.
- At the next step, Ca^{2+} starts the contraction-relaxation process known as “cross-bridge cycling.”
- The contraction-relaxation process is done through the contractile proteins located in thick and thin filaments discussed in previous sections of this chapter.
- Ca^{2+} concentration which is necessary for activation of concentration in cardiomyocytes is always lower than the “saturation” level: it has been demonstrated that *decreased myofilament response* to effects of Ca^{2+} in the contractile system is one of the main mechanisms for heart failure.

The very unique contractile proteins of sarcomere could be classified as “functional classification” and “structural classification.”

1.2.3.1 Functional Classification of Sarcomere Proteins

Functional classification of sarcomere proteins divides the sarcomere contractile proteins functionally as two protein classes:

Contractile proteins: the contractile proteins are mainly composed of actin, myosin, and titin; cardiac contraction is the final outcome of interactions between myofilaments, presented at cellular level as *cross bridges* of myosin head with actin.

Regulatory proteins: contraction of all muscles including cardiac sarcomeres is a very delicate and ordered phenomenon needing precise regulatory and control systems; in sarcomeres, this regulatory function is a duty by the *regulatory proteins* which work “shoulder to shoulder” of contractile proteins to control their cross-bridge-induced contractions; the main regulatory proteins are “troponin,” “tropomyosin,” “tropomodulin,” and “myosin-binding protein C”; when sarcomere is in relaxation phase, these two proteins attach to actin and myosin to prevent contraction. However, when action potential goes to the activation phase, Ca^{2+} is attached to troponin in order to activate interactions between myosin head and actin; contraction starts immediately afterwards.

1.2.3.2 Structural Classification of Sarcomere Proteins

Structural classification of sarcomere proteins divides the sarcomere contractile proteins in one of the two following classes:

- Thick filament
- Thin filament

These two filaments are formed as interdigit strands going “in between” each other and coming out in a sliding manner; this sliding back-and-forth movement of thin and thick filaments forms the cardiac “systole” and “diastole,” respectively (see Figs. 1.2 and 1.6).

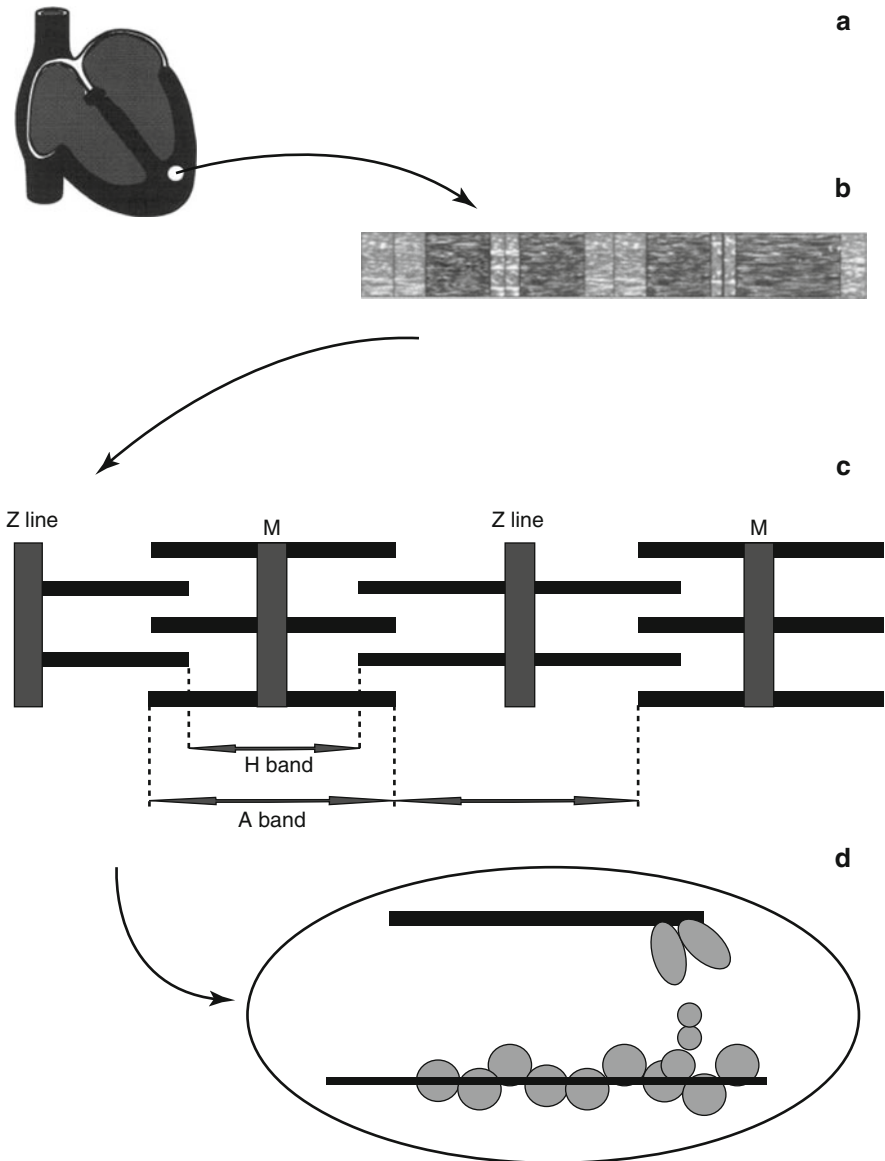


Fig. 1.6 Detailed sarcomere anatomy in different aspects; also, see Fig. 1.2. (a) Macroscopic schematic presentation of the heart. (b) Myocardial filaments as seen under microscope. (c) Microscopic structure of a sarcomere; thin and thick filaments are presented as thin and thick interspersed horizontal rods; a sarcomere is defined as the part of sarcomere between two Z lines. (d) Thick filament with its two myosin light chains and also thin filament with F actin and tropomyosin molecule between actin monomers (see text)

Thick Filament

The contractile proteins are the “workforce” of the myocardium; the more the *cross bridges* of actin and myosin, the more the contractile force of the sarcomere. Cross bridges are the result of interactions between myosin head and actin after trigger of Ca^{2+} .

Myosin is the largest and heaviest protein of sarcomere among the others which are in the form of rods; being about 15 nm in diameter, it composes thick filament of myofibrils and interacts with actin during contractions as cross bridges; myosin rods are made of myosin molecules in the following features and characteristics:

- One myosin heavy chain (MHC) plus two myosin light chains (MLC) are composed together as a single strand.
- Two single strands twist round each other to produce one molecule of myosin.
- Each myosin molecule has two functional domains, a head (composed of four MLC's and the lever like end of two MHC's) coming out of the main molecule.
- Myosin heads are the *main location* for interactions with actin and create hinge-shaped features, coming out of the bouquet like “lever arm” and are inhibited by TnI; after interaction with Ca^{2+} they attach to actin in order to produce cross bridges.
- Three hundred molecules of myosin are attached together in a parallel fashion to form the myosin rod, whose microscopic figure is similar to a number of parallel golf clubs forming a bouquet, twisting together in an orderly fashion forming the *body of myosin rod*; while their heads are exposed out of the bouquet, the bodies are attached together.

Cross bridges between actin and myosin (the principal mechanism of muscle contraction) are formed repetitively and released after a very short period of time; great amounts of ATP molecules are used for production of actin-myosin interactions and cross bridges leading to muscle contractions. These interactions cause a rotation in myosin along actin filament; the main interaction site is the head and hinge region of myosin.

Myosin-binding protein C (MYBPC) is another important and determining protein of sarcomere, being among the regulator proteins; a number of life threatening arrhythmias and some types of hypertrophic cardiomyopathies are the results of genetic impairments in this protein; new treatments of heart failure are in development regarding the role of this protein.

Titin is the 3rd most common filament in sarcomere (after actin and myosin), being the main factor for passive features of the myocardium in lower ventricular volumes; this is why the main role of titin is muscular assembly of the heart and its elasticity features. Regarding the molecular structure, titin is a giant filamentous protein, extending as long as “half sarcomere from Z line to M line”; this giant structure of titin provides a continuous link between the Z line and the M line inside each sarcomere; so, titin functions as an extensible filamentous protein to preserve the structural integrity of sarcomere and also to function in sarcomere to reach its

normal length after systolic contraction and returning to normal length in diastole. This is why titin has a central role in patients with ischemic or diastolic heart failure.

As it is demonstrated in Figs. 1.2 and 1.6, the force created by titin helps keep the thick filament in its central position in sarcomere, maintaining the balance inside the sarcomere between sarcomere structures during systole and diastole.

Titin could be divided to two main parts: the *extensible part* which is located in the “I band” area of sarcomere and the *non-extensible part* located in the “A band” area of sarcomere. Also, the extensible parts of titin are mainly composed of two segments, both taking part in passive force development of sarcomere during stretch:

- Immunoglobulin-like segment.
- PEVK segment in which four amino acids are abundant: proline (P), glutamate (E), valine (V), and lysine (K).

Finally, if we want to describe titin in just a two-word phrase, we could name titin as *molecular spring* of the sarcomere which creates elastic properties for the sarcomere.

Thin Filament

Thin filament is composed of the following ingredients discussed here; if we consider an “imaginary unit” for thin filament, this unit consists of:

- 1 F actin strand
- 2 tropomyosin strands (i.e., 2 TM)
- 2 troponin complex (i.e., 2 Tn)

These “imaginary units” are attached together in a row, from head to tail, to compose the thin filament in such a way that:

- F actin (the actin strand) makes the foundation of the filament.
- The two tropomyosin molecules lie in the two grooves of the filament as long as the entire thin filament.
- Troponin complexes are attached to actin filament at defined intervals.

Actin is one of the main contractile proteins and also a main protein of the thin filament; actin filaments are double-stranded filaments composed of actin molecules, arranged in a special configuration; actin is a 43-kd, 7-nm globular protein *G actin*; 13 G actin monomers are polymerized to form the two-stranded filament *F actin* which is a 360° twisted filament as the contractile element. F actin in cardiomyocytes is mainly “alpha actin” isomer. Pathogenic mutations in actin-related genes are responsible for some cardiac diseases like idiopathic dilated cardiomyopathy.

Tropomyosin (TM) is a part of the thin filament, being an inhibitory protein; this protein is formed as α -coiled coil dimmers attached head to tail; in other words, each TM molecule is attached to another TM molecule; then, these two twist round each other to create the first coil and afterwards, the first coil twists once more round itself to produce the coiled coil; this final configuration is repeatedly formed in thin filament and is located inside the groove of F actin between two adjacent lines of actin monomers in such a way that each TM is in attachment with seven actin monomers; however, this line of repeated TM molecules are attached together from the

head of one molecule to the tail of the next and so on. This special configuration of TM has a very determining role in coordination and cooperation of the functions of thin filament.

Troponin is part of the thin filament; each troponin complex is attached to one actin monomer after each seven repeated monomers; troponin is in fact a complex of three proteins totally named as troponin complex “Tn”:

- Troponin C (TnC) is the Ca^{2+} receptor protein in the contraction-relaxation process; 4Ca^{2+} could attach to each TnC molecule.
- Troponin I (TnI) binds to actin to inhibit actin-myosin interaction.
- Troponin T (TnT) is responsible for attachment of troponin to TM; it binds to TM on one side and on the other side binds to TnC and TnI.

Tropomodulin is a regulatory filament located at the end of actin to prevent excessive elongation of the filament.

Now, let's once go back to Ca^{2+} which is the *ignition switch* of the contraction-relaxation process. When Ca^{2+} binds to TnC, there is a structural change in TnI which would move away from F actin, in such a way to expose the special site on actin for attachment of myosin head; after Ca^{2+} removal from TnC, TnI resumes its primary structural form to inhibit the actin-myosin attachment. TnI-actin interaction has an inhibitory nature; hence, the release of TnI from actin causes detachment of actin from one myosin head and its attachment to another myosin head; the detachment-attachment of actin-myosin head is an ATP-consuming process.

TnC and TnI form the head of Tn, while TnT forms the tail of Tn. These three subunits of troponin have determining roles in contraction-relaxation phases of cardiomyocytes. There are a series of *pathogenic mutations* in amino acid sequence of TnI, resulting in impaired function of TnI as an inhibitory protein in cardiomyocyte contractile system, leading to some type of “diastolic dysfunction” or “hypertrophic/restrictive cardiomyopathies”; also, TnI has the diagnostic role in myocardial infarction.

The specific site for Ca^{2+} in TnC is the unique location and the sole place which has a direct and central role in contraction process of cardiomyocytes through Ca^{2+} , performing its function through the following mechanism:

- When Ca^{2+} is attached to TnC, it would induce a “structural change” in troponin.
- This configuration change will result in dissociation of tropomyosin from actin.
- Then, when actin is released, “myosin attachment site” on actin filament is freed.
- Myosin attachment site could start a new the “cross-bridge formation.”
- “Inappropriate phosphorylation of sarcomere contractile proteins” especially *troponin* and *myosin* should be mentioned among the important etiologies for heart failure (like ventricular hypertrophy, diabetic cardiomyopathy or heart failure).

The following factors are the main determinants of force generation in cardiac sarcomere:

- Ca^{2+} activation level (i.e., level of sensitivity of sarcomere proteins to Ca^{2+})
- Sarcomere length (i.e., the Frank-Starling relationship)
- Myofilament phosphorylation and other changes in sarcomere proteins (this is why in some cardiac pathologies phosphorylation of cardiac contractile proteins has a central role in progress of the disease)

Table 1.3 A summary of the main sarcomere proteins

	Thick filament	Thin filament
Contractile proteins	Myosin Titin	Actin
Regulatory proteins	Myosin-binding protein C	Tropomyosin Troponin Tropomodulin

On the other hand, the two latter factors could affect the sensitivity of contractile filaments to Ca^{2+} (Table 1.3).

(McLachlan and Stewart 1975; Hill et al. 1980; White et al. 1987; Pan et al. 1989; Schoenberg 1993; Thierfelder et al. 1994; Farah and Reinach 1995; Marston et al. 1998; Redwood et al. 1999; Wick 1999; Gordon et al. 2000; Linke 2000a, b; Morimoto and Goto 2000; Craig and Lehman 2001; Agarkova et al. 2003; Marston and Redwood 2003; Agarkova and Perriard 2005; Granzier et al. 2005; Bragadeesh et al. 2007; LeWinter et al. 2007; Vahebi et al. 2007; Hitchcock-DeGregori 2008; Kobayashi et al. 2008; Ohtsuki and Morimoto 2008; Rice et al. 2008; Teerlink 2009; Campbell 2010; Offer and Ranatunga 2010; Gautel 2011; Kruger and Linke 2011; Malik et al. 2011; Malik and Morgan 2011; McDonald 2011; Posch et al. 2011; Tardiff 2011; Balse et al. 2012; Eisner et al. 2013; Herzog et al. 2012; Kajioka et al. 2012; Knoll 2012; Kuster et al. 2012; ter Keurs 2012)

1.3 Cardiac Cycle and Cardiac Work

1.3.1 Normal Cardiac Cycle

The final goal of all cardiac treatments (medical, surgical, or interventional) is to change the situation from a diseased pathologic heart towards a normal physiologic heart, which would pump the blood appropriately. In other words, our interventions need to go, as much as possible, towards a normal physiologic heart which could pump the blood appropriately with appropriate force and in appropriate time manner. In other words, we need to go, as much as possible, towards a normal cardiac physiology or, more specifically, a normal *cardiac cycle*, filling normally in diastole (with appropriate time schedule and normal pressure, without overpressurizing the pulmonary vasculature), then ejecting enough blood in systole. The above process could be translated into a 4-phase repetitive cycle, as the following:

Phase 1 “Diastolic filling” during which the atrioventricular valves (i.e., mitral and tricuspid) open, while aortic and pulmonary valves are closed. In this phase, the ventricular cavity is filled with blood based on three factors:

- Pressure gradient between atria and ventricles
- Ventricular diastolic compliance
- Atrial contraction (atrial kick)

Phase 2 “Isovolumic systole” during which the ventricular cavity pressure raises without any volume change. The atrioventricular valves are closed in early stages of this phase. However, in a fraction of time, the intracavity pressure increases to a critical level which is more than aortic and pulmonary valves, going to the next phase.

Phase 3 “Systolic ejection” in which blood is pushed with a high pressure to the aorta or pulmonary bed, i.e., blood ejection, to perfuse each of the two vascular beds. The size of the ventricles decreases as blood ejects and their blood content exits as fast as possible.

Phase 4 “Isovolumic relaxation” in which both ventricles are relaxed, starting to increase their size. The aortic and pulmonary valves are closed due to decreased intraventricular pressure, while mitral and tricuspid valves begin to open. Again, the cardiac cycle goes to phase 1 to start a new cycle (Tanaka et al. 1993; Gibson and Francis 2003; Chatterjee 2012).

1.3.2 Cardiac Work

Cardiac work implies the product of myocardial performance and is the algebraic sum of two different items: first, the *external work* which is equivalent to the total myocardial energy used for ejecting blood out of the ventricles to the systemic and pulmonary vascular bed. The second parameter is the *internal work* which is the total energy needed by myocardial tissue to maintain cell energy, myocardial integrity, and homeostasis of cardiomyocytes. For calculating the external work, we use the product of “stroke work multiplied by ventricular cavity pressure.” However, we usually calculate the external work by calculating the area under curve of pressure-volume loop of left ventricle (i.e., LV pressure-volume AUC). The main myocardial need for energy reserve and its oxygen consumption is for used for external work; however, myocardial ischemia would jeopardize mainly the external work. There are a number of clinical indices for assessment of cardiac work. Since we could not measure the cellular energy easily in clinical practice, we use a number of indices which are discussed here. These are stroke volume, cardiac output, and ejection fraction.

1.3.2.1 Stroke Volume

Each “stroke volume” is the amount of blood ejected from the heart in each cardiac beat. Stroke volume (SV) is the result of “end diastolic volume (EDV) minus end systolic volume (ESV)” or, simply, “ $SV = EDV - ESV$.” According to this equation, both EDV and ESV could affect SV. However, which factors could affect EDV and ESV?

- EDV depends directly at two factors:
 1. *Venous return* is the returned blood to the ventricles from veins, i.e., from inferior and superior vena cava (IVC and SVC) to RV and from pulmonary veins to LV.
 2. Diastolic time of ventricular filling or simply “filling time” which is the time in diastole that blood accumulates in ventricles; the longer the filling time, the more the SV would be.

- ESV depends on three factors:
 1. *Preload* is the amount of ventricular stretching; the more stretch in ventricle, the more contractile force; this is discussed more in the Sect. 1.3.3; the relationship between preload and ESV is a converse relationship.
 2. *Contractility* is the contractile force of the myocardium; this factor has a converse relationship with ESV, i.e., the more contractility, the less volume would remain in the ventricle; however, there are a multitude of factors affecting contractility which are discussed later.
 3. *Afterload* is the resistance against the pumping action of ventricles; there is a direct relationship between ESV and afterload; for LV, afterload is mainly the systemic vascular resistance (SVR) which is about 90 % of LV afterload; however, pulmonary vascular resistance (PVR) produces about 50 % of RV afterload, and the RV wall stress is responsible for the other half of RV afterload.

1.3.2.2 Cardiac Output

Cardiac output, abbreviated as CO is the amount of blood which is pumped out of the heart during a 1-min interval; so, CO is the product of SV multiplied by heart rate; so, “cardiac output (mL/min)=stroke volume (mL/beat)×heart rate (beat/min)” or simply: $CO = HR \times SV$.

1.3.2.3 Ejection Fraction

Another important variable is ejection fraction or more commonly known as “EF.” EF is calculated based on this equation: $EF = SV/EDV$. (In this formula, EDV stands for end diastolic volume.) Usually EF is expressed in percentage. Normal EF is usually between 55 and 70 %; though more than 50 % is considered normal for EF and consider patients having $EF > 50\%$ as good LV performance. EF is directly a very determining index of cardiac function and global clinical outcome. Patients with $EF < 30\%$ are often considered as very high risk cases impressing the global outcome.

Among the above three main factors (i.e., SV, ESV, and EDV), the cardiac work is much related to EDV and less to the other two factors; this is due to the length-tension concept of sarcomere which affects the cardiac contractility, cardiac work, and cardiac output more than the others. To understand this latter fact, we have to discuss Frank-Starling relationship in the next paragraph (Germano et al. 1995; Ababneh et al. 2000; Rozanski et al. 2000; Sharir et al. 2006; Lomsky et al. 2008; Mahadevan et al. 2008).

1.3.3 Frank-Starling Relationship

Otto Frank in 1895 and Ernest Starling, two decades later, demonstrated in animal models that the heart has a very important basic and intrinsic characteristic: “length-dependent activation” or the “Frank-Starling relationship.”

The Frank-Starling relationship tells us that the more blood accumulated in each of the ventricles in diastole, the more pump output would be pushed out in systole.

This interesting feature is seen even when the heart is removed out from the body to work in a lab environment. So, the Frank-Starling relationship tells us that the heart has a wide range of capacity for adaptation against preload, afterload, and their related imposed work; this fundamental concept of cardiac physiology explains the ability of the heart to change its contractile response under different physiologic and pathologic states, in such a way to save the cardiac output as much appropriate as possible to physiologic body demands. This adaptation capacity is both due to the cellular structure of the heart (especially the sarcomere structure) and also the effects of neurohormonal effectors and the cardiac reflexes. So, considering these length-force changes, we reach to a final conclusion which is the general concept of Frank-Starling relationship: within a defined length of sarcomere, there is a clear and direct “optimal interaction length” for sarcomere; however, in human sarcomere, this “optimal length” between actin and myosin is when the sarcomere length equals 2.2μ . The cellular basis for Frank-Starling relationship is in general known as “length-dependent activation,” which is a mechanism seen in every other sarcomere in all of the cardiomyocytes. In physiologic measurements of the Frank-Starling relationship, any sudden increase in diastolic length of a contractile segment of cardiomyocyte (i.e., sarcomere) would result in a sudden increase of its systolic force reaching a plateau after a short time. Before this plateau, the more length of sarcomere, the more force produced by myocardium; however, after reaching this plateau, the sarcomere could not produce more contraction since the actin and myosin heads start going far from each other and the sarcomere length goes far from its optimal length. Meanwhile, any sudden decrease in diastolic length of the contractile elements would result in decreased systolic force, again reaching a plateau phase after a short time. Though Frank-Starling relationship has been discovered for more than 100 years, its underlying mechanism(s) is not fully clear yet. In other words, its cellular and subcellular mechanisms are not limited to one single mechanism. Instead, Frank-Starling relationship is “the end product of a complex system of interacting elements”; however, there are many different molecular mechanisms cooperating together in each of the cardiac sarcomeres “to produce strain dependent activation.” Here, two main classes for its mechanisms have been introduced:

- First, “increased diastolic tension” results in “increased number of cross bridges” which in turn will improve the “myofilament overlap” status, favoring more effective contractions. In other words, the interdigitations of actin and myosin in diastole will become more effective in producing systolic contractions. Though this is the main mechanism, another proposed mechanism seems important.
- Second, improved efficacy of sarcomere contractile function to produce increased contractile force in response to Ca^{2+} concentration is seen when the length of the sarcomere is increased. In other words, according to this mechanism, Frank-Starling relationship is due to improved response of myofilaments to Ca^{2+} when the length of the sarcomere is increased. The interested reader could find more extended explanations in other sources, being beyond the scope of this chapter (Markwalder and Starling 1914; Patterson et al. 1914; Fuchs and Smith 2001; Solaro 2007; Bollensdorff et al. 2011; Campbell 2011; Ribaric and Kordas 2012; Cingolani et al. 2013; Goldhaber and Philipson 2013).

1.4 Cardiac Reflexes

1.4.1 Bainbridge Reflex

Bainbridge reflex was described first in 1915 by Francis Bainbridge (English physiologist, 1874–1921). He discovered and demonstrated that “saline or blood infusion into the jugular vein of the anesthetized dog” would result in reflex tachycardia. This reflex is also called the “atrial reflex” and involves increased heart rate in response to dilation of “the main systemic veins and left and right atrium.” In response to dilation of the right atrium, stretch receptors located in the right atrium (i.e., venoatrial stretch receptors) are activated and send their impulse through the vagus nerve (10th cranial nerve) to CNS; this is why the reflex is blocked if the patient is premedicated with atropine. Also, in animal studies, this reflex is blocked by “bilateral vagotomy or combined cholinergic and beta-adrenergic blockades.” After being processed in the CNS, the response to the afferent impulse would result in increased sympathetic tone, which in turn would cause increased contractility and tachycardia which finally helps emptying of the heart. Simply saying, the “Bainbridge reflex” causes “hypervolemia-induced tachycardia.” The efferent limb of the reflex is mediated through the sympathetic pathways. In cardiovascular physiologic pathways, the Bainbridge reflex plays an important role and has control over heart rate and other hemodynamic variables; also, the effects of the Bainbridge reflex are in contrary to the effects of the “carotid baroreceptor reflex.” This reflex is sensed in the atria through the atrial type B mechanoreceptors; these receptors are located at the junction of venae cavae and the right atria and the junction of pulmonary veins and left atria, which in turn would trigger the neural pathway of the reflex (Vatner and Zimpfer 1981; Boettcher et al. 1982; Hakumaki 1987; Hajdu et al. 1991; Barbieri et al. 2002; Crystal and Salem 2012).

1.4.2 Baroreceptors Reflex (or Carotid Sinus Reflex)

This reflex results in regulation of blood pressure, especially if it is highly elevated or severely depressed; however, the reflex is usually elicited in systolic blood pressures over 150–170 mm Hg; the other part of the reflex is not often seen when the systolic blood pressure is below 50–60 mm Hg. However, in patients with underlying hypertension or atherosclerosis, or in the elderly, the reflex thresholds might be altered and at times, the reflex would not be seen partially or totally. The main receptors of this reflex are located in the walls of carotid arteries and aortic arch and its sequence is as follows:

- The circumferential and longitudinal stretch receptors are located in carotid sinus and aortic arch; increased blood pressure triggers these receptors leading to impulse firing.
- The transport of impulse from carotid sinus is through the 9th cranial nerve and from the aortic arch through the 10th cranial nerve.
- The impulses from these two locations are sent to the nucleus solitaries in the medullary cardioregulatory and vasomotor centers.

- The nucleus solitaries, however, have two different parts: the first part is lateral and rostral known as the “pressor center,” and the second part is located at the central and caudal part which is known as the “depressor” center; in these two parts, the limbic and hypothalamic inputs are integrated to create the final response as either of the two following responses:
- Decreased *sympathetic* tone (mainly through inhibition of sympathetic chain and sympathetic nerves) leading to hypotension and bradycardia and also decreased vascular tone, leading to blood vessel dilation (i.e., systemic vasodilation).
- Increased *parasympathetic* tone (mainly through vagus nerve) leading to decreased heart rate and decreased myocardial contractility.
- These interactions would bring the blood pressure to normal, hence relieving the pressure over the baroreceptors.
- If the initial event is decreased blood pressure, the decreased tone on the baroreceptors would initiate the opposite response (Vasquez et al. 1997; Pilowsky and Goodchild 2002; Campagna and Carter 2003; Kashihara 2009).

1.4.3 Bezold-Jarisch Reflex

This reflex, known as a “cardioinhibitory” reflex, was described first by *von Bezold* and *Hirt* in 1867; it was more studied and completed in the late 1930s by *Adolf Jarisch* and *Richter*. Describing the reflex in brief, it is a triad of “bradycardia, hypotension, and peripheral vasodilation” usually accompanied with hypopnea or apnea. Also, coronary artery vasodilation has been mentioned among the items of the reflex. This reflex seems to have some cardioprotective effects; for example, it is seen during some myocardial stress states including during acute phase of myocardial ischemia, infarction, or reperfusion syndrome, especially when involving posterior or inferior myocardial walls.

The main physiologic phenomenon underlying the reflex is *parasympathetic* overactivity; however, some degrees of *sympathetic* inhibition have an etiologic role in the reflex. The sequence of the reflex in brief is as follows:

- The reflex is initiated after mechanical stimuli (like volume overload or pressure) or chemical stimuli (like metabolites of myocardial ischemia or chemicals like veratrum alkaloids) trigger the specific receptors of the reflex in the heart.
- The sensors of the reflex are located in a number of locations over the cardiac walls including the left ventricle wall, the atrial walls, atrial-caval junctions, and other cardiac chambers.
- The majority of the afferent fibers are nonmyelinated C fibers (75 % of the afferent pathways located over all the cardiac chambers) and myelinated fibers (25 % of the afferent pathways located in the atrial walls and the atrial-caval junctions).
- The afferent fibers inhibit the medullary vasomotor center which would have two effects: directly leads to bradycardia and also suppresses the sympathetic output.

- Decreased sympathetic output leads to decreased peripheral vascular tone leading to peripheral vasodilation, presented as systemic hypotension (Robertson et al. 1985; Hakumaki 1987; Meyrelles et al. 1997; Campagna and Carter 2003; Kashihara et al. 2004; Salo et al. 2007; Kashihara 2009).

1.4.4 Valsalva Maneuver

The “Valsalva maneuver” first described by Valsalva in 1704 is the name for a cardiac reflex starting with a forced expiration against a “closed glottis”; this act results in sudden increase of intrathoracic pressure resulting in increased central venous pressure (CVP); the increased CVP would cause decreased venous return which leads to decreased “cardiac output” and decreased blood pressure. The decreased blood pressure would be sensed by baroreceptors located in the arterial system and would stimulate the sympathetic pathways leading to tachycardia. After glottis opening, venous return would be resumed leading to increased contractility, and finally, the blood pressure returns to normal which this time would inhibit the baroreceptors leading to “normalized” heart rate; all these changes are as a matter of fact “a sequence of rapid changes in preload and afterload stress” imposed to the heart; this maneuver has a number of clinical therapeutic and diagnostic implications (Sharpey-Schafer 1955; Porth et al. 1984; Smith 2012; Wang et al. 2013).

1.4.5 Cushing Reflex

The Cushing reflex was introduced in 1901–1902 by Harvey Cushing (1869–1939) and is presented clinically as a triad of:

- Bradycardia
- Hypertension: presented as increased systolic blood pressure and wide pulse pressure
- Respiratory depression: presented as respiratory irregularity leading to bradypnea and apnea

This reflex is due to increased ICP (often an abrupt increase of ICP), and many times this clinical presentation is associated with cerebral herniation and death; in other words, the Cushing reflex is associated with the cerebral perfusion status; increased cerebrospinal fluid (CSF) production or its decreased reabsorption or, in another way, a mass effect in the CNS would lead to increased intracranial pressure which causes cerebral ischemia; however, cerebral ischemia would trigger sympathetic activity in an attempt to compensate for reduced cerebral perfusion leading to increased heart rate, blood pressure, and myocardial contractility; the increased blood pressure would be sensed by the baroreceptors in the aortic arch and carotid sinus, which leads to reflex bradycardia, well known in Cushing reflex; finally, the triad usually seen after elicitation of Cushing reflex is “increased systolic and pulse pressure with bradycardia and respiratory irregularity,” all due to increased intracranial pressure (Grady and Blaumanis 1988; Dickinson 1990; Ayling 2002; Fodstad et al. 2006; Molnar et al. 2008; Wan et al. 2008).

1.4.6 Oculocardiac Reflex

This reflex is elicited due to traction on the extraocular muscles (especially rectus medialis) or pain in the eyeball. The pathway of this reflex is as follows:

- The afferent limb of the reflex passes through the ophthalmic division of the 5th cranial nerve (trigeminal nerve); the other branches of the trigeminal nerve (maxillary and mandibular branches) might also be involved.
- The impulses go to CNS, i.e., trigeminal sensory nucleus.
- The efferent limb of the reflex is the 10th cranial nerve (vagus nerve) which causes sinus bradycardia as the final clinical presentation of the reflex; at times, junctional rhythms, asystole, or other types of arrhythmias, atrioventricular blocks, or hypotension may occur.

The frequency of occurrence of the reflex is diminished with aging and also could be somewhat prevented by anticholinergic pretreatment like atropine (Lang et al. 1991; Smith 1994; Gao et al. 1997; Seshubabu 1998; Kim et al. 2000, 2012; Paton et al. 2005; Chung et al. 2008; Yi and Jee 2008; Arasho et al. 2009; Simon 2010; Tsai and Heitz 2012).

1.4.7 Chemoreceptor Reflex

This reflex is another important one among the cardiac reflexes:

- Chemoreceptors are located in carotid body and aortic arch.
- Acidosis, hypercarbia (increased CO₂ pressure in blood), or a drop in blood oxygen pressure triggers the chemoreceptors.
- Afferent nerves are the 9th (glossopharyngeal) and 10th (vagus) cranial nerves.
- These nerves send the impulses to the medulla.
- The response would be increased sympathetic tone to compensate for hypoxia and hypercarbia.
- However, if hypoxia and hypercarbia do not resolve, the response would be parasympathetic stimulation to decrease heart rate and oxygen demands (Schultz and Sun 2000; Schultz and Li 2007; Ding et al. 2011; Schultz 2011; Campanucci et al. 2012; Schultz et al. 2012; Schultz and Marcus 2012).

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