Macroscopic Structure and Physiology of the Normal and Diseased Heart

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Abstract

This paper outlines the macroscopic anatomy and physiology of the heart, linking the micro and macroscopic structure of cardiac muscle fibre to its function during contraction and dilatation. The properties of cardiac muscle cells and the process of contraction at a cellular level are described. The macroscopic structure of the myocardium is further explained as one muscle band wound into a double twist. This helps to elucidate the muscle architecture and structure of the ventricles. Ventricular dynamics are also described as the twisting and untwisting of this muscle band to produce shortening and lengthening. Myocardial perfusion and causes of disease are discussed. Coronary artery disease and its effect on contractility is then described and ways of measuring contractility are introduced.

Introduction

The structure of the heart and its relation to myocardial function is a challenging problem that has troubled anatomists and physiologists for centuries.[1] The heart is a "complex three-dimensional fibre-wound structure with mechanical properties that are nonlinear, anisotropic, time varying and spatially inhomogeneous"[2]. As can be seen in Figure 1, the heart consists of four chambers, four valves and various vessels bringing blood to and carrying it away from the heart by veins and arteries. The *superior* and *inferior vena cavae* are the veins that bring blood from the rest of the body to the *right atrium*. The blood then enters through the *tricuspid valve* to the *right ventricle* (RV). From there it is pumped through the *pulmonary valve* entering the *pulmonary artery* and then through to the lungs to be re-oxygenated. Once re-oxygenated, the blood is carried back to heart through the *pulmonary veins* to be circulated to the rest of the body. It enters the *left atrium* and once that is filled, the blood is pushed through the *mitral valve* into the *left ventricle* (LV). The *left ventricle* does the majority of the work by then pumping the blood through the *aortic valve* to the *aorta* and hence out to the rest of the body.[3]

Although the microscopic structure of the heart can be explored relatively easily, the macroscopic muscle structure has remained an unresolved problem, depending on how dissection is performed.[2, 4] Despite this, studies have verified the relation of dissection techniques to conclusions on architecture using non-invasive imaging techniques.[5,6] To relate the macroscopic muscle structure to the functional behaviour of the heart, however, non-invasive imaging techniques such as echocardiography and magnetic resonance (MR) imaging have to be used.

Studies into the structure of the heart are at different levels. One of these is at the cellular level, or histological studies. These usually explore the myocyte structure, alignment and ionic pathways or overall fiber architecture[2]. The next level, the muscle level, is what we are particularly interested in. This level of study can give us clues to how the heart functions and hence an indication of where and how things go wrong in disease.

This paper briefly describes the general micro and macro structure of the heart, the changes in muscle structure in disease, the measures currently used to define function/contractility and explores in depth the ideas developed by Torrent-Guasp over the last 50 years of the relationship between structure and function.

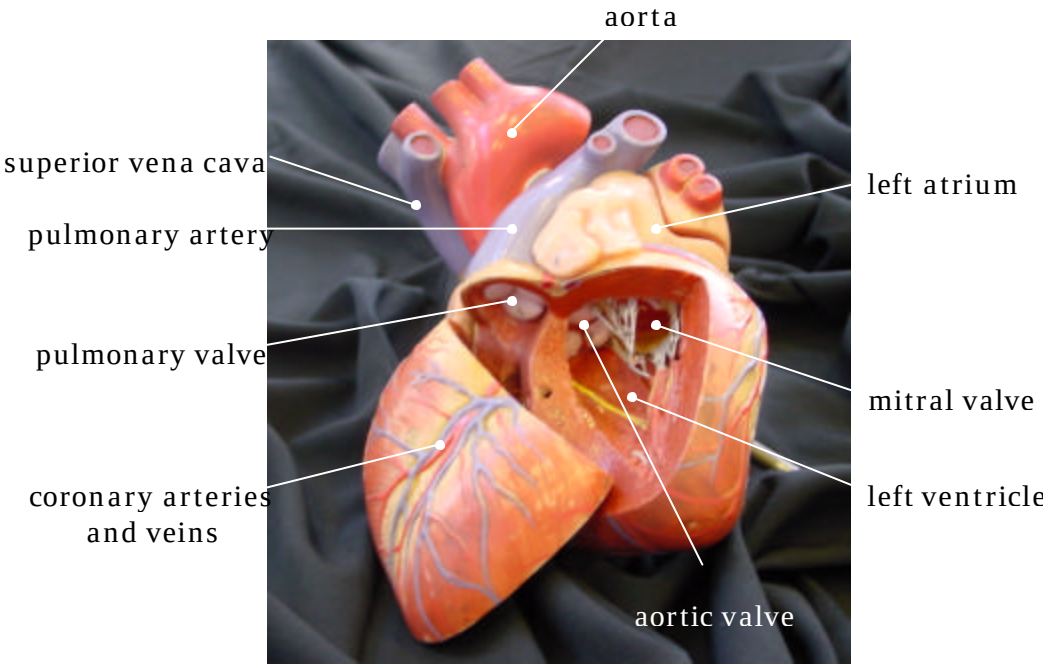

Figure 1. The anatomy of the heart. The arteries carrying blood away from the heart, from the LV, are marked in red while the veins carrying blood to the heart, to the right atrium, are in blue.

Histology and Cellular Structure

To understand how the myocardium functions, we first need to understand the muscle structure at a basic level. Cardiac muscle tissue is unlike any other muscle in the body. Cardiac fibers consist of elongated cells with central nuclei and branching attachments.[7] About 75% of the total volume of the myocardium is composed of cardiac myocytes, representing about one third of all cells in the myocardium.[8] They are smaller than skeletal muscle fibers measuring around 110µm long and 15µm wide.

Figure 2 is a photograph of a slide of cardiac muscle. It can be seen that cardiac myocytes are connected to each other end to end by intercalated discs which are usually at right angles to the long axis of the cardiac myofibers (a myofiber is defined as a group of myocytes connected by collagen.) These are specialized cell-cell junctions that form regions of low electrical resistance, hence providing not only mechanical but also electrical coupling between cells. This leads to a branching network of interconnected muscle fibers. Thus the entire tissue can theoretically be treated as a single muscle cell, called a functional syncytium.

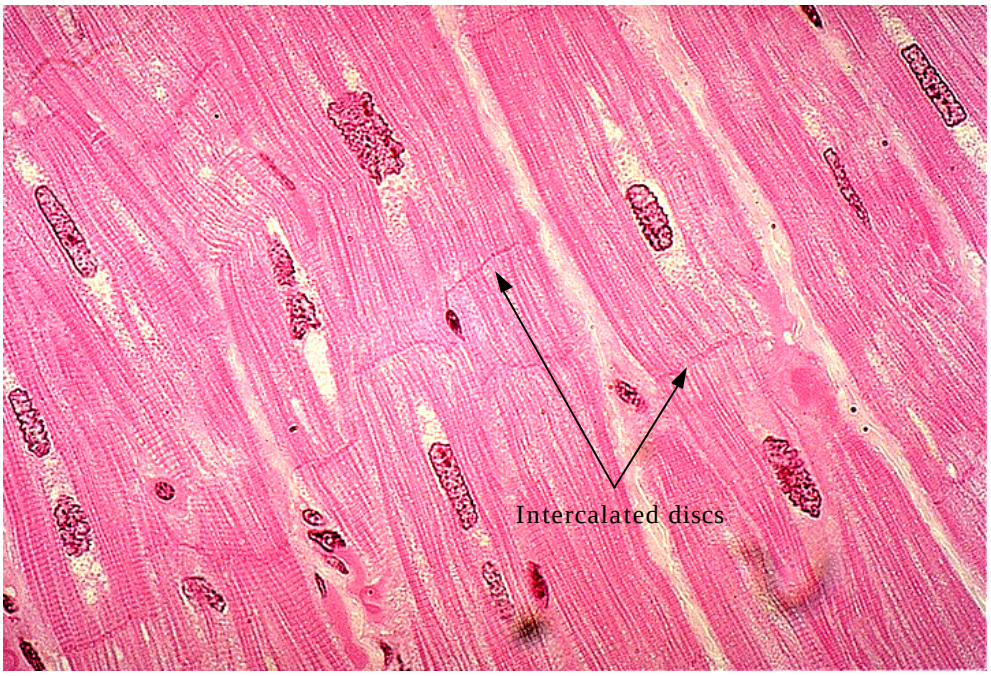

Figure 2. Cardiac muscle tissue is striated with the myocytes containing usually just one central nucleus and being connected to each other by intercalated discs. (image courtesy of Dr R Wagner, Biological Sciences, University of Delaware)

Cardiac myocytes are also unique in their contraction properties. They contract without neuronal stimulation, instead, specialized cardiac pacemaker cells establish a regular rate of contraction. The action potentials in cardiac muscle fibers are also very different to those established in axons and skeletal muscle. In cardiac muscle, the action potential lasts much longer, 200 – 350 ms in the ventricles. This means the refractory period, *i.e.* the period when the cell will not respond to a second

stimulus, is quite long, thus preventing any further contraction to take place and keeping the whole muscle in synchrony.

Cardiac muscle cells are bounded by the cell membrane, the sacrolemma, and filled with rodlike bundle of myofibrils, which are the contractile elements. The sacrolemma extends to form an extensive network, the extensions are known as T-tubules. The cell also contains mitochondria which are interspersed between the myofibrils and usually located immediately beneath the sacrolemma. The main function of the mitochondria is to produce adenosine triphosphate (ATP). Proper function of the myocardium requires highly controlled regulation of the calcium concentration within the cardiac myocytes. Contraction is initiated by calcium ions, discharged by the sacroplasmic reticulum in response to electrical stimulation. The major molecules involved in contraction are the proteins actin and myosin. The thin actin filament and the thick myosin filament contract by sliding over each other, not by actual shortening. This is commonly called “cross-bridge cycling”. The actin filament is actually composed of actin and tropomyosin, which in turn consists of the three proteins troponin I (TnI), troponin C (TnC) and troponin. Calcium binding induces a conformational change in TnC, causing it to elongate. This causes the TnI to close up to TnC and the normal inhibition of the TnI on the actin-tropomyosin is released, allowing the repositioning of tropomyosin in relation to actin and hence contraction.[9] This relationship between electrical stimulation and intracellular calcium release is called excitation-contraction coupling.[10] The “calcium cycle” is integral to the regulation of contractility of the myocardium. Perturbations of either release (systolic) phase of the cycle or reuptake (diastolic) phase of the cycle can contribute to heart failure and sudden cardiac death.[8]

During heart failure, the force of contraction is reduced and there is an abnormal delayed pattern of relaxation. Unlike other muscle tissue, cardiac myocytes are incapable of dividing and hence cardiac muscle tissue once damaged by injury or disease cannot regenerate.

Macroscopic Muscle Structure

A picture of the muscle structure on the macroscopic scale can be obtained by dissecting the heart. Researchers have studied the structures of different mammalian hearts extensively.[11] The established method used consists of firstly boiling the hearts in water to soften the connective tissue and then performing a blunt dissection of them using fingers with the help of non-toothed forceps, scalpel and scissors, after first removing the atria, aorta and pulmonary artery. This blunt dissection method is used as it was found to be the best way of identifying the direction of the laminar pathways followed by the muscle bands *i.e.* the cleavage planes. Using this dissection method, the natural cleavage planes of the muscle can be examined, and a clearer picture of the macroscopic muscle fiber architecture obtained.[1, 4,11,12,13,14] Firstly, we need to clarify the nomenclature of the different regions of the heart. The base is at the top of the heart, *i.e.* where the ventricles connect to the atria, and the apex is the bottom tip of the heart. To make the explanation of the anatomy easier, the heart can then be divided up into four regions, the LV apical and basal halves, and the RV apical and basal halves. The apical halves of the ventricles describe the lower half of the heart, whereas the basal halves describe the upper half, *i.e.* from base to midway.

Left Ventricle Apical Half

To examine the apical half of the LV, a transverse cut made between the middle and apical third of the heart was found to be useful. Pulling on the fibres revealed a cleavage plane showing that the muscle layer always took a helical path from the periphery to the center. Torrent-Guasp *et al* found that the sub-epicardial fibres undergo a twist turning into sub-endocardial fibres around a central tunnel, bounded by the endocardium on the inside and the epicardium on the outside. They concluded that, looking from the apex up towards the base, all fibres pass clockwise from the sub-epicardium to the sub-endocardium.

Left Ventricle Basal Half

The free wall of the basal half of the LV is similar to the apex in that the muscle layers take a helical path from the periphery to the center. The fibres of the basal half pass beneath, but do not insert into, the mitral ring. The study showed that the fibres of the free wall of the base, passed anti-clockwise, again looking from the apex up towards the base, from the sub-epicardium to the sub-endocardium.

The basal and apical halves of the LV may seem similar but there are four differences worth noting:

1. The apical orifice is virtual while the basal orifice is real.
2. The edges of the apex had structural uniformity, while the base had two segments, *i.e.* the free wall and the interventricular septum.
3. The basal superficial fibres are in contact with a fibrous ring, i.e. the mitral annulus, while the apical superficial fibres are at a distance from the mitral fibrous ring.
4. The most fundamental and probably anatomically the most important difference is that the fibres at the base pass in an opposite direction, from periphery to center, than those at the apex.

Right Ventricle Apical Half

The free wall of the RV displays two groups of fibres. The sub-endocardial fibres run from the posterior interventricular sulcus to the pulmonary artery in an ascending course to the basal region. The sub-epicardial fibres run from the posterior interventricular sulcus to apical regions in a descending course. There is also a third group of fibres whose path runs from the direction of the first to the direction of the second group. This explains why dissection reveals a series of circularly overlapping muscle layers in the apical border of the free wall.

In conclusion, the apical half of the free wall of the RV consists of myocardial fibres which pass from a sub-epicardial to a sub-endocardial position in a clockwise helical course (looking from apex to base).

Right Ventricle Basal Half

The myocardium around the tricuspid orifice can be divided into three segments: the free wall, the supra-ventricular bridge and the interventricular septum. It was found that the free wall segement at the base corresponded well with the free wall at the apex but, as in the LV, at the apex the fibres pass in an opposite direction to those at the base.

One Muscle Band

Dissection shows that the heart is a helically wound structure. It also shows that there is a clear difference between the structures at the base and apex, since at the base the muscle fibers, in their helical course from the epicardium to the endocardium, run in an opposite direction to those at the apex. A rubber mould of a real heart is shown in Figure 3. Through unwinding, it reveals the helical winding of the muscle band to create the different chambers. Two loops can now be defined, the basal and apical loops. The basal loop can be further divided into the right and left segments and the apical loop into descendent and ascendant segments, as illustrated in Figure 6.

The rope model shown in Figure 4 also helps to explain the differences in thickness of ventricular walls. It is known that the RV wall is much thinner than the LV wall, and the rope model illustrates that this is due to the fact that the LV wall is made up of two windings of the rope and hence thicker. The fiber architecture of the LV wall can now be explained, as histological studies have always shown the fiber angles of the muscles change from epicardium to endocardium, with the angles at the endocardium being directly opposed to those at the epicardium and transmural angles varying between the two[1].

It can be concluded that “the ventricular myocardium consists of a singular muscle band twisted on itself as a rope, that, extending from the origin of the pulmonary artery to the root of the aorta, define, while describing two turns in a helical fashion, two cavities, the right and left ventricles” [4,11].

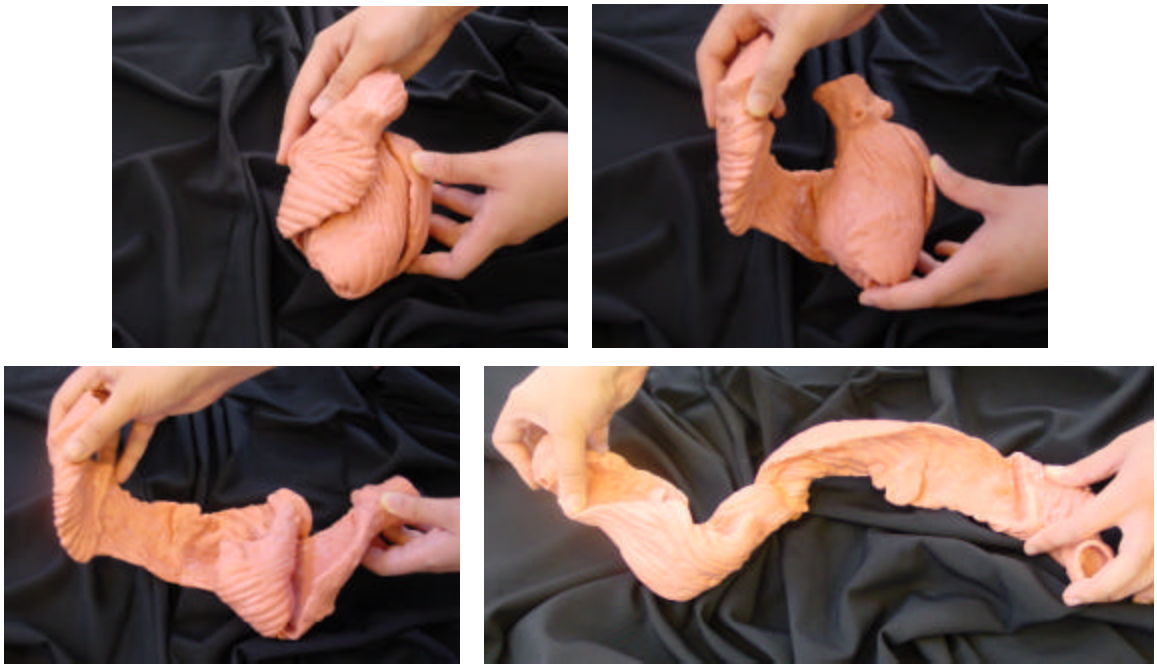

Figure 3. A rubber mould of the heart reveals it to be a single muscle band which can be unwound to reveal the helical structure of the fibres making up the ventricles. There is a "double twist" in 3D if using a rope as a model.

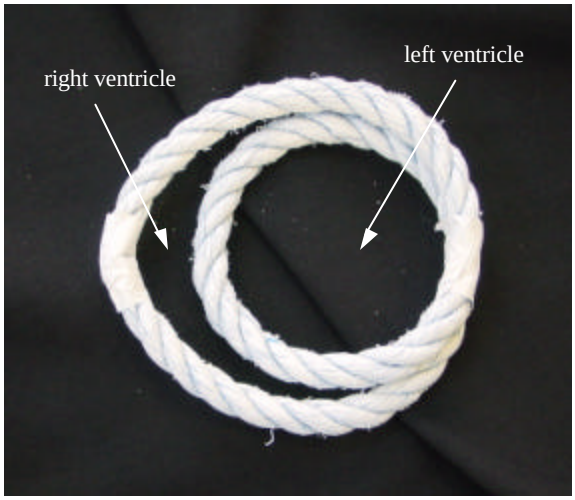

Figure 4. Rope model of the heart. It can be seen that the free wall of the right ventricle is made up of only one winding of the rope while the free wall of the left ventricle is made up of two windings of the rope, hence explaining the difference in width of the two walls.

The Cardiac Cycle and Ventricular Dynamics

The cardiac cycle was fully assembled by Lewis[15], but the idea was first conceived by Wiggers[16]. In their view, the cardiac cycle consists of three basic events: LV contraction, LV relaxation and LV filling.

The cardiac cycle can be characterized by using the pressure curve shown in Figure 5. The LV pressure starts to build up when the arrival of calcium ions at the contractile proteins triggers actin-myosin interaction. This is followed by the closure of the mitral valve leading to isovolumic contraction. (This period of contraction refers to a time when the volume of the LV is constant as both the aortic and mitral valves are closed.) When LV pressure reaches a point where it is greater than aortic pressure, the aortic valve opens and rapid ejection ensues. LV pressure then starts to fall and calcium ion concentration also falls causing the myofibers to enter a state of relaxation. As LV pressure falls the aortic valve closes and the LV goes into isovolumic relaxation. Finally, when LV pressure reaches a point when it is lower than atrial pressure, the mitral valve opens and filling begins.

In terms of overall muscle motion, it can be seen that at diastole there is a dilation of the ventricles resulting in a drop in pressure which leads to filling and at systole the ventricles contract to increase the interventricular pressure, hence expelling the blood into the arteries. In addition to this motion there is a lengthening and shortening in the longitudinal direction, which entails the base of the heart moving down towards the apex. Observation of the beating heart using magnetic resonance (MR) imaging or echocardiography shows that the apex remains motionless while the base moves up and down. This is a strange phenomenon considering the fact that the apex of the heart is free and unattached while the base is fixed and attached to the pulmonary artery, aorta and atria. There is also the additional torsion of the heart[17] that has remained unexplained until quite recently. This torsion consists of the base twisting in one direction while the apex twists in the opposite direction, making the motion of the heart something like the wringing of a wet towel.[11,14] However, after explaining the four main motions involved in a

beating heart and how they arise from the muscle structure, it will become obvious how the ascent and descent of the base and the torsion of the heart occurs.

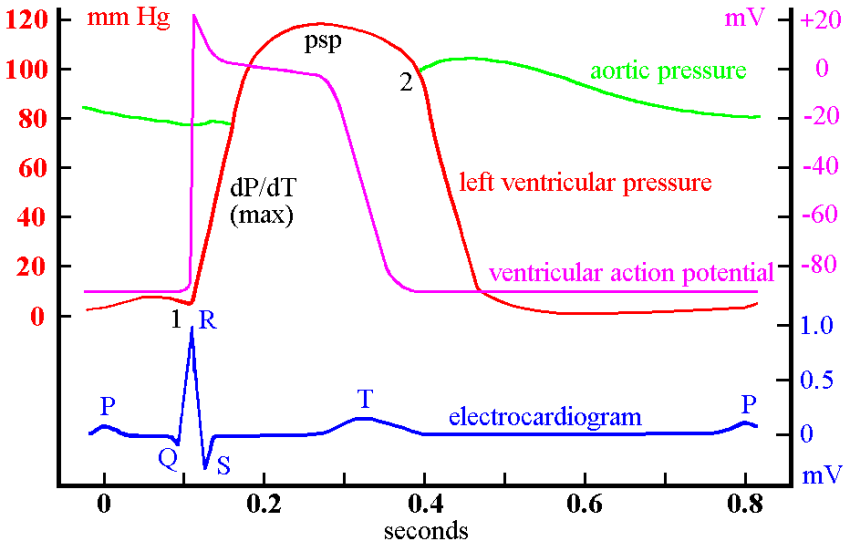

Figure 5. The blue line shows the echocradiogram trace, in mV, during one cardiac cycle. The purple line is the ventricular action potential, *i.e.* the electrical stimulus to the ventricle. The red line, a trace of the ventricular pressure, rises rapidly after the mitral valve closes until the aortic valve opens to allow rapid ejection of the blood into the aorta. The green line is the aortic pressure which rises in systole and then decreases slowly as flow slows due to ventricular pressure decreasing. (plot courtesy of Dr JA Illingworth, Dept of Biochemistry and Molecular Biology, University of Leeds)

The four main motions are two longitudinal and two transversal motions that occur in the following order: narrowing of the base, shortening in the longitudinal direction, lengthening in the longitudinal direction, and widening of the base. The last two motions are in a sense opposing motions to the first two.

The contraction of the heart is controlled by electrical impulses which travel through its pacemaker cells. The impulse begins at the sino-atrial (SA) node, which is located in the wall of the right atrium near the entrance of the superior vena cava. The SA node is also known as the cardiac pacemaker. The impulse takes about 50ms to travel from there to the atrio-ventricular (AV) node. The conduction

through the AV node is quite slow, about 100ms, causing the atria to start contracting before the ventricles. The impulse then travels down through the Bundle of His, also known as the atrial bundle, in the interventricular septum to the Purkinje fibers, which then fan out throughout the ventricles. By this time, around 225ms into the cycle, atrial contraction is complete and ventricular contraction begins. The Purkinje fibers conduct action potentials very rapidly hence allowing a smooth contraction of the whole ventricle.

The electrical activation of the different sections of the muscle band should correspond to the different motions. So the activation proceeds as follows, as observed experimentally by Armour & Randall[18]; right → left → descendent → ascendant. Figure 6 schematically illustrates the definition of these segments.

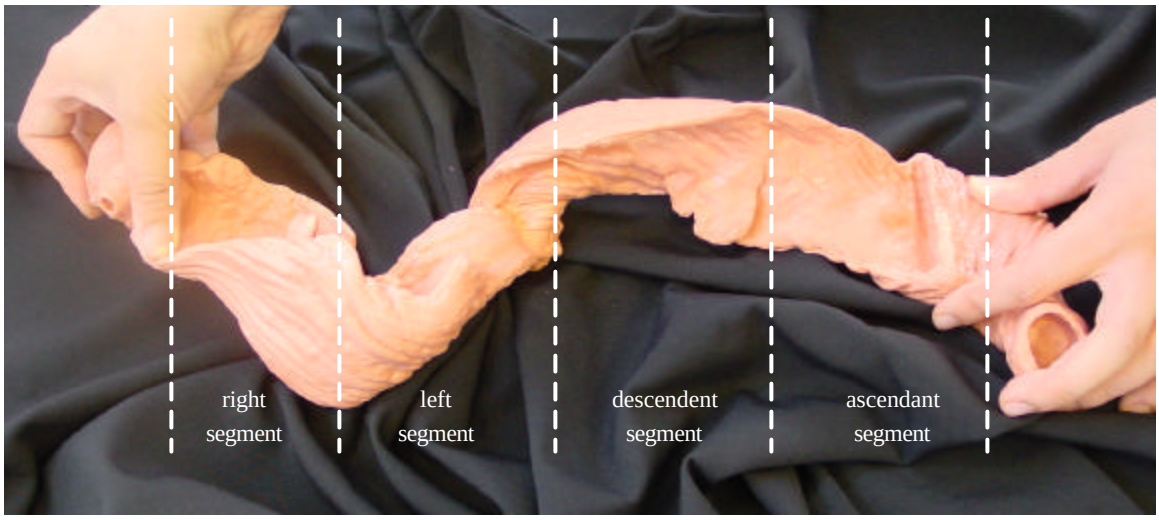

Figure 6 The muscle band can be divided up into four segments; right, left, descendent and ascendant depending on the orientation of the muscle fibre. Electrical stimulation has been shown to proceed from right to left to descendent and lastly to the ascendant segment, giving rise to the torsion seen during contraction.

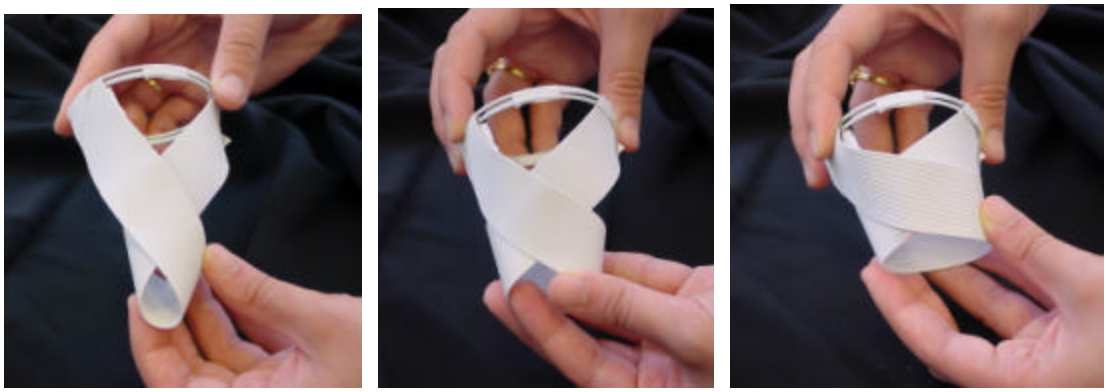

Figure 7. Lengthening and shortening of the ventricles is produced by the torsion involved. Two counter rotations occur; a counterclockwise one at the base and a clockwise one at the apex (looking up from the apex towards the base), causing the muscle band to behave as a towel being wrung dry.

Narrowing of the ventricles

This can be explained by looking at the way that the contraction proceeds. When the right and left segments receive electrical activation, they cause the muscle in the basal loop to contract forming a "stiff outer shell" inside which then occurs "the subsequent contraction of the bulk of the myocardium" [18]. This contraction of the basal loop causes a slight reduction in the diameter of the ventricles at the isovolumic phase of systole (no blood is being ejected as the valves are closed at this stage). The almost horizontal fibers of the basal loop prevent the spreading of the almost vertical fibers of the apical loop. This can be further evidenced by the fact that in the diseased state of dilated cardiomyopathy the belt of the basal loop fails.

Shortening of the ventricles

The electrical activation continues immediately into the descendent and ascendant segments of the apical loop. Due to the way the two segments cross each other, two contrary rotations also occur; looking from apex to base (this convention is used from here onwards), a counterclockwise rotation at the base and a clockwise rotation at

the apex. These rotations obviously imply a shortening of the ventricles as in a towel being wrung dry as shown in Figure 7.

Lengthening of the ventricles

The lengthening of the ventricles is not so obviously explained. However, if we look closely at the ascendant segment and the motions it is going through it becomes clear how the lengthening is taking place. The segment's contraction is preceded by a forced distension due to the contraction of the descendent segment. So when the ascendant segment contracts, its muscular fascicles stiffen, as happens with the paravertebral musculature of snakes when they attack going up.

This stiffening gives rise to the rapid ascent of the base of the ventricles, and the clockwise rotation of the base and a counterclockwise movement of the apex, thus leading to the lengthening of the ventricles. The theory that the shortening and lengthening of the ventricles is actually due to a torsion and untorsion of the myocardium around its longitudinal axis, is supported by the work done by Lorenz *et al*[10] and Moore *et al*[19] using MR tagging.

Widening of the ventricles

To explain the widening of the ventricles we need to again consider the ascendant segment of the apical loop. Coming from the anterior aspect of the LV, the fibers of the ascendant segment divide, when they arrive at the interventricular sulcus, into the aberrant fibers and the intraseptal fibers. The aberrant fibers are named thus due to the unusual pathway they take. They, after jumping onto the interventricular sulcus, pass to cover subepicardially the free wall of the RV. This pathway is considered unusual as most of the fibers of the ascendant segment run intraseptally to terminate in the root of the aorta.

By using the rope model, if we now consider the contraction of the ascendant segment, it can be seen that the widening of the ventricles is initiated by the untwisting motion caused by the contraction and is helped along by the contraction

of the aberrant and intraseptal fibers. The untwisting motion implicates the development of a centrifugal force that will tend to the spreading of the ventricular mass.

Coronary Circulation and Myocardial Mechanics

The energy used by the heart is provided by the nutrients carried by the coronary circulation. The blood supply to the myocardium is via large epicardial coronary arteries. The main coronary arteries are depicted in Figure 8. They are the left main coronary artery (LEFT MAIN), right coronary artery (RCA), left anterior descending (LAD), circumflex (LCX) and posterior descending (PDA) coronary arteries. The LEFT MAIN and RCA branch out from the aorta. The LEFT MAIN then divides into the LAD and LCX, and the RCA, LAD and LCX form three clinically significant vessels. Anatomically, the major coronary arteries lie in grooves that separate the heart chambers. The LEFT MAIN, which branches into the LAD and LCX, provides virtually all of the blood supply to the LV, and hence these are clinically significant.

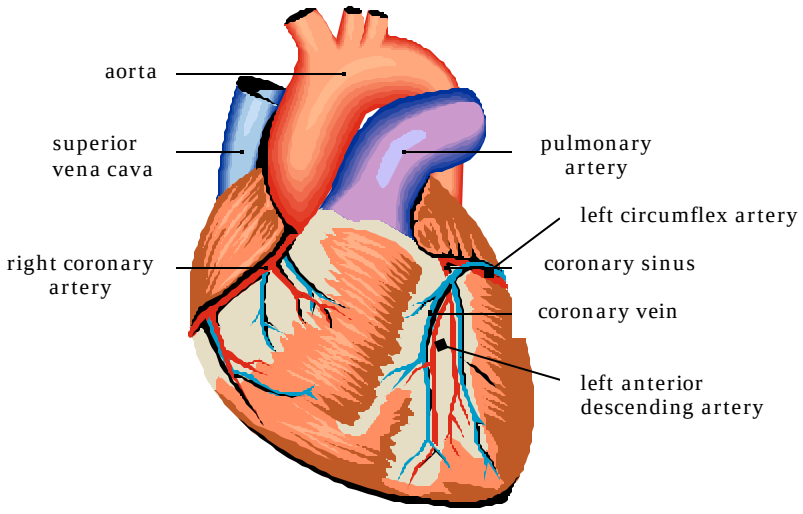

Figure 8. The major coronary arteries supplying blood to the myocardium and their location anatomically.

The heart is usually divided into four distinctive regions to ease classification of perfusion and dysfunction. If looking at a short axis view, as in Figure 9, the

anterior of the LV is the part facing the chest wall, the septal region is the side connected to the RV and the posterior and lateral are their opposites respectively.

The LAD supplies blood to the anterior septum, the anterior wall, and in most cases apex. It might wrap around the apex and supply the most apical portion of the posterior and lateral wall as shown in Figure 9. The LCX supplies the lateral wall and the RCA, which runs down the groove connecting the LV and RV, supplies the posterior lateral segments, the inferior segments, and the posterior septum.

The delivery of the blood to the myocardium is determined by intramyocardial pressure, *i.e.* when the intramyocardial pressure is low the blood can flow into the myocardium. Hence, almost all the nutrient coronary flow takes place during diastole.

Occlusion of the coronary arteries can lead to "one-vessel", "two-vessel" or "three-vessel" disease depending on which major arteries are occluded. Sudden occlusion of a major coronary artery causes ischaemic infarct with sharply demarcated borders. Venous drainage of the coronary circulation is via the coronary sinus and the anterior cardiac veins.

Perfusion

The constant activity of the beating heart means there is a high demand on oxygen consumption at about 5 to 10 ml/min/100g (higher than brain, 4ml/min/100g, and skeletal muscle, 0.2 ml/min/100g.) The Fick principle can be used to calculate an organ's metabolic rate from the blood flow. So for the heart it is:

$$Metabolic \quad Rate = Q(C_a - C_v)$$

where Q is the blood flow and C_a and C_v are the arterial and venous constants respectively. At rest, myocardial oxygen extraction is nearly maximal which implies that coronary flow rate has to increase during stress to keep up with the increased

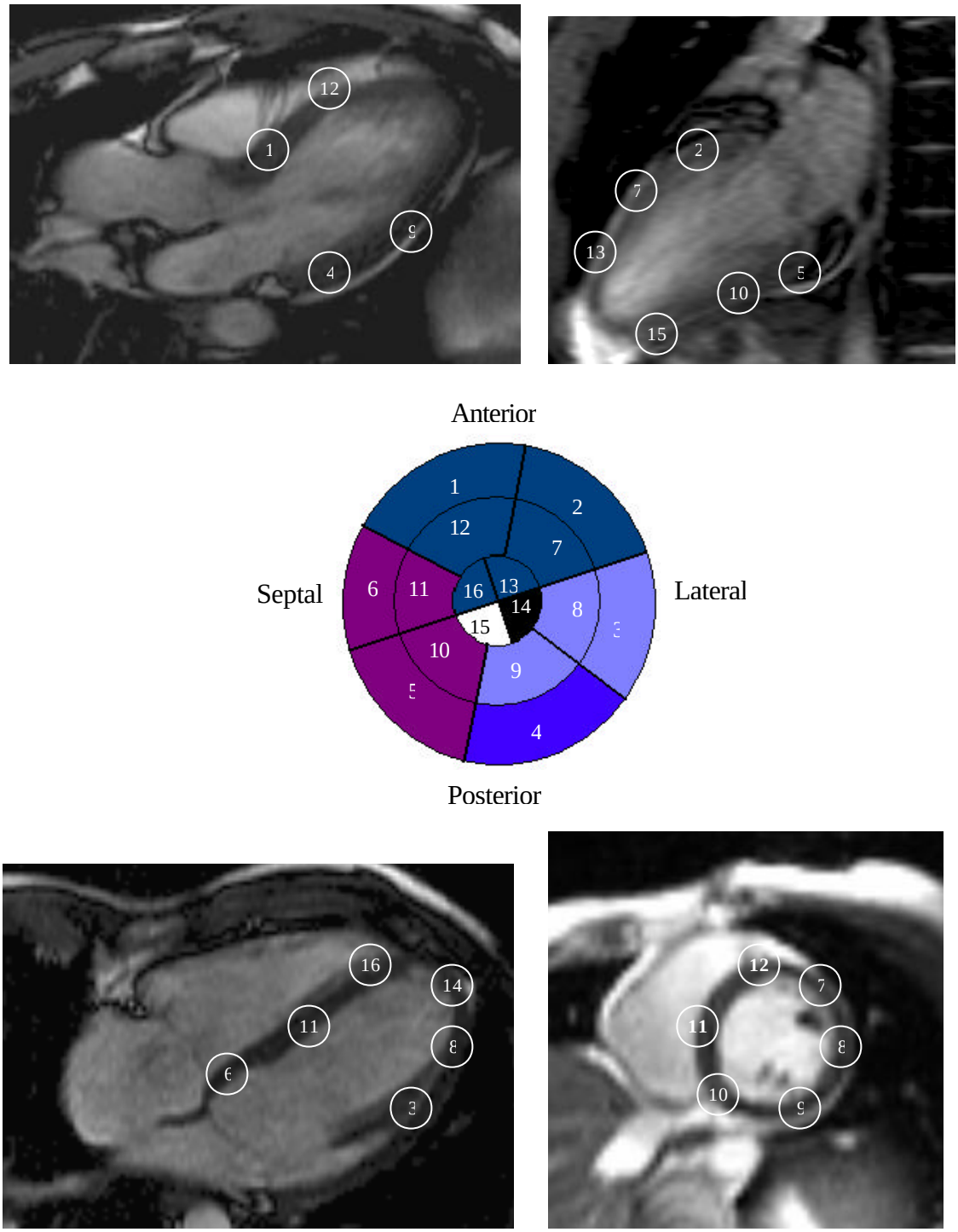

Figure 9. Schematic illustration of the perfusion of the heart. The main regions supplied by the three main coronary arteries are described.

oxygen consumption. Hypoxia and ischaemia stimulate vasodilatation to allow increased coronary flow rates.

It has been shown that perfusion and metabolism in the heart are not heterogeneous. The first evidence for this was obtained using the indicator dilution technique. Firstly, there is a transmural gradient of perfusion, where the subendocardium has 20%-40% greater perfusion than the subepicardium. Then there is spatial and temporal heterogeneity of flow. However, it is not clear whether heterogeneity of contractile function of the myocardium echoes this perfusion heterogeneity.[10]

Atherosclerosis

Atherosclerotic disease is the leading cause of death in most of the developed world. It is a complex disease process involving the development of plaque composed of variable amounts of connective tissue matrix (collagen, proteoglycans, glycosaminoglycans), vascular smooth muscle cells, lipoproteins, calcium, inflammatory cells (monocyte-derived macrophages, T-lymphocytes and mast cells), and new blood vessels. Figure 10 illustrates the morphology and the formatio of an artherosclerotic plaque. The transitional thrombus zone is where the lipid-filled plaque has ruptured and caused thrombus to develop in the artery. The causes and pathogenesis of atherosclerosis are so far not completely understood. The emerging theories state that atherosclerosis may reflect a chronic inflammatory response to vascular injury caused by a variety of agents that activate or injure endothelium and promote lipoprotein infiltration, lipoprotein retention and lipoprotein oxidation.

In relation to heart disease, athersclerosis affects the aorta, and large- and medium-sized elastic and muscular arteries of the heart, predisposing the heart to ischaemic injury. Specific sites in the circulation predisposed to atherosclerosis are characterized by increased influx or prolonged retention of lipoproteins, evidence of endothelial activation with expression of leukocyte adhesion molecules, and low shear stress. Studies of the vasculature have shown that alterations in blood flow appear to be critical, making sites such as branches, bifurcations and curvatures

naturally susceptible. This being due to the decreased shear stress and increased turbulence at these sites leading to the rolling and adherence of monocytes and T-cells. Studies suggest that the earliest steps in artherscleroses are endothelial activation, injury or dysfunction with infiltration and retention of lipoproteins.

Various factors that may contribute to endothelial activation or the development of endothelial injury or dysfunction including risk factors associated with artherscleroses are elevated and modified LDL/VLDL (low density lipoprotein/very low density lipoprotein) cholestrol (reduced high-density lipoprotein cholestrol, oxidant stress caused by cigarette smoking, hypertension, diabetes mellitus), genetic alterations, elevated plasma homocysteine concentrations, infectious microorganisms, estrogen deficiency, and advancing age. Vascular remodeling can occur in atherscleroticdisease 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.

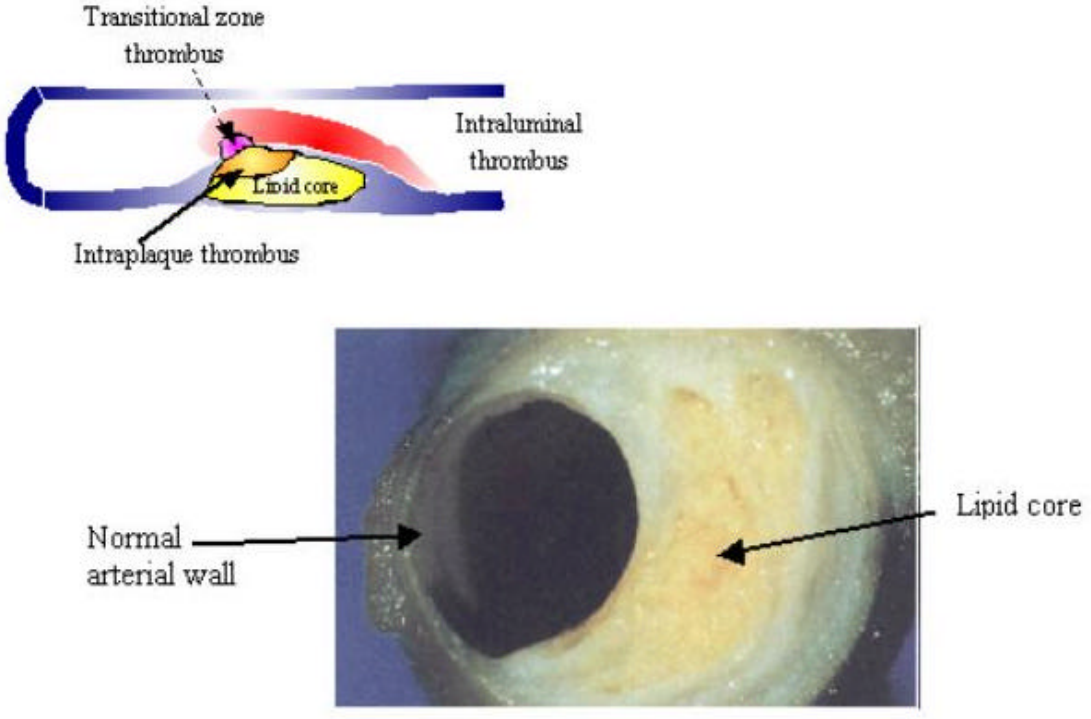

Figure 10. Illustration of an artherscleroticplaque. The transitional thrombus zone is where the lipid-filled plaque has ruptured and caused thrombus to develop in the artery.

The arthersclerotic plaque can be unstable with a risk of thrombosis developing as a result of uneven thinning and rupture of the fibrous cap of the lipid-filled plaque. This can lead to acute ischaemic syndromes such as unstable angina, myocardial infarction and sudden cardiac death.

Myocardial Ischaemia: Causes and Effects

Ischaemia, in general terms, refers to a low oxygen state usually due to obstruction of the arterial blood supply or inadequate blood flow leading to hypoxia in the tissue. Myocardial ischaemia is characterized by an imbalance between myocardial oxygen supply and demand. On a macroscopic level, the effects of this include myocardial stunning, hibernation and necrosis, which will be explained in further detail later. Ichaemia can be explained by the fact that coronary blood flow is closely linked to myocardial oxygen consumption in normal hearts. This linkage is needed as a) the myocardium depends almost entirely on aerobic metabolism, b) the oxygen saturation of coronary venous blood is low, permitting little additional oxygen extraction and c) oxygen stores in the heart are meager.

Ischaemia is caused by a reduction of blood flow and oxygen supply due to increased vascular tone, intracoronary platelet aggregation or thrombus formation. This is termed supply or low-flow ischaemia. The other form of ischaemia, demand or high-flow, is caused by the fact that increased coronary flow is insufficient to meet oxygen demand. This can be caused by a chronic coronary obstruction combined with exercise, tachycardia (an excessively increased heart rate) or emotional stress. Typically, a myocardial infarct is the result of both an increase in oxygen demand and a fall in oxygen supply.

Low-flow ischaemia is further characterized by not only inadequate oxygen supply but also by inadequate removal of metabolites. The buildup of metabolites can lead to the reduction of calcium sensitivity of myofilaments hence leading to diminished contractility. As coronary flow and perfusion pressure supplement LV systolic

performance and reduce LV diastolic distensibility, LV systolic performance is lower and LV diastolic distensibility higher in low-flow ischaemia.

The subendocardium is most susceptible to ischaemia. Epicardial coronary stenoses cause a reduction in the subepicardial to subendocardial flow ratio, hence making the endocardium predisposed to ischaemia. It should be noted however, that after total or near-total occlusion of a coronary artery, perfusion of ischaemic myocardium occurs by way of collaterals – vascular channels that interconnect epicardial arteries.

Ischaemia can lead to myocardial stunning, hibernating myocardium or cell death. Stunned myocardium has been described as prolonged myocardial dysfunction with a gradual return of contractile activity after a brief episode of severe ischaemia. This condition has been observed in patients with coronary artery disease and after exercise-induced ischaemia. Studies have shown that a number of factors converge in the pathogenesis of stunning, including a) generation of oxygen derived free radicals, b) calcium overload, and c) reduced sensitivity of myofilaments to calcium and loss of myofilaments. These mechanisms interact together to result in stunned myocardium. Clinical treatment involves using inotropic agents, agents which affect the force or energy of muscle contractions, to reverse the stunning.

Hibernating myocardium is muscle that at rest has impaired function, due to poor coronary blood flow, but its function can be restored to normal after revascularization. Hibernation was first noted in patients with coronary artery disease whose systolic LV function was improved after coronary bypass graft. Hibernating myocardium is present in about one third of patients with coronary artery disease. Recovery of hibernating myocardium can be from days to months; this is thought to be dependent on the period of hibernation. Observations of hibernating myocardium led to the notion that the myocardium can reduce its contractility to match reduced perfusion, preserving its viablitiy. Detection of hibernating myocardium is of utmost importance as the earlier it is caught, the more likely the chances of restoring function. Methods used to detect hibernating myocardium include stress echocardiography, thallium-201 redistribution study,

imaging with technetium-99m sestamibi, positron-emission tomography with agents that detect residual metabolic activity, and, more recently, MR perfusion studies at rest and stress.

As was mentioned earlier, the subendocardium is most vulnerable to ischaemia due to low collateral flow and high myocardial oxygen consumption. In a normal heart, thickening and shortening are greater in the subendocardium, as is wall stress, accounting for the greater energy requirements. Higher metabolic activity, lower tissue oxygen tension and greater oxygen extraction have also been found in this area, which is consistent with the fact that the energy requirements are high. Consequently, the subendocardial cells are the first to undergo necrosis due to the likelihood of severe ischaemia occurring there first. So the 'wavefront of necrosis' travels from the subendocardium towards the epicardium gradually involving the less ischaemic outer layers. However, it can be slowed down by residual blood flow if the coronary occlusion is incomplete and by collaterals forming in the region.[8]

Myocardial Remodeling

Heart disease can cause structural and functional changes accompanied by molecular changes that affect multiple signaling pathways. Functional changes in the heart due to heart disease are closely linked to the fact that structural remodeling of the ventricle occurs at macro and microscopic levels. Features of remodeling are hypertrophy (the enlargement or overgrowth of an organ or part due to an increase in size of its constituent cells), disruption of the extracellular matrix and LV dilation. It is still not definitely known whether functional deterioration is caused by a defect in function of individual myocytes, a defect in the extracellular matrix or a combination of the two. By Laplace's law, the increased diameter of the ventricle places a greater mechanical burden on the mycoytes. This means that the structural remodeling leads to reduced efficiency of contraction, due to greater wall stress and increased work, even if the individual myocytes are healthy.

Chronic changes in heamodynamic load can cause changes in chamber size and shape in the heart. Remodeling, in the context of coronary artery disease is

described as ventricular enlargement and distortion of regional and global geometry as a result of an infarct. Thinning and stretching of the infracted area (infarct expansion) are usually the first changes seen. On the cellular level, there is myocyte slippage, myocyte cell lengthening, and alterations in the intercellular matrix.

As time goes on, eccentric hypertrophy of non-infarcted myocardium, progressive LV dilation, and increased chamber sphericity develop. Remodeling may progress even with the lack of further ischaemia and can produce heart failure several months after the initial injury. Remodeling in other disease such as hypertension and valvular disease tends to produce global rather than regional changes.

At the myocyte level, remodeling may result in apoptosis, or in hypertrophy due to increased heamodynamic load. In concentric hypertrophy (the ventricular cavity becomes more spherical), cell surface area increases while in eccentric hypertrophy cell length tends to increase. Myocyte slippage is thought to be the cause of chamber dilation, and myocyte disarray has been found to be a characteristic feature of hypertrophic cardiomyopathy, but has also been found in cases of other myocardial hypertrophies, ischaemic heart disease and even in normal, healthy hearts.

The collagen interstitial matrix has many functions in heart muscle including transmitting force, maintaining alignment of myocytes and muscle bundles, preventing over-distention of the myocardium, and determining the shape and architecture of the heart. It also supports the intramural coronary arteries, stores energy in systole and repairs myocardial damage and responds to stress. Failing hearts have shown an increase in the collagen content from 4% (normal) to 25% (worst cases), which causes progressive functional impairment. The increased collagen content can impair both diastolic relaxation and systolic contraction. There can also be breakdown of the fibrillar collagen matrix that runs perpendicular to the myocytes, causing myocyte slippage, the cause of ventricular thinning in the remodeling process.

On a functional level, the contraction properties of myocytes have been found to be impaired in failing hearts. It is thought that irregularities in important cellular

processes explain these contractile changes. The overall effect of these irregularities is that the action potential is prolonged, the duration of contraction is increased, reducing both the rates of contraction and relaxation.

Myocardial Infarction

Myocardial infarction (MI) is defined as the death of myocardial tissue due to lack of oxygen. The exact events leading up to infarction are not clearly understood. However, it is clear that coronary artery occlusion has a large part to play. It has been found that nearly all cases of MI occur in patients with already existing athersclerosis. It is thought that there is a continuum of events, from stable plaque to plaque rupture and thrombus formation, leading to MI. Examination of patients reveals that it is not always so clear and in some cases the later stages of thrombus formation etc. are not evident.

As mentioned earlier, the subendocardium is most vulnerable to ischaemia, hence necrosis usually begins there, with a "wavefront of necrosis" traveling to the subepicardium. In experimental animals, it has been observed that within the first hour of occlusion, patches of irreversibly injured myocytes develop in the subendocardial third. By three to four hours, fingers of the necrotic wavefront extend into the middle third of the myocardium. By twelve to twenty-four hours, the entire wall thickness is involved in the necrosis.[20]

The body exhibits its natural inflammatory response on detection of necrotic tissues, which leads to some healing by fibrosis. Immune cells are dispatched to destroy the necrotic tissue. Macrophages destroy the necrotic myocytes and interstitial cells. The remaining intersitium, of collagen and reticulin, is used as the scaffolding to build fibrous scar tissue. Fibroblasts then proceed to manufacture dense and collagenous scar tissue; this usually consists of extracellular collagen.[20] This fibrous tissue can help to restore some of the lost function of the myocardium as it is linked to the healthy tissue and moves with it.

The amount of impairment of LV function can be good indicator of survival rates for the patient. However, we have to remember 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, making re-vascularisation therapy, *i.e.* surgery, the best option for treatment.

Contractility: a Basic Representation

Contractility is defined as the "inherent capacity of the myocardium to contract independently of changes in the preload or afterload"[8]. It is associated with the heart's inotropic state, *i.e.* its contractile state. Increased contractility of the heart refers to an increased rate of contraction, to reach a greater peak force. Contractility is an important regulator of myocardial oxygen uptake. Factors that increase contractility include exercise, adrenergic stimulators, digitalis and other inotropic agents. Contractility is usually measured using generalized quantities such as stroke volume, cardiac output, and ejection fraction.

Myocardial oxygen uptake is closely linked to the work done by the heart and hence the contractility. Increases in heart rate, preload or afterload cause an increase in oxygen demand.

$$\begin{gathered} cardiac\ output = mass\ moved \\ blood\ pressure = resistance \\ minute\ work = systolic\ blood\ pressure \times stroke\ volume \times heart\ rate \end{gathered} \qquad [1]$$

So it can be seen that an increase in ventricular radius or pressure will cause an increase in wall stress, as defined in Equation [2] below, leading to increased myocardial oxygen uptake as more ATP is consumed by the myofibrils to develop greater tension.

As mentioned earlier, changes in contractility should be independent of loading conditions. However, we first need to define preload and afterload. Preload is the load present at end-diastole before contraction starts. This reflects the venous filling

pressure that fills the atrium and consequently the LV. If preload increases, the LV becomes distended and stroke volume rises according to Starling's Law. The heart rate also rises as the arterial mechanoreceptors are stimulated making the rate of the SA node discharges increase. This has the effect of increasing cardiac output, which is the product of stroke volume and heart rate. The wall stress at end-diastole is a direct measure of preload. Laplace's law to calculate wall stress is the following:

$$wall \quad stress = \frac{pressure \times radius}{2 \times wall \quad thickness} \qquad [2]$$

However, measurement of wall stress *in vivo* is difficult as measurements of LV radius ignore the complex anatomy of the LV.

The afterload is the systolic load on the LV after it has started to contract. Clinically, the arterial blood pressure is usually taken to represent the afterload. In a normal heart, the LV can overcome any physiological acute increase in afterload. However, in a chronically increased afterload as in sustained arterial hypertension or significant stenosis, the LV must hypertrophy.

Starling's Law of the heart, formulated by Starling in 1918, is used to describe the effect of volume and pressure changes on the cardiac cycle. It states that the greater the volume of the heart, the greater the energy of contraction and the amount of chemical change at contraction. The modern version of this law states that stroke volume is directly related to end-diastolic volume. The graph in Figure 11 can be used to illustrate this relationship, end-diastolic pressure is used as an indicator of LV volume. As systolic pressure rises, the heart operates further up the graph, causing end-diastolic pressure to increase as well.

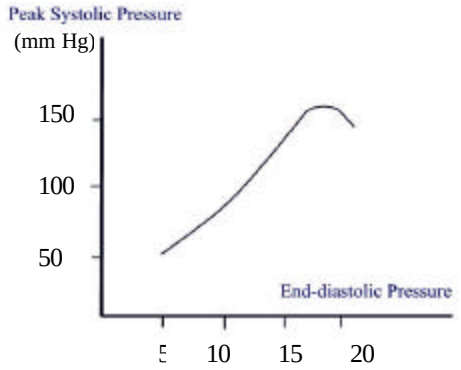

Figure11. Starling's Law: the end-diastolic pressure reflects the initial passive 'stretch' of the myocardium in response to systolic pressure. The relationship is not fixed and the shape of the curve depends on the outflow resistance.

Frank, in 1895, reported that the greater the initial LV volume, the more rapid the rate of rise, the greater the peak pressure reached and the faster the rate of relaxation. Hence he was able to describe both a positive inotropic effect and an increased lusitropic (relaxation) effect of increased cardiac volume at onset of contraction. Combining the Frank and Starling laws gives us the Frank-Starling law, which illustrates the link between preload and afterload. It says that an increased LV volume leads to increased contractility, which in turn leads to an increased systolic blood pressure and hence afterload.

The Need for Non-Invasive Imaging Techniques

Measuring the heart's contractility practically is not an easy task. Currently, pressure-volume curves are among the best approaches. However, major criticisms arise when trying to use the slope of the curve as an index of "absolute" contractility. Also, the ventricular pressure needs to be measured invasively to obtain the full pressure-volume loop, making it an impractical technique. It has also been found that the contractility is affected by the heart rate and loading conditions *in vivo*, although in theory it shouldn't be. Therefore, different indices of contractility have been used instead as indicators of the healthiness of the heart, these include wall thickening and shortening, ejection fraction and stroke volume.[10]

Imaging techniques may be used to assist the evaluation of ventricular function, and hence contractility. The most commonly used imaging techniques are radionuclide scintigraphy, echocardiography, electron beam CT and MRI. LV ejection fraction is the most widely used index of LV function. It is defined as the ratio of the difference between end-diastolic and end-systolic volume to the total volume of the LV. Research has shown that LVEF is decreased in dilated and ischaemic cardiomyopathy, with most cases eventually leading to LV failure.

Echocardiography is useful for detecting ventricular hypokinesis and dilatation of the left atrium and ventricle. Examination of the patient with stress induced, using exercise or drugs, can be employed to observe changes in ventricular function. Nuclear imaging is extensively used in perfusion studies. Perfusion imaging, again combined with physical or drug-induced stress, has been found to be very useful in determining myocardial viability. For studying LV function using nuclear imaging, the most commonly utilized technique is equilibrium radionuclide angiocardiography. In this technique, ECG gated images in three views are acquired and used to assess LV wall motion and LV ejection fraction. Time activity curves can be plotted reflecting LV volume changes, and the ejection fraction can be calculated from the curve. Peak ejection and peak filling rates can also be calculated from the slopes of the curve. Additional information that can be obtained includes LV end-diastolic, end-systolic and stroke volumes. Recently, the technique was enhanced by using a forearm Doppler-based device for indirect measurement of aortic pressure, hence allowing pressure volume curves to be obtained. These curves can then be used to calculated the heart's contractility. [10]

Electron beam CT, on the other hand, allows assessment of coronary artery calcification and general morphology of the heart and major vessels and useful measurement indices such as chamber volumes. A contrast agent has to be used to allow demarcation of the chamber borders. This then allows ejection fraction, myocardial mass and the chamber volumes to be measured. MR imaging has also been used for assessing global and regional RV and LV performance. It is also useful for evaluating abnormal morphology of congenital heart disease, for

characterizing myocardial tissue and measuring wall thickness and ventricular volume. Actual ventricular function can be assessed using cine MR, especially when combined with rapid imaging. MR velocity mapping and MR tagging have already proven their usefulness in assessing ventricular function and eventually providing an index of contractility.

Conclusion

The heart is a structure with a complex anatomy which is linked to its functional properties. It is not easy to elucidate the relationship between its anatomy and function. Different levels can be studied from the cellular to the macroscopic. At the cellular level, cardiac myocytes are quite different from skeletal or smooth myocytes having a prolonged refractory period to stop contractions from interfering with each other, and not being able to repair on injury. They are also uniquely connected by intercalated discs, junctions which allow chemical, electrical and mechanical linkage between cells, allowing the cardiac muscle to be described as a functional synctium.

At a larger scale the heart muscle can be described as a singular muscle band. Dissection reveals that following the natural cleavage planes of the muscle allows a "ventricular band" to be identified. This is a helically wound structure that winds twice to form the left and right ventricles. This double-winding also explains the thickness of the ventricles, *i.e.*, the fact that the LV wall is almost twice as thick as the RV wall, and the orientation of the muscle fibres from endocardium to epicardium. This muscle band model also explains the dynamics of the LV during the cardiac cycle. The cardiac cycle can be divided into four basic motions: narrowing of the base, shortening in the longitudinal direction, lengthening in the longitudinal direction, and widening of the base. The last two motions are in a sense opposing motions to the first two. Using the rope or muscle band model, these four motions can be explained by the twisting and untwisting of the band. As the ends of the "rope" move closer and it twists the ventricles shorten causing contraction and the untwisting causes lengthening and dilation of the ventricle.

The work done by the heart, and hence the mechanics of the heart, is directly related to myocardial oxygen consumption which in turn is related to the coronary circulation. Defects in perfusion of the myocardium can lead to ischaemia and eventually infarction leading to impairment of ventricular function. Contractility, defined as the inherent ability of the myocardium to contract, can be used to measure LV function. However, it is not easy to measure this non-invasively and different quantities, such as ejection fraction and stroke volume, are used as basic indices of contractility. Recently methods such as MR tagging and velocity mapping have allowed non-invasive measurement of strain, which can also be used as an index of contractility. It is hoped that these techniques will allow a much more sensitive measure of contractility and hence the ability to predict and model disease.

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