Routes of Cardiology

I am very happy with the reception this article has received. After three years, our journal is once again publishing "Routes of Cardiology", a section that I myself coordinated in its beginning during the Tenure of Max Grinberg.

The present "Route" is rich in information. Following a short introduction on inexpressive scientific periods, the author begins his treatise with data about the end of the 16th century and the entire 17th century. The latter, as is already known, was characterized by individualist innovations, not only scientific but also social, political and spiritual as well.

Then, the author follows the steps of those who were great. We can recognize the pioneering presence of careful observers, followed by the physicists and chemists, who provided solid foundations, and later by the physiologists with their fertile discoveries of functions and interrelations.

The whole succession of men and facts is delineated in a logical sequence, where the value of each step for the next step is understood. This way, the present is reached with a complete vision of the preceding steps and of the logic of the results.

This article is a true lesson on the fundaments of the basic steps.

Luiz V. Décourt

The Greatest Medical Discovery of the Millennium
(Fundamental Steps to the Understanding of Cardiac Performance)

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Harvey´s discovery of blood circulation in 1628 is considered the greatest medical finding of the last millenium due to its far-reaching effects on Physiology, on the birth of Cardiology and also on all other fields of Medicine. So great an importance probably arises from the fact that circulation is the primary conduit for the gathering of functionally different cells, the basis itself for the development of superior organisms. In addition, Harvey's model is widely accepted as fact, untouched and unchanged for centuries. The prime importance of Harvey's model is that it is the basis for other findings and theories that have expanded it and keep on widening its range, with no need for changing the model [1]. Observing correctly the steps that have erected it, one can confirm that the steps taken have been made slowly and arduously through tortuous paths over almost 400 years.

This article reviews the fundamental steps in the evolution in understanding physiological cardiac performance as viewed throughout the seminal works that constructed it, ever remembering that these ideas represented a new link to the truth, with numerous ancestors and descendants, whose sum over the centuries has taught us how the heart performs its function.

Myth or scientific truth - Up to the beginning of Renaissance, Medical concepts were based on the teachings of Galen (A.D. 130 to 199) who was born in Pergamon - Asia Minor. In 161 A.D. Galen went to Rome as the personal physician to Marcus Aurelius and other emperors. With regards to circulation and respiration, according to Galen's doctrine that was greatly inherited from Greek medicine (which was based on inspiration rather than on experimentation), life depended on three "pneumas" or "life-supplying spirits". The blood, originating from food - which was absorbed as "chyle" from the alimentary canal – was produced in the liver where it received the "natural spirit", after which it passed to the right heart. From there, the major part of it went towards the pulmonary artery to nourish the lungs, while a minor portion of blood passed through the invisible pores from the right to the left ventricle. Getting in contact with the "pneuma" or the universal spirit of inspired air ("spirituous air"), the pulmonary veins carried it to the left ventricle where the "living spirit" was produced and

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blended with it. That living spirit was delivered to the aorta and all arteries of the body; a fraction of it reached the mind where the blood was supplied with another pneuma, the "animal spirit", and then delivered to the nerves which were thought to be hollow. The production of arterial blood in the heart and its mixing with the living spirit produced animal heat - a synonym for life - so that the heart was considered as the hottest organ of the body. The function of the lungs, involving the heart with its bellowous movement, was to cool the heart and body, keeping the body temperature at normal levels while the function of the trachea was to clean the lungs from the foul air. As already seen, it was taught that pores in the heart allowed the passage of blood from right to left ventricle, and the idea of blood's circular movement was not yet foreseen. It was believed through observation of (arterial) hemorrhage in the a severed human body that blood moved in a tidal fashion inside the vessels. These conceptions were considered immutable, and those who dared to defy them were burned at the stake [2,3].

Only in the last 400 years have religion and science separated as fountains of knowledge. It was during the Renaissance – historically known as a movement of human liberation and expression – that the scientific method based on observation, experimentation, evidence, refutation and mathematical expression started to bring rationality back to culture. In science, all important names, maybe only the most well-known, are preceeded by others less famous names which placed the "scaffolds" for the following construction.

A new discovery can only take place if several conditions are present: historical stage, perceptive ability, and the luck that that ability is available at the right moment. Among those necessary conditions, certainly the most important is the genious of the author. Nevertheless, it is not the most important when the subject is the diffusion of an idea. For a new idea to be accepted, society, political, religious and economic interests must be receptive. In addition to this, knowledge changes unmistakably into science when it is liable to demonstration or mathemathical expression.

The apparent logical linearity of ideas that are to be revealed represents the remainder of truth that was left among delays, nonsense, fraud and parallel mystification that History has forgotten. Many times, truth has followed the most difficult and less accepted path, winning its way only after triumphing over immobilism, prejudice and special interests.

The circle is full - The discovery of blood circulation was dependent on the contribution of Andreas Vesalius, the father of modern Anatomy, who was appointed Professor of Anatomy at Padua University at age 23 He provided understanding through the observation and dissection of human corpses, in addition to physiological experiments defying everyone and everything in an age when to contest did not attract attention or cause popularity but was indeed dangerous. He showed the real anatomic relations between the organs, which up to that time had been represented by myths and not by truth. Despite predecessors of considerable value, Vesalius illustrates the spirit of the Renaissance in Medicine with the presentation to medical science in 1453 of the seven volumes of *De Humani Corporis Fabrica*. In 1555, already in the 2nd edition, Vesalius denied the existence of interventricular pores; but he still did not anticipate how the blood passed to the left side of the heart [4].

The idea of "circulation" probably already existed before Harvey, since the Italians Servetus, Columbus and Cesalpinus described pulmonary circulation between 1553 and 1571, perhaps unaware that it was already known among the Arabs through the work of Ibn an-Nafis in the XIII century. Servetus, who preceeded and probably influenced the others was burnt at the stake as a result of his ideas, which were considered heretical by Calvin. Cesalpinus, who was Professor of Medicine and Botany at the University of Pisa and later in Rome, found in experiments with animals that veins dried up at the distal side of a ligature. He was the first one to use the term *circulation*. In 1571, in his paper *Questiones Peripateticae*, he had also recognized systemic circulation, he described correctly the route made by blood in that circulation, with no proof, however, of how this was done and admitting that blood could also flow backwards through cava and pulmonary veins [3]. Certainly, Harvey who was born in 1578 in Folkestone England and studied Anatomy in Padua, Italy around 1600. He had personal exposure to the opinions of all great anatomists of that age (modern Physiology started with Harvey) and surely was aware of those ideas. In addition to that, Harvey was impressed with the finding of venous valves by the famous Hieronymus Fabricius ab Aquapendente, concluding that they should continuously direct the blood flow to the right ventricle. In 1602, he graduated as a Doctor in Padua, continued his study in Cambridge, and started his medical career in London. In 1609, he was assigned to St. Bartholomew's Hospital and in 1615 he was promoted to a tenured position, corresponding to Professor of Anatomy. From his comments, one can see that by that time he already had a clear notion of how blood circulation occurred in the entire organism. In 1618, he was designated physician to King James and later to Charles I. He was ostracized when the latter was decapitated in 1649. Only in 1628, after several years of observation, experimentation, reflection and logical thinking, did William Harvey publish his *Exercitatio Anatomica de Motu Cordis et Sanguinis in Animalibus* [5] (fig. 1).

Harvey's observations, refuting Galenic teachings and assembling scientific proof, taught that the heart is a muscular organ with an active contraction phase (systole) and a resting position where it relaxes (diastole). Also, blood returned continuously from the periphery to the right heart through the cava veins; from the right heart to the lungs through pulmonary arteries; from lungs to the left heart through the pulmonary veins and from left ventricle to the entire organism through the aorta. At each atrial contraction, the blood is forced to pass to the corresponding ventricles and from this point to the great arteries by


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legio Medicorum Londinens.
FRANCOFVRTI,
Sumptibus GVILIELMI FITZERI.
ANNO M. DC. XXVIII.

Fig. 1 - Frontispiece of the 1st edition of "De Motu Cordis", by William Harvey, in 1628.

ventricular systole, its returning to the heart being prevented by the action of cardiac valves. He reasoned that as the amount of blood passing through the heart in an hour weighed three times more than a man, the blood must pass again and again through the organ, in a circular movement throughout the body [5]. However, despite the genious of that finding, Harvey's circulatory model was not completed by himself, because, as he did not know the existence of capillaries, he made use of the "porous flesh"of the lungs to explain how the blood could pass from the right to the left side of the heart. William Harvey died in 1657 believing this [3,6]. It was the correct way of thinking, and lacked only a link.

By an irony of destiny, progress toward the discovery of that link began in 1628, the year of Harvey's greatest glory, with the birth of Marcello Malpighi, later Professor of Medicine in Bologna who, taking advantage of the systematic application of the microscope by the Dutch tradesman Anton van Leeuwenhoek, years before, discovered capillaries and their function by studying lungs of frogs, demonstrating that pulmonary circulation is a closed-circuit and changing a briliant theory into an histological fact, and in 1660 completing anatomically Harvey's circulatory model. Malpighi also described the structure of pulmonary alveoli and their relation to lung capillaries, presenting two basic anatomical substrata for the understanding of respiration and circulation. For this reason, he is officially recognized as the creator of Histology [3,4,7].

Despite believing in his theory, Harvey died thinking that the function of lungs was to cool the heart, unaware of the existence of respiratory gases, hematosis, tissue respiration and variations in cardiac output. The notion of cardiac output was still vague and the main objective of circulatory system – the O_2 transportation to the tissues and CO_2 removal from them - was unknown. However, his circulatory model established modern Physiology and Cardiology as a sciences.

After all, for what purpose? - After the establishment of the circulatory model, the next logical step was to determine its purpose. In 1660, Robert Boyle from Oxford, in his *The Spring and Weight of the Air*, made the analogy between fire and life – to exist or be extinguished both fire and life depend on an essential anonymous element in the atmospheric air, i.e., air is as necessary to life as it is to combustion - generating the idea of organic combustion. The similarity between life and fire noted by Boyle was the seed for calorimetric and organic metabolic studies developed from then on. It also inspired Boyle and a group of British scientists – whose majority created the *Royal Society of London* – to begin research that would lead to the discovery of the respiratory gases [4].

Later, Robert Hooke demonstrated that it was possible to save the life of a dog with its thorax motionless by inserting air through the trachea, and concluded that the air, and not the thoracic movements, was essential to life as well as to combustion. In 1669, Richard Lower, a bright Oxford scientist, published the results of an experiment (*Tractatus de Corde*) that demonstrated that venous blood (dark red), if inserted into fresh-air-ventilated lungs, would change there into arterial blood (bright red), and not in the left ventricle, as it was believed. He explained that finding as a consequence of the absorption of air by the blood. The identification of the mysterious substance would require more than another hundred years [3,4]. In 1674, John Mayow, another bright Oxford scientist who lived only for 36 years, called nitroaerial spirit the substance of air necessary to sustain life and fire (*Tractatus Quinque)*, the absence of which prevented both from being kept in a closed container, questioning the idea that the main function of the lungs was to cool the heart . But how could the air, or a mysterious substance inside it, get into the organism? In order to explain that, the Italian Giovanni Alfonso Borelli not only stated, as did others, that "the air taken into respiration is the main cause for animal life", but also foresaw the mechanism of diffusion by organic membranes of gases dissolved in liquids, with no need for pores. In 1774, the Scottish theologian and scientist Joseph Priestley extracted a gas, which he called "dephlogisticated" air, from mercury oxide by heating it. This gas was capable of producing a lusty flame and extending the life of animals that breathed it. However, he did not understand the role of that gas in respiration as well as in combustion, because he was a follower of the confusing "phlogiston" theory of Stahl, that is something that burning bodies waste. In 1754, that theory had already been weakened by the Scottish chemist Joseph Black who had also identified CO_2 in expired air. The so-called "gas

sylvestre", CO_2, had been found by the Belgian Jean Baptiste van Helmont (who coined the expression "gas") almost a century earlier. The identification of CO_2 in the expired air, as well as a result of burning, strengthened the idea that combustion occurs inside an organism [3,4].

However, it was the ingenious French chemist Antoine Laurent Lavoisier – elected to the Academy of Sciences in 1768 at just 25 years of age – who in 1775, repeating Priestley's experience but using a strictly scientific method, supplied with an exact balance, precise measurements and interpretative feeling, demonstrated scientifically the liberation of an essential substance whenever the oxide changed into metal. At the moment when the metal was warmed up again to become oxide, an increase in weight occured. Thus, Priestley's so-called "dephlogisticated" air, the substance that transformed into metal when calcined, was the characteristic component of acids. Lavoisier adopted the term oxygen (acid generator) referring to that substance and at the same time put an end to the "phlogiston" theory. Mayow conceived the existence of something like or similar to O_2 in the air (nitroaerial spirit) but did not succeed in demonstrating it. Priestley discovered O_2 but did not identify it correctly as a respiratory agent. Lavoisier succeeded in doing so and much more: he was the first to explain the nature of combustion and respiration, showing that they are similar processes, including the absorption of O_2 from the air and production of CO_2. In 1780, together with Laplace, he created the ice calorimeter. Using such a calorimeter he showed that the oxidized amount of carbon was related to the heat produced by a guinea pig. Internal organic combustion had been demonstrated. In 1794, Lavoisier was decapitated by the coarseness of Terror ("La révolution n'a pas besoin de savants"), among other faults for being a scientific opponent to the simple-minded Marat. His friend Lagrange said: "It took but a second to cut off his head; a hundred years will not suffice to produce one like it." Despite ample proof that respiration is similar to combustion, the great Lavoisier wrongly located its site in the organism, putting it in the lungs [2,3].

The mistake of Lavoisier was corrected in the posthumous memoirs of the Italian abbot Lazaro Spallanzani, published in 1803 by Jean Sénébier [8]. Spallanzani showed that the tissues of young animals, even without pulmonary respiration, and isolated tissues of vertebrates and invertebrates used O_2 and released CO_2, proving the existence of tissue respiration. With Spallanzani's demonstration of O_2 utilization and CO_2 production by peripherical tissues of live organisms, a search began to discover how they could be transported from the pulmonary alveoli to the periphery and vice versa. In 1837, Gustav Magnus [9], professor of Physics in Berlin, extracted O_2 and CO_2 from arterial and venous blood by means of a mercury pump and concluded that the corresponding contents of those gases were bigger in one compartment than in another. So, part of O_2 should have been used by the tissues, which should also produce CO_2. Magnus, making use of Borelli's ideas, was also the first man to postulate that O_2 and CO_2 crossed by diffusion the alveolar-capillar membrane of the lungs. The difference between arterial-venous O_2 and the CO_2 and the explanation of that cardiopulmonary linkage with the periphery in the respiratory process had now been demonstrated.

Mainly due to Lavoisier, oxygen was identified as the substane most essential to life on the planet, the transportation of which the cardio-pulmonary system had been made for, linking Chemistry and Medicine and opening the way towards the study of all forms of oxygen production in nature and its use by live organisms. The question of how that substance was transported and used by the organism still remained.

The "S"-shaped curve - The enigmatic process of transporting O_2 and CO_2 by the blood continued to puzzle observers. In the first half of the XIX century, the basic laws of gases had already been established. In 1857, Lothar Meyer demonstrated that the amount of O_2 released under reduced pressure by the blood was less than expected, i.e., O_2 did not dissociate from blood as determined by Dalton's Law. So, Meyer concluded that O_2 was not only dissolved in the blood but that something kept it there too. In 1864, observing the dry substance of the erythrocyte, Felix Hope-Seyler started to solve the mystery of that strange affinity between blood and oxygen. He obtained the crystalline form of hemoglobin and its spectrum, concluding that when that substance was combined with O_2 they formed the oxyhemoglobin. The observation that one gram of hemoglobin was capable of retaining 1.34ml of O_2, or 70 times more than O_2 just dissolved in the blood, is owed to G. V. Hüfner [10], in 1877. However, his O_2 dissociation curve (1888) was shown as a rectangular hyperbole, as for using pure hemoglobin in contact with ambient air. Meanwhile, the relationship between partial pressure of O_2 in the blood (PaO_2) and hemoglobin saturation in O_2 ($\%HbO_2$) needed to be solved. In 1878, Paul Bert [11], professor of Physiology at the Sorbonne, in his classic *La Pression Barometrique*, examined the blood of dogs at various PaO_2 and reported that blood at body temperature loses 1/2 of its 0_2, but only drops 20% in PaO_2. Bert established then the basic principle that it is the partial pressure of a gas - not its percentage - in the atmosphere that has physiological importance.

In 1904, Bohr, Hasselbach and Krogh [12] gave the present "S"-shape to the hemoglobin dissociation curve of blood, establishing the precise correspondence between blood PaO_2 in mmHg and $\%HbO_2$, and stressing that the curve for a pure hemoglobin solution differed from the blood curve. Despite the fact that $\%HbO_2$ depends on PaO_2 and in spite of their variation in the same direction, the relationship they keep is not a linear one, but is expressed by a typical "S"-shaped curve, the upper part of which is flat. Among others, the dissociation curve shows two particular properties: a) with PaO_2 above 80mmHg, the hemoglobin is almost completely saturated; b) with PaO_2 below 50-60mmHg it releases O_2 quite easily. The first property stands for an effective defense of the organism against hypoxia, and the second one ensures an easy and ready tissue oxy-

genation. In 1904, Bohr, Hasselbach and Krogh [12] also described the physiological reinforcement received by the hemoglobin dissociation curve in order to release O_2 at the periphery, through the higher $PaCO_2$ and lower pH both present in the tissues. In 1909, Barcroft and Camis [13] showed that the "S"-shaped curve of hemoglobin dissociation in human blood depends on the saline content of the erythrocyte and on the "freshness"of the solution, being hyperbolic (Hüfner) when globin is denatured (fig. 2).

The oxygen dissociation curve of the HbO_2 fits basic physiological needs and represents the linkage between Harvey's circulatory model and the possibility of measuring cardiac output. Its discovery has permitted the routine and exact determination of the amount, transportation and consumption of O_2 in the body, allowing quantification of cardiac and respiratory functions.

Adolph Fick - The vast majority of cardiologists and some physicians associate the name of Adolph Fick only with the formula for determining cardiac output and cardiac shunts. They are not aware that he was probably the greatest mathematician and physics genius dedicated to Cardiology [14]. Fick was born in 1829, in Cassel, Germany, into the bossom of a highly intellectual family. After a proper time he succeeded Carl Ludwig, in Zurich, "perhaps the greatest teacher of physiology who ever lived" [7], and later von Bezold in Würzburg. He was the first to explore mathematically the relationship between blood flow and gas exchange in the lungs. He reasoned (today it appears obvious) that the flow of blood throughout the lungs, propelled by the right ventricle, and in the absence of a shunt, must be equal to the entire cardiac output at the same time that oxygen is absorbed as the blood traverses the lungs. Only a small step was needed to conclude that cardiac output could be calculated from the oxygen consumption of breathing,

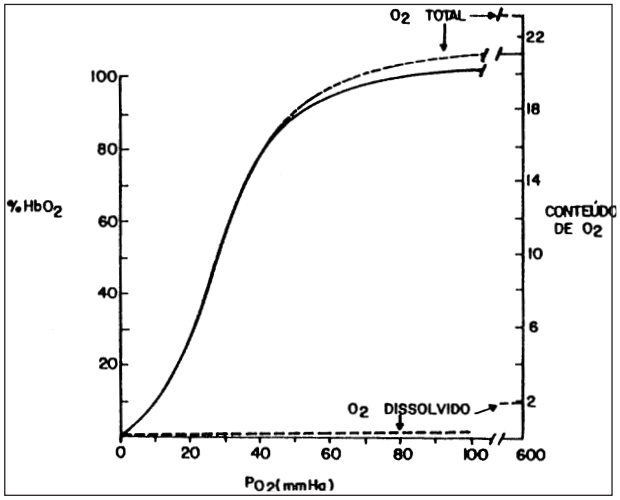

Fig. 2 - Dissociation curve of hemoglobin (Hb). With a PaO_2 of 100 mmHg, the Hb is almost completely saturated (%HbO_2). The dissociation curve of Hb deviates to the right (greater release of O_2 to the tissues) as a result of isolated or combined temperature, PCO_2 and pH effects. With a PaO_2 of 600 mmHg, saturation practically does not increase and the O_2 content dissolved in the plasma is around 2 vol% in opposition to the 20 vol% de O_2 transported by Hb[1].

divided by the difference in oxygen content of the blood between the left and right heart chambers (O_2 absorption). So, Fick established the formula:

$$CO\,(ml/min) = \frac{VO_2\,(ml/min)}{CaO_2 - CvO_2\,(ml/100ml\,blood)}$$

such as CO = cardiac output, $VO_2 = O_2$ consumption of the body, and CaO_2-CvO_2 = arterial-venous O_2 content difference per 100 ml of blood. Such a formula published in 1870 represents in numbers the capacity of the cardiac pump (CO), the body capacity for using oxygen (VO_2) and the capacity of peripheral tissues in extracting O_2 from the blood (CaO_2-CvO_2). It also demonstrates mathematically the relation among their terms in normal and pathological situations, and quantifies the sufficient or insufficient cardiac performance as it has never been done before. If one divides the CO by the number of heart beats one can calculate the stroke volume. The simplicity of this formula surprised the author who was astonished because nobody had deduced it before. At that time, VO_2 was measured through a basal metabolism spirometer, and the O_2 content in the arterial and venous blood through a primitive, almost unapplyable method. Based on normal values, Fick in his *Compendium der Physiologie des Menschen* reported that cardiac output is 4.6 l/min in a resting adult [14]. The Harvey's circulatory model began to be measured 242 years after it was described, changing the physiological demonstration into a mathematical certainty. Most impressive is that Fick's foresight was theoretical, before the knowledge of hemoglobin dissociation curve and 60 years before the first human being had undergone cardiac catheterization. A bright brain is always more valuable than a good machinery. How many people today should learn it yet! The indirect methods used after Frick that replace blood with dyes, gases or, presently, thermal dilution are validated by comparison with Fick's original method.

Besides his inherent genious, Fick's aptitude and training in mathematics and physics enabled him to recognize scientific truths long before his comtemporary physicians. At the age of just 26, he published what is known today as Fick's Diffusion Law: Diffusion in solutions is proportional to the concentration gradient. Fick supplied physiology with numerous precision instruments: the plethysmograph, the pneumotacograph, the pendulum myograph, the collodian membrane, the dynamometer, the myotonograph, and an improved aneroid manometer. He contributed decisively to the diagnosis of glaucoma (the Imbert-Fick Law). In 1856 when he was 27 years old, he published *Medizinische Physik*, the first book in the world dedicated to Medical Physics. Although very dedicated to metabolic studies, Fick's major consuming interest for 48 years of prolific production, research and learning was the mechanics of skeletal muscle. In this field, he wrote 37 papers and initiated 16 doctoral theses. The terms isotonic and isometric in relation to muscular contraction were conceptualized and defined by him. In his studies he concluded that, during muscular contraction, chemical energy is transformed directly into kinetic energy, and that the strength of contraction is related, within limits, to the

length, or stretch, of the fiber. This proposition, known as Fick's Law of skeletal muscle, was utilized by Otto Frank, in his classical experiments with frog cardiac muscle in 1895. He acknowledged: "I have shown in this paper that the difference in the courses of isometric and isotonic curves in skeletal muscle, as discovered by Fick, also exists in cardiac muscle"[15]. It is not too much to say that the so-called Frank-Starling law of the heart stands with its feet on Adolph Fick.

Human judgement is unpredictable. There is no reason for justifying why the postumous vision of such a genius is so unrelated to his importance. Fick has been frequently forgotten, and his name is notoriously absent from the classical book of Garrison [7]. Perhaps the most convincing explanation for that lies in that Fick never published in English, the universal idiom of science today, resulting in the possibility of hidden stollen ideas and the reward of mediocracy and ignorance of genius.

Fick established the most important method for studying the heart's performance. The measurement of cardiac output has broadened the frontiers of physiopathological studies of heart action, giving it a mathematical validation from the basal state to maximal exercise. After Fick´s lessons for measuring the final effect of cardiac performance knowledge was directed toward elucidating its determinant factors.

Frank-Starling law - Based on Fick's ideas and suggestions, Otto Frank (1865-1944), also born in Germany, in Odewald, expanded the observations on skeletal muscle to the myocardium. He also studied two additional years of Mathematics, Physics, Chemistry and Zoology, in addition to Medicine. In 1895, at Voigt's Laboratory of Physiology in Munchen - whom he succeed from 1908 to 1934, being then retired by the Nazis, he published meticulous records of isometric and isotonic contractions of frog myocardium and established that, within limits, myocardium resembles skeletal muscle in developoing greater tension as the resting tension is increased, thus producing a more potent subsequent contraction. Frank's observations constitute a link between work on skeletal muscles and that on the myocardium. After describing its experiments he compared changes in the length of skeletal muscle with changes in ventricular volume, and changes in tension with changes in interventricular pressure. Measuring an isometric contraction he showed that "The peak of the isometric curves rises with initial tension (filling)...Beyond a certain level of filling, the peaks decline..." [15]. He discovered these relations for the atria too. In determining the rate of rise of intraventricular pressure, which is related to greater fiber tension, he anticipated the study of myocardial contractility. Besides these basic contributions, Frank had an extremely large production in the field of cardiac and circulatory physiology for his entire life, also contributing to the knowledge about valvar cardiac dynamics and to the understanding of events in the cardiac cycle [15].

The so-called law of the heart rediscovered years later for mammalian hearts by Patterson, Piper and Starling [16] is implicit in Frank's paper on frog cardiac dynamics. At London University, they used a heart-lung preparation of dog for studying the influence of venous return, of arterial resistance and of heart rate on cardiac function. In these experiments they were able to produce diastolic and systolic overload respectively by increasing the quantity of blood entering the ventricles or elevating the resistance to the outflow ("arterial") pressure by aortic constriction. In both cases the ventricular response was a less than complete emptying for some beats, followed by a progressive increase in both ventricular end diastolic volume and pressure. According to the author's ideas this indicated disproportion between ventricular diastolic filling and systolic emptying, until sufficient diastolic distension enabled progressively more potent contractions. These effects provided a new circulatory equilibrium to the preparation that increased the stroke volume to adequate values (fig. 3). They concluded that the blood volume pumped by the heart at a given time is a function of the venous return, i.e., that the peripheral tissues are able to control their own flow without allowing excessive venous congestion. As the authors state, in both cases, the stretch of myocardial fibers increases tension in accordance to Frank's length-tension diagram. "The law of the heart is therefore the same as that of skeletal muscle, namely that the mechanical energy set free on passage from the resting to the contracted state depends on the area of `chemically active surfaces`, i.e., on the length of the muscle fibers" [16]. Deriving from this mechanism, the pumping action of the heart, within physiological limits, was explained by the following steps: a) the ventricular end diastolic volume depends on venous return; b) the tension of the myocardial fibers depends upon their length at end diastole; c) the stretching of myocardial fibers (end diastolic volume) on passage from the resting to the contracted state (end systolic volume) set free mechanical energy; d) if the heart rate is constant, the stroke volume, and the cardiac output, are determined by the venous return.

Although it was enunciated from studies in a dog heart-lung preparation, with the chest open and the heart beats semi-limited inside a cardiometer (a device invented years before by the Frenchman Marey to measure cardiac volume), besides cardiac depression and shrinkage in these conditions, the Frank-Starling mechanism has been posteriorly validated through many catheterization studies in man.[17] Free from additional influences, this mechanism acts in multiple physiological and pathological situations.

From these studies, the relationship between myocardial stretching (cause) and contraction (effect) was named Starling's law of the heart, more properly Frank-Starling's, and provided the explanations for heart function adaptations to multiple circulatory requirements until the middle of this century when the changes in myocardial contractile state emerged as an important clue in explaining modifications in heart performance.

X-Ray, cannulas and wave shapes - The insight of Wilhelm Konrad Röntgen who, by the end of the last cen-

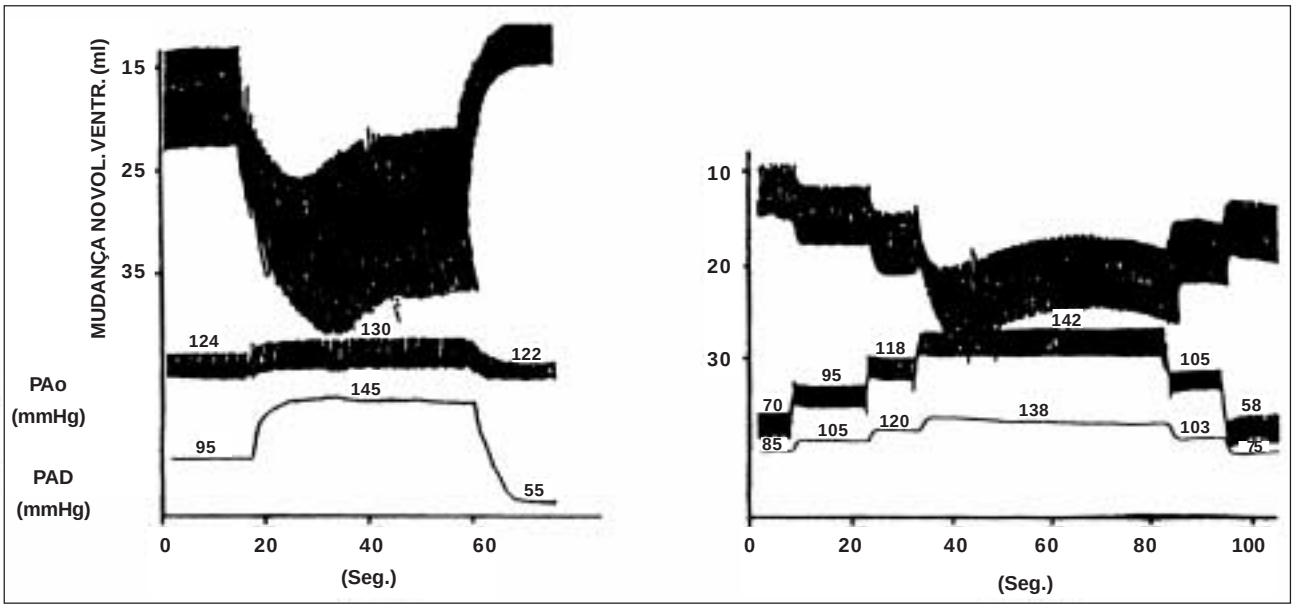

Fig. 3 - Left: Modifications in ventricular volumes of a dog's heart, aortic pressures (PAo) and right atrial pressures (PAD) when elevating the venous chamber of heart-lung preparation (right atrial pressures - PAD of 95 to 145, and afterwards reduced to 55 mmHg_2O). Right: Modifications during raising and lowereing of peripheral resistance in several degrees. Notice that increase of ventricular volumes is seen as a displacement underneath the volume tracings (Redrawn as of Starling et al. [16]).

tury [7] had found applications for the x-ray in Medicine; the daring of Werner Forssmann [18], who in 1929 inserted a ureteral catheter into a vein of his own left arm and advanced it to the right atrium beginning cardiac catheterization in man; the methodology of Carl Wigger's [19] in the 1920s, documenting and detailing cardiac pressure curves, which provided the precise explanation for the phases of the cardiac cycle; and Cournand and Richard´s [20] pragmatism in the 1940s, combining Physiological experimentation and the diagnostic application of knowledge in the recently established field of cardiac catheterization allowed the great accumulation of physiological teaching, which had been confined up to that time, to now be applied to clinical cardiology.

Baumann and Grollman [21] in 1930 were the first to measure cardiac output in man through arterial and right ventricle punctures. They taught didactically that cardiac puncture should precede the arterial puncture, because pain caused by the latter was less bearable and could artificially increase cardiac output. In that same year, Klein [22], in a more civilized manner, this time collecting blood from the right atrium by means of a catheter inserted through the basilic vein, confirmed also Fick's theoretical previsions. Notice the absolute prevalence of the German school during this period. The perfect understanding of the phases of the cardiac cycle, especially due to the studies of Carl Wiggers et al [19], clarifying the importance of measurements in the ventricular isometric and expulsive phases and their physiological significance, allowed for the comprehension and application of pressure curve measurements and dP/dt to the study of cardiac performance. In 1931, the contrasted visualization of pulmonary circulation by Egas Moniz [23], in Portugal, and later in 1938, of cardiac chambers by Robb and Steinberg [24] in the U.S.A. were decisive for anatomical and functional visualization of the heart. In 1950, also in the USA, the entry of a catheter into the left ventricle represented a battle – not free of victims – won by Zimmermann et al [25].

From then on, mainly through the study of pressure curves and of volumes obtained radiologically, a series of functional measures could be used in cardiac and medical practice. The clinical application of cardiac catheterization allowed the measurement and/or the recordation of the following parameters [1]: 1) trajectory and position of catheter; 2) intravascular and intracavitary pressures; 3) myocardial contractility measurements; 4) determination of cardiac output; 5) venous and arterial oximetry; 6) vascular resistances; 7) valvar areas; 8) intracavitary phono- and electrocardiogram; 9) angiocardiography and cineangiocardiography; 10) cavitary volumes; 11) therapeutical applications.

In 1956, Werner Forssmann, Andre Cournand and Dickinson Richards shared the Nobel Prize in Medicine for the application of cardiac catheterization in the study of pulmonary and systemic circulation in man.

Ventricular function curves - Around 1950, the development of new techniques that provided instantaneous measurement of volume, movement and cardiac pressure allowed the investigation of functional alterations in a physiological fashion and showed that modifications in stroke volume and at-cardiac output were not just a result of previous alterations in the diastolic volume. In order to clarify emergent discrepancies, Sarnoff et al [26] published from 1954 onwards a description of experiences that improve understanding of cardiac function. Working in the Physiology Laboratory at Harvard University, Sarnoff et al showed that ventricular function could be manifested through a "family" of curves, and not by an isolated curve alone. From their studies in dogs with hearts exposed by thoracotomy, the vagus nerves cut and the aorta and right

and left atria cannulated, they constructed graphs relating the stroke work of the left ventricle and pressure variations in the left atrium. It was demonstrated that in the same curve ("stable functional state") when the volumetric and/or pressure load increase, ventricular performance reaches the maximum. When the optimum limit of myocardial distension was exceeded, decline of the curve started with a drop in the stroke volume, causing a downward and rightward curve deviation. A distended heart, with low or normal load is considered depressed, although it may maintain a normal stroke volume when operating in that larger volume. However, until that point in time those verifications were similar to Frank´s [15] and Starling et al's [16] experiences.

A new finding - of great physiological and clinical significance - was that adrenaline had the ability to change the myocardial functional state, and the new function curve would deviate upwardly to the left, increasing the ventricular systolic work in all levels of atrial filling. Myocardial depression by coronary occlusion or drugs deviated the curve downward to the right (fig. 4). Those studies confirmed that length-tension relationships in the functioning myocardium derive from an inherent response mechanism that automatically suits it to the increased filling pressures (Frank-Starling) [16] but that, in parallel, the functional state of the myocardium may be affected by other factors capable of stimulating or depressing it (Sarnoff-Berglund) [26]. Those external factors - the main stimulators of which are myocardial and circulating cathecholamines as well as other inotropic agents, and depressors are vagal discharge and other physiological and pharmacological inhibitors - act through

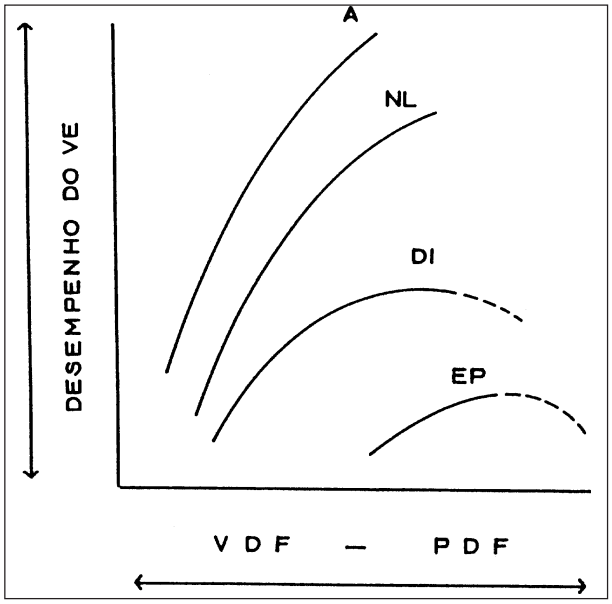

Fig. 4 - Ventricular function curves relate cardiac performance (stroke volume, cardiac output, systolic ventricular work) with the distension of the myocardium (end diastolic volume - VDF, end diastolic pressure - PDF or Pd_2). Increase in contractility (A) means a curve deviation to the left of normal curve (NL), while decrease in contractility (DI) means a deviation to the right. An extremely depressed left ventricular function means a poor performance with a very large distension (dilation), producing pulmonary edema (EP). Delineated lines represent a possible descending phase of Frank-Starling's curve [1].

cardiac nerves, altering myocardial contractility to a low or to a high level the - which means velocity of shortening for a given load. Meanwhile, as the heart volumetric changes used to stop around 40% of the maximum VO_2, it is the linear increases in the heart rate - with their intrinsic inotropic properties - that are the main cause of the cardiac output and VO_2 attaining their maximum level, as has been demonstrated by Astrand et al [27].

Although the idea of the variation of myocardial contractility had existed since Frank, and was more clearly elaborated later on by Wiggers, from Sarnoff's studies the idea materialized that the two basic generalizations of cardiac function are myocardial distension and myocardial contractility. Based on these generalizations, systematic investigations of contractility were begun. Contractility came to be considered an inherent property of the myocardium, and as that contractility should be measured, interpreted and valued.

The intrinsic myocardial property - Historically, information about the cardiac muscle has been derived from experiences with skeletal muscle. That was the case with Frank - who was inspired by Fick - and with the subsequent concept of contractility, originating from Hill's [28] ideas in 1938. Hill, in England, working with frog sartorium muscle, created the idea (before the existence of electronic microscopy) that the muscle is formed by contractile and elastic elements in series or in parallel in such a manner that to develop tension in the isometric phase the elastic elements occupy space when the contractile ones shorten, thus maintaining the same fiber length. He also ascertained that the velocity of muscle shortening was inversely proportionate to the load applied over it. When the muscle moves against a load (force) through a given distance (space) work is produced, and the contractile potency is represented by the velocity of production of that work. Hill's ideas were confirmed by mathematical equations and subsequently supported by Abbott and Mommaerts [29], with regards to its applicability to the human myocardium. Meanwhile, Abbott and Mommaerts called attention to the fact that the myocardium has a higher resting tension, contracts more slowly and cannot be tethanized

In 1962, in Bethesda, M.D., U.S.A., Sonnenblick [30] showed the possibility of relating force and velocity of myocardial contraction through a curve whose interpretation showed a maximum shortening velocity at zero load (Vmax) and at maximum tension developed by the muscle (Fo). Unlike the skeletal muscle that has a fixed F-V curve - and considering that its contractile activity increases only through the engagement of additional muscle fibers and through the increase in the frequency of nervous impulses - the number of activated cardiac muscle cells remains the same during each contraction, but the contractile state of each one, as previously seen, may be physiologically changed by: a) alterations in resting length (stretch-out), since simple distension of myocardial fibers by a bigger pre- or afterload will produce a more potent contraction; b)

alterations in contractility since, if in the previous situation the myocardium is stimulated with a sympathetic discharge, contractile power will increase even more (contractile state modification). Within limits, a cardiac muscle that experiences several preloads (different stretch-outs) will not change its intrinsic shortening velocity (Vmax), since all curves converge at the same point (zero load) at the vertical axis. Calcium, digitalis, and norepinephrine not only increase the F that muscle is able to displace but also increase the velocity of shortening in the surcharged muscle [30] (fig. 5). Measurements of contractility and Vmax can be made during cardiac catheterization by registering curves of the rate of rise of intraventricular pressure (dP/dt) in the isometric phase of the ventricular contraction [31,32].

Therefore, in the functioning heart, as a result of inotropic stimulation, the velocity of cardiac contraction increases for the same fiber length and the same load. In the intact left ventricle such a behavior leads to: a) increase in the rate of rise of intraventricular isovolumetric pressure; b) increase in the velocity of ejected blood; c) shortening of systolic time; d) faster diastolic relaxation and aspiration, in addition to other effects [1].

The identification of myocardial contractility as an intrinsic property of the fiber - independent of distension- provided an explanation for how the normal heart is able to increase stroke volume and cardiac output without changing volume, or even reducing it, which could not be explained by the Frank-Starling law alone, and allowed researchers also to distinguish clearly the activity of the cardiac pump from that of the cardiac muscle.

The sun, the factory and the explosion - With the development of studies in metabolism in the XIX century, it was clearly evident that the contractile activity of skeletal muscle and the heart depended upon oxygen consumption and metabolism of foodstuffs, mainly carbohydrates. Until 1920 it was believed that lactic acid was the agent that drove the contractile mechanism of the muscle. By that time Lundsgaard demonstrated the persistence of contraction even after all respiration and lactic acid formation had ceased. He stated that the chemical event supporting contraction was the breakdown of phosphocreatine. In 1934, Lohmann demonstrated that the prime energetic role belonged to ATP (adenosine triphosphate) whose breakdown in ADP (adenosine diphosphate) and AMP (adenosine monophosphate) liberates a great amount of energy for contraction. Soon after this discovery, it became evident that the prime function of glycolysis and respiration was to furnish ATP by synthesis from ADP and phosphocreatine [33].

The mechanisms by which the intracellular factory releases energy for contraction was elucitated step by step by Krebs [34] in 1943 when he demonstrated that all the carbon atoms of the common fatty acids, two thirds of the carbon atoms of the carbohydrates and approximately one half of the carbon atoms of amino acids are incompletely metabolized mainly to acetyl coenzyme and to ketoglutarate or oxaloacetato. These three metabolic end products take part in the most important phase of free energy release in the cell: the citric acid cycle and the electron transport system, the final common pathways for the complete combustion of the foodstuffs. The combustion occurs inside mitochon-

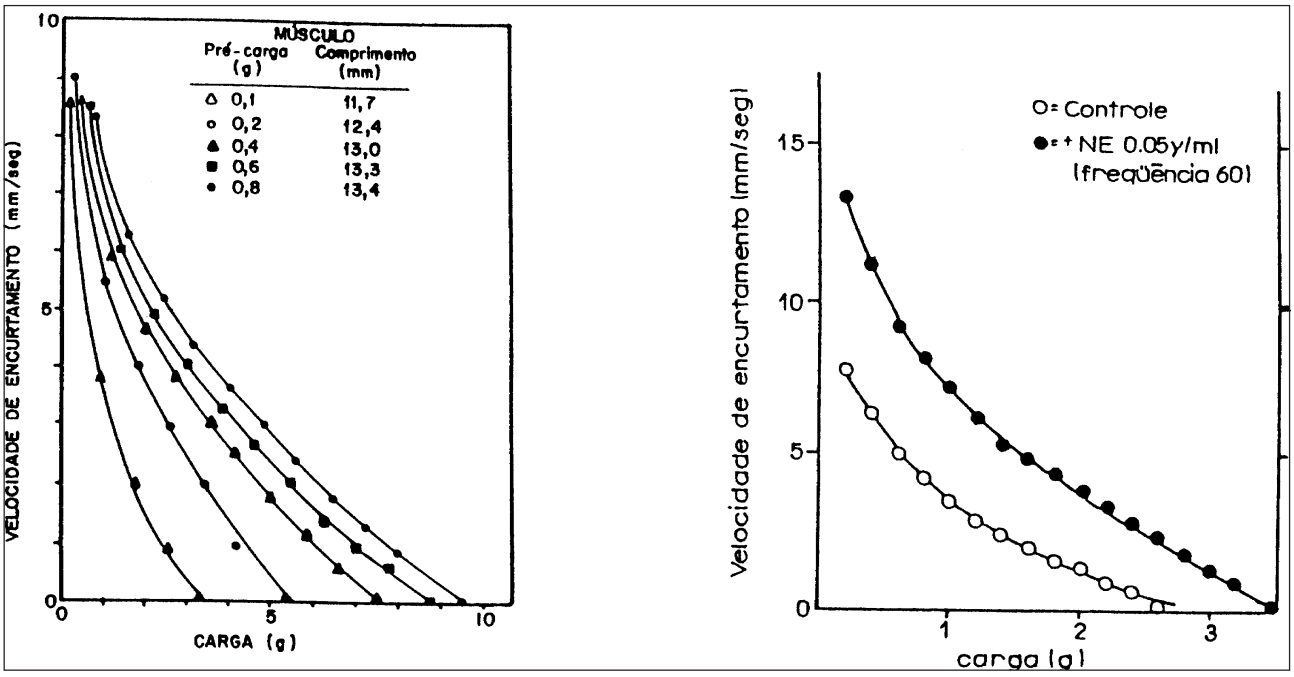

Fig. 5 – A: Relationship of afterload shortening velocity, isotonic shortening and total load in several initial muscular lengths, in a papilary muscle of cat. A greater initial muscular lenght increases the active developped force, and the shortening velocity in a given load. At zero load (Vmax), all curves converge to the same point, showing that the largest force of contraction was due to a greater stretch-out only. B: Effect of norepinefrine (NE) in the force-velocity relationship. NE increases the shortening velocity in a given load, at maximum isovolumic force of contraction (Po) and at maximum shortening velocity at zero load (Vmax) (Modified by Sonnenblick [30]).

drias, the cell factories, whose quantity is directly related to the cell metabolic activity, the muscle cells having the greater number of mitochondrias than other tissues. In mitochondrias, six molecules of oxygen and one of glycosis join to start a catabolic process that ends with the formation of six CO_2 and six H_2O molecules The breakdown of glycosis liberates the solar energy that was previously incorporated into it by photosynthesis. Although the anaerobic glycolysis (until the formation of lactic acid) forms only two ATP (6% of the oxidative energy), the Krebs aerobic cycle that follows it produces H^+ ions rich in energy and CO_2 molecules. The explosion of energy of the H^+ ions is utilized to transform 34 ADP into 34 ATP, the main fuel of the cells. Because the acidification of mitochondrias with H^+ ions may block the aerobic process, two H^+ and one O^- form water (H_2O), which neutralizes the acid threat. That is, the ultimate metabolic goal of oxygen is only that of a hydrogen acceptor after some substances are dehydrogenated (aerobic metabolism), and the respiratory enzymes that utilize oxygen are the cytochromes, flavoproteins and pyridine nucleotides, all of which are mitochondrial components [34,35].

The study of the biochemistry of muscular contraction touchs the intimacy of life and provides the necessary substrate for a better understanding of the cardiac performance. Krebs provided explanations to Lavoisier and Spallanzanni.

The heart of everything - Muscular structure has been demonstrated since the last century by optical microscopy, mainly due to Krause's works in Germany and striation modifications accompanying contraction were fully described by microscopists of that period. It was known that heart walls are composed of a bundle of muscle fibers 10 to 25 µm in diameter and 50 to 100 µm in length, formed by dark and clear in-series segments, revealing ramifications and anastomosis of fibers. In 1859, Kühne discovered that a viscous protein could be extracted in great amounts from muscle. He called that protein myosin. Only after 1930, it was this protein described as the contractile component of myofibril. In 1939, Engelhardt and Ljubimowa took a basic step showing that myosin was also the ATPase enzyme catalysing the passage of ATP to ADP, with its energy deriving from ATP hydrolysis. In 1941, Szent-Györgyi et al described the actomyosin, an actin-myosin complex, originating the idea that, separated and in rest, ATP and ADP would unite during the contraction phase as a result of ATP action [33].

Relating those innermost mechanisms to the biochemistry of cardiac performance with the cellular ultrastructure would only be possible through an invention outside of cardiology: the electronic microscope, in the 1940s. With that device, tissue resolution increased a hundred times in relation to the optical microscope. It was up to Huxley [36], in Cambridge, England, in 1953, to identify in a coherent fashion the structure and the functioning of myofibril, showing that it (0.5 to 2 µm in diameter) is composed of in-parallel and in-series morpho-functional units, the sarcomeres, measuring at rest 1.6 to 2.2 µm in length. He showed that in the sarcomere there are two types of myofilaments; a thick one, with high molecular weight (500,000), the myosin, and a thin one, the actin, the nonenzymatic contractile protein, with a molecular weight of 47,000. Actin reversibly combines with myosin in the presence of ATP and Mg^{++}. Between the two filaments there is a transversal bridge system. Starting from the sarcomere end, the clear actin filaments stretch out towards the center, but do not succeed in reaching it. The dark central band is occupied by parallel disposed myosin and actin filaments, with only myosin existing in the center of the sarcomere. Tropomyosin and troponin, which stands over actin molecules, are contraction regulator proteins. The mitochondria, site of ATP production, occupies approximately 20% of the sarcomere volume.

Awareness of the model, made it possible to understand the function. In 1954, Huxley et al [37] proposed a theory assuming that contraction of striated muscle is a process in which the interfibrillar bridges shrink making the actin slide parallel over myosin towards the center of the sarcomere. The dark band remains stable during contraction and relaxation, and the clear band shortens according to sarcomere shortening [36,37] (fig. 6). As early as the 1940s it was known that calcium played an important role in that process [33]. In 1955, Huxley and Taylor [38], utilizing fine electrodes, showed that only depolarization alongside the line between the sarcomeres caused shortening of the clear band, proportionally to the excitation degree. Afterwards, it was found that those sites were saturated with calcium [39]. The control of the contraction-relaxation mechanism is situated in a superficial longitudinal and deep transverse channel system invaginating in the sarcoplasm, and in the subsarcolemmal cisternae at the ends of sarcomere that function as calcium deposits.

As a consequence of activation, Ca^{++} drops slowly into the myocardial cell where - after diffusing in the cytosol - releases it in great amounts from intracellular calcium reserves of sarcoplasmic reticulum. Contraction starts and is maintained through the inhibition of troponin molecules by Ca^{++}, releasing the tropomyosin that had been inactivated by troponin C. The free tropomyosin activates the myosin

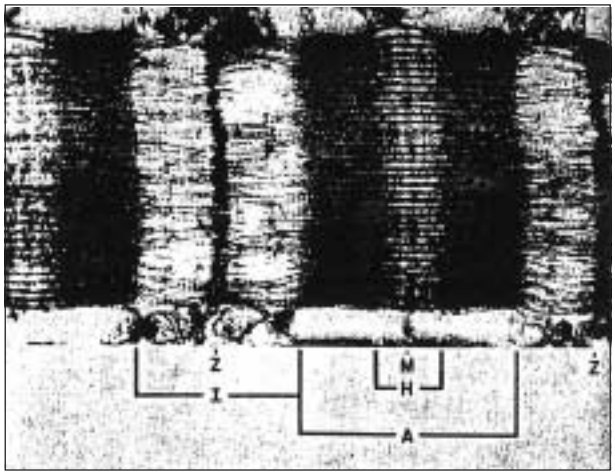

Fig. 6 - Sarcomere in a longitudinal section, magnification of 50.000 vezes. See text for details (According to Huxley, em [1]).

that degrades ATP into ADP in the mitochondrial membrane, thus releasing inorganic phosphate and energy. The intensity of sarcomere shortening is parallel to the energy release. As usual the entering Ca^{++} does not saturate all sites of troponin union, the number of activated bridges may increase if cytosolic Ca^{++} rises. Myocardial relaxation occurs through an active process of calcium expulsion from cytosol that regains its normal concentration of 10^{-7} mol per litre, which allows actin and myosin to recover the pre-contractile configuration.

The ultrastructural explanation related to the effects of myocardial distension and contractility is based on these findings: 1) the major initial fiber length increases the number of force-generating sites, without any qualitative alteration in the cyclic process inside of them, which is provided by a more favorable superposition and interaction of actin and myosin contractile filaments (reduction in length causes the opposite effect); 2) the increase or decrease of inotropism at a same sarcomere length results, respectively, in intensification or depression of cyclic generating force process at the contractile sites, without any alteration in the number of activated sites, due to the increase caused by catecholamines or other inotropic agents in the calcium excitatory mechanism [1].

The 330-year period between Harvey and Huxley represents an age of cardiological knowledge acquisition and of medicine in general that has never been matched by any other in human history; that learning whenever duly substantiated may be expanded, complemented, specified but no more changed in its basis.

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