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Research Article

Clinical and Experimental Research on Negative Intraventricular Pressure. Contributions to the Pathophysiology of Heart Failure with Preserved Ejection Fraction

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Abstract

Following Torrent Guasp's description of the myocardial band in the last third of the 20th century, we initiated a prolonged investigation encompassing studies of human, bovine, pig and anuran hearts including its anatomy, histology and biochemistry. Hemodynamic, electrophysiological and echocardiographic studies were also performed on patients, as well as physiological investigations in the laboratory with experimental animals. Among many findings, all of them led us to the importance of the negative intraventricular pressure that we have recorded in both the left and right ventricles, which occurs in a limited time after the closure of the aortic valve in the first ms of diastole, in cardiac and therefore circulatory function. The importance of this period (PPMC) lies in the fact that it allows the circulatory cycle to reach the negative pressure necessary to achieve the optimal gradient in the ventricular chambers. During this period, the pressure drops to -3 mmHg, according to our measurements taken in patients, as discussed in this article.

Regarding Heart Failure with Preserved Ejection Fraction (HFpEF), this syndrome requires a pathophysiological understanding that allows interrelating the symptoms with the diagnostic instrumental findings, but for this to be possible it is essential to begin its understanding from cardiac anatomy and physiology. It must be considered that the myocardium, in its structure, is not globular and homogeneous, but rather a continuous muscle, coiled upon itself to form a helix supported by a fulcrum to generate its considerable power; that it is not only an active organ of ejection (positive pressure) but also of suction (negative pressure), which entails energy expenditure in the first 100ms of diastole; that its ventricles are

complementary, not parallel; that it does not contract as a single unit but rather by integrating its parts in a concatenated manner, and that for this it needs an antifriction mechanism (hyaluronic acid) for the timely sliding of its overlapping muscle segments. The functional association between the venous Thebesian and Langer ducts, together with the considerable amount of hyaluronic acid found in our research in human and animal hearts, and knowing the lubricating role it plays in the rest of the body, could be crucial in understanding the dynamics of the helical heart. In this way, ventricular torsion is correlated with a lubricating mechanism that facilitates the sliding of myocardial segments to prevent energy loss. Through these venous ducts and helical contraction, plasma fluid containing hyaluronic acid would be continuously propelled through a rich capillary network. In our research, we have found spaces with a capillary mesh and plasma fluid rich in hyaluronic acid between the cardiomyocytes.

Keywords: Heart Failure with Preserved Ejection Fraction, Cardiac Suction, Cardiac fulcrum, Helical heart

"A new scientific truth does not triumph by convincing its opponents and making them see the light, but rather because they eventually die and a new generation is born that is familiar with it".

Max Planck

Introduction

Since according to our previous research [1-4], the right and left ventricles have two energetically active phases, suction and ejection, functions that must be fulfilled with a single chamber each, the complementarity between them, resulting from the interplay of pressures in the cardiac cycle, plays a fundamental role in functional continuity. At this point, we can discern that suction prior to systole, during the Protodiastolic Phase of Myocardial Contraction (PPMC), improperly referred to as isovolumetric relaxation phase, because it is active and involves energy expenditure, is what allows, as we will analyze, the subsequent expansion of the ventricles during filling. This phase is complementary to the systolic plunger property developed by the opposite ventricle. Circulatory movement requires a dynamic relationship between the ejection of one ventricle and the suction of the opposite one. With two available circuits - systemic and pulmonary- complementarity acts between the ejection of the Left Ventricle (LV) and the suction of the Right Ventricle (RV) in the systemic circulation, while the ejection of the RV forces the suction of the LV in the pulmonary circulation. The heart is an open system in terms of energy and closed in terms of organization, which feeds back and self-organizes to maintain homeostasis with cybernetic behavior. Here, we must include the interrelationship between structure and function [5-8]. Structure implicitly carries the concept of form and systemic function. For example, what happens when we unfold the continuous helical myocardium and transform it into a linear muscle [9] is the loss of its pattern (Figure 1 and 2). Its components do not change, but its functional organization is lost. The heart cannot be reduced in function to its isolated parts. The communion of its parts implies a pattern of organization because it leads to an adequate level of functionality.

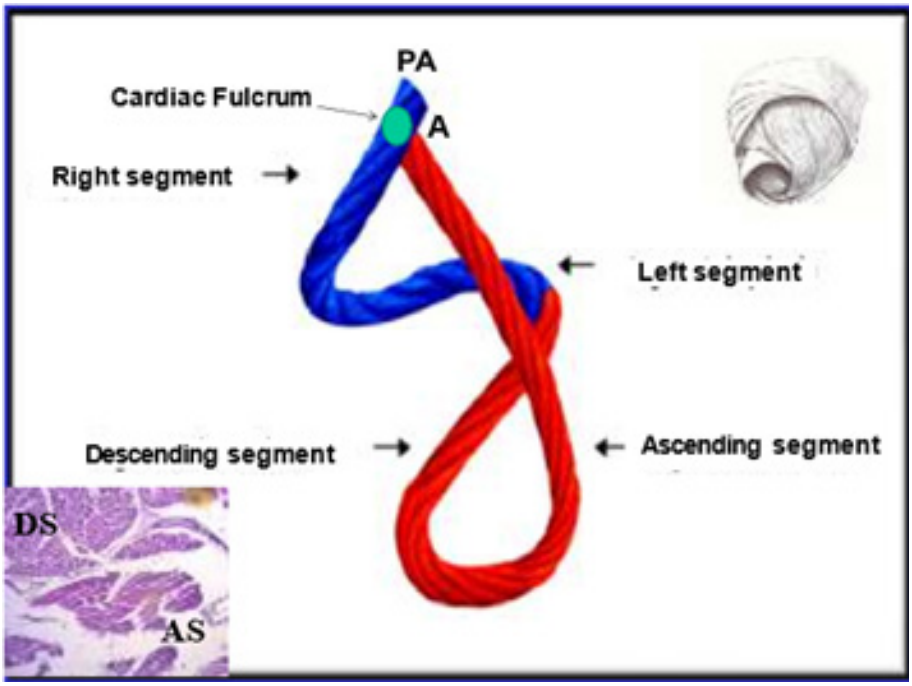

Figure 1: Helical myocardium in the cord model that simplifies the spatial structure. The figure shows the different segments forming it. In blue: basal loop. In red: apical loop. **PA:** location of the Pulmonary Artery; **A:** location of the aorta. The location of the heart's support, called the fulcrum, is shown. The figure in the right angle illustrates the three-dimensional arrangement of the continuous myocardium. Histology (left inset) details the different orientation of the longitudinal fibers (Ascending Segment, AS) in relation to the descending fibers (transverse fibers, DS). Given the different orientations of the fibers, the area marked with the black circle corresponds to the beginning of the opposite helical movement that produces myocardial torsion.

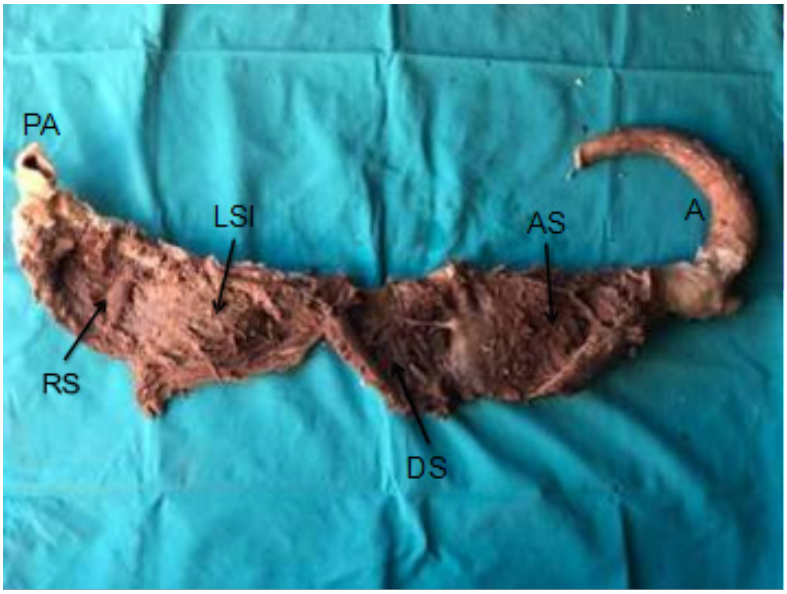

Figure 2: Myocardium unfolded in its entirety showing the segments that compose it. **PA:** Pulmonary Artery; **RS:** Right Segment; **LS:** Left Segment; **DS:** Descending Segment; **AS:** Ascending Segment; **A:** Aorta.

Through research that we have continuously conducted in recent years, including the sequence of electrical activation of the LV, anatomical and physiological studies on PPMC, ventricular septal interdependence, clinical and experimental research on negative intraventricular pressure and the suction mechanism, the cardiac cycle, the filling curves of the left and right ventricles, and comparative echocardiographic studies between normal patients and those with heart failure with preserved ejection fraction (HFpEF), we have come to understand biventricular complementarity, in which active suction of both ventricles is a critical point in circulatory motion.

Suction Mechanism

Classical Model

Ventricular filling is performed by the atrial beat, according to Harvey, or by the pressure gradient, the latter hypothesis being proposed in the 1920s by Wiggers [1-4]. During the beginning of PPMC, active proto-diastolic suction phase classically referred to as isovolumetric relaxation phase, the pressure in the left ventricle drops below the pressure in the left atrium shortly after the peak of the left atrial V wave. On the other hand, the rapid ventricular filling phase at the end of this phase coincides with a continuation of the decline in atrial pressure that began during mitral opening, while the end of the rapid ventricular filling phase and the beginning of the slow ventricular filling phase are characterized by a change in slope in the ventricular volume curve. During the slow ventricular filling phase, the pressures in the atrium and left ventricle slowly increase until the next atrial systole. In the classical concept, atrial contraction and the resulting increase in ventricular filling are manifested by an increase in ventricular pressure and volume.

Suction Due to Negative Intraventricular Pressure

The pressure in the circulatory circuit decreases from the aorta to its minimum value at the venous end. This decrease in pressure is due to changes in the effective cross-sectional area along the circuit and to the reduced "pressure loss" caused by friction between the walls of the circuit, due to blood viscosity [10,11]. At this point, it should be understood that the variation in pressure due to changes in the effective section can be reversed with new changes in that section, but in the case of "pressure loss," the pressure decreases without being able to be recovered since the energy is dissipated in the form of heat or work and the circuit does not recover it without a new supply of energy. Nevertheless, this pressure loss in the blood circuit is very reduced in comparison with to a normal pipe due to biological effects as the movement of the glycocalyx.

The energy input required for circulation is generated by suction inserted into the circuit, as the circulatory system needs to introduce an engine so that blood can reach the ventricles. In this way, the heart is not only responsible for blood progression through the arterial system ("vis a tergo"), but also for its passage through the veins via ventricular suction ("vis a fronte"). This function is performed by the PPMC. Consequently, low venous pressure cannot create the drive that forces blood into the ventricle, especially since all this happens in less than 500ms. The ventricle, made up of resistant muscles, does not expand with low venous pressure, much less with the contraction of the atrium, which has very thin walls and lacks an adequate structure to prevent the backflow of blood (Figure 3). Venous pressure is not the cause of ventricular expansion but its consequence. We must admit that the entry of blood into the ventricle is the result of aspiration due to the contraction of its walls in PPMC. We deduced this concept from our research.

The histoarchitecture present in the vena cava-RA and pulmonary vein-LA sequence should be interpreted as passive ducts for transporting blood to the ventricles. Due to their structural characteristics, they cannot provide sufficient propulsion to fill the ventricles. All the histological sections in Figure 3 show that

the venous structures from the vena cava to the left atrium do not show propulsion capacity. The different histology of the PA, with propulsion capacity, is what allows the RV to function as a plunger towards LV suction.

The components of the three-dimensional reduction of the heart interact synergistically through the continuous myocardium that coils unto itself, achieving torsion-ejection and subsequently ventricular detorsion-suction. In systole, there is a three-dimensional reorientation of the helical cardiac architecture, that shortens longitudinally and transversely and produces a twisting motion. The atrioventricular annulus contracts, the aortic annulus expands slightly, the mitral and aortic planes descend, and the left ventricular outflow tract remains open [12-16]. In early diastole, during PPMC, conditions are created for ventricular suction. During this PPMC period, the presence of negative intraventricular pressure has been documented, both in human clinical practice and in the laboratory during the biological experiments we have conducted, as will be seen below [17-23], but it is not passive as was considered in the classical concept, but active and with energy expenditure produced by the terminal contraction of the ascending segment [24, 25].

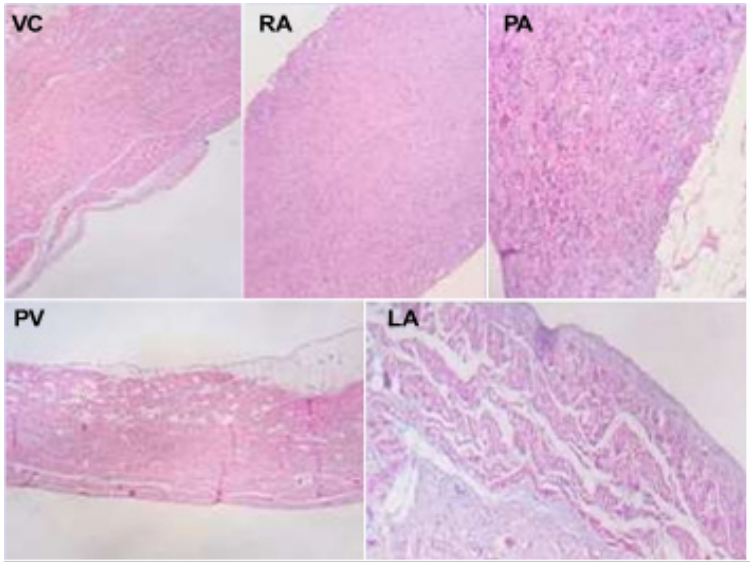

Figure 3: VC: Vena Cava: a 3mm thick vena cava structure is observed, formed in its middle layer by smooth muscle cells in parallel fascicles. **RA: Right Atrium:** wall formed by myocardial 4mm-thick muscle fibers. **PA: Pulmonary Artery:** myocytes formed by smooth muscle cells are observed in a loose stroma with a spiral structure. **PV. Pulmonary Vein:** structure similar to the pulmonary artery with myocytes formed by smooth muscle with a fasciculated structure. **LA: Left Atrium:** layer of myocardial 4mm-thick muscle fibers. (All histological sections belong to a bovine heart with H&E staining 10x).

During systole and PPMC, mechanical energy is consumed and released in favor of rapid dilation during the filling phase [26,27]. Suction following PPMC is an active process due to contraction of the ascending segment, as we have found in our electrophysiological research [28-34]. This suction force (similar to a "suction cup" mechanism) acts on PPMC by lengthening the fibers of the ascending segment to generate the negative pressure that allows the atrioventricular valves to open and the ventricles to fill rapidly. Changes in wall thickness, i.e., thinning, condition ventricular filling. Then, diastolic relaxation (ventricular expansion) becomes almost explosive, and the sarcomere bounces back like a spring to regain its original length [35]. If the end-systolic volume is reduced, the restorative expansive forces are greater; whereas in pressure or volume overload (hypertrophic cardiomyopathy, heart failure), relaxation slows down and suction becomes less effective.

Ventricular wall tension, after mitral valve opening, increases rapidly due to an increase in intracavitary radius and a reduction in wall thickness, in accordance with Laplace's law. Diastolic filling in the coronary arteries may participate in active myocardial expansion. The plethora of the coronary reservoir during diastole distends the myocardial mass as if the ventricle were a cavernous body and an erectile mechanism were generated that prolongs the ventricular cavity. Coronary circulation becomes a protection for the ischemic ventricular muscle during systole and expands in diastole with coronary bed filling. Based on this principle, a cardiac model composed of a double elastic sac has been developed, whose hydraulic increase in intramural pressure generates ventricular diastolic expansion, a system that has been applied in extracorporeal circulatory assist devices. The right ventricle is designed to eject large volumes of blood against low resistance thanks to the large surface area of its semilunar shape. Unlike the left ventricle, where blood is transferred from then mitral orifice to the apex before being directed to the aorta, in the right ventricle, blood is sent directly from the tricuspid orifice to the pulmonary artery following a central washout line that forms a 90º angle.

Interpretation of Diastolic Filling

The process of ventricular expansion has not been analyzed historically as thoroughly as it deserves, with diastolic filling being overlooked in the physiological mechanism in terms of its true active significance. In this regard, only systole has been classified as an active phase, involving muscle contraction and energy

expenditure [36]. Based on what has been expressed so far, how should diastolic filling be referred to? Is it the cause of expansion or a consequence of it? As a result, would it be produced by venous pressure (vis a tergo) or by an active myocardial suction mechanism, which generates a "vacuum effect"? As a rule, venous pressure has been considered the cause of atrioventricular valve opening. However, the maximum pressure that occurs at the exit of the aorta and pulmonary artery decreases steadily until it reaches minimum values at the entrance to the atria. In a system of ducts through which a viscous liquid circulates, such as the circulatory system, energy losses occur due to friction between the fluid particles and between the fluid and the walls, due to its viscosity. This phenomenon is known as pressure drop, which is not constant throughout the circuit because it depends on the local diameter of the circuit and the local velocities of the circulating fluid. This pressure drop is a loss of pressure throughout the circuit, which translates into added resistance to the free circulation of the fluid.

Thus, venous pressure would be unfeasible as a cause of ventricular expansion, since, in addition to occurring in only 500ms, it would be incompatible for such an achievement. This minimum diastolic filling time, approximately 400ms if we substract the 100ms of the protodiastolic phase, implies the need to consider an aspiration mechanism, a ventricular suction. Here arises the necessary discussion that each ventricular chamber, by fulfilling two energies, ejection and suction, is forced into asynchrony to maintain a continuous circulatory cycle. The asynchrony found in our research between the onset of RV ejection, which occurs approximately 40ms before LV ejection, allows for the second filling of the latter in period 3 (second rapid filling) of diastole Ventricular expansion thus results from the functional interaction of ejection and suction in each of the ventricular chambers, knowing that each ventricle operates with this functional duality through muscle contraction with energy expenditure. Thus, the circulatory circuit consists of a positive pressure that is responsible for making the blood progress through the arterial system and another that has negative pressures to achieve the necessary gradient and achieve the filling of the ventricles, which requires an asynchrony. If we did not consider active ventricular suction, the drop in venous pressure to negative values in the heart chambers would not make sense.

We must also conceptualize that the atria do not have the appropriate morphology to develop the adequate pressures that determine ventricular filling, and they also lack valves that prevent blood backflow. Furthermore, they contract at the end of diastole, when the ventricles are already two-thirds full of blood, during period 3 of ventricular filling. Evidence of this fact can be seen in patients with atrial fibrillation, which demonstrates the non-incidence of the atria predominantly on cardiac filling. From this analysis, it can be reasoned that neither venous pressure nor atrial systole justify ventricular filling and that it is necessary to consider the need for an inserted energy in the circuit, an impulse based on ventricular suction, which has been thoroughly investigated during this work. This raises a necessary point for discussion: can the RV have a suction phase despite having half the thickness of the LV? Let us recall that the pressure and resistance ratio between the LV and RV is 6:1, meaning that the RV is proportional to 15% of the LV. Subjected to less resistance the Pulmonary Valve (PV), given the relationship with the thrust to which it is subjected, opens before the Aortic Valve (AV), which is fundamental to the complementarity of the ventricles in a dynamic interaction between ejection and suction.

The suction phenomenon appears to be a necessary element, since without it in both ventricles, flow would stop at the slightest difficulty [37]. This research shows that the ventricles cannot be studied independently, but rather that the two circuits, systemic and pulmonary, must be analyzed with the complementary intervention of both chambers, considering ejection and suction and, more importantly, their synchronization, whose causes could be due to the interrelationship of both the sequence of muscle activation and the pressure variations in the circuits. The blood circuit that is pumped from the left ventricle is longer, and it takes several heartbeats for a blood particle leaving the left ventricle to be drawn into the right ventricle, completing the cycle. The volume ejected by the right ventricle must be the same as that ejected by the left ventricle, but the number of heartbeats needed to send blood from the right ventricle to the Left Atrium (LA) is less than that needed to send blood from the LV to the Right Atrium (RA). The volume of the LV-RA circuit is greater than the volume of the RV-LA circuit [38]. Since diastolic filling time is about 400ms, this preliminary phase of ventricular suction is consistent. This suction in the PPMC of about 100 ms, given the low gradients reached at the entrance to the atria, must be considered the fundamental element for venous return in complementarity with systolic propulsion. This situation is supported by the subatmospheric pressures ("depressions") recorded in these chambers during PPMC. The driving role of the atria ("atrial kick") is minimal. Its power is 1% relative to that of the ventricle. Obviously, this low gradient is related to the need for active ventricular suction [39].

The spatial arrangement of the continuous helical myocardium (Figure 1) clearly indicates that propulsion is provided by its walls in the ventricular chambers delimited by this structure. Composed of two loops, basal (right and left segments) and apical (descending and ascending segments), the muscular unit they form are the walls of the ventricles, to which they provide propulsion power. It is not the ventricles -mere cavities- that perform this action, but rather their muscular walls, which form the helical continuity of the myocardium as a single mass and give it its prominence. The atria are outside this morphology and therefore lack adequate walls to generate momentum for their contents, their function being that of reservoirs and decompression chambers for the pressure surge produced by atrioventricular valve closure.

This is clear because, if we go back to the primary stage in the evolution of the circulatory system, we can see the phylogenetic milestones of the different species. In this process, the atria belong to the venous segment and the ventricles to the arterial segment. This defines their origin, and the lack of a muscular wall that allows blood propulsion.

Between the atria and ventricles there is simply connective tissue, which means that these chambers can be easily separated during dissection. This assertion coincides with what was

historically maintained by Claudius Galen in the 2nd century AD [40,41], establishing that the atria can be separated from the ventricles without any incision, simply by separating them from the respective ventricles. This situation supports the integral evolutionary, anatomical, and independent arrangement of the ventricles in relation to the atria. In the classical concept, there is only one active function in each ventricle, systole, with positive pressure that was historically determined to be the cause of venous return. This is not justified according to observations; on the contrary, venous pressure is fundamentally a consequence and not a cause of ventricular expansion, according to the pressure gradient values of the venous circuit. This situation is reflected when observing the time of PPMC, in which the filling pressure in both the systemic and pulmonary circuits tend to be suction. The mechanical action of the heart is complex because it is the result of integrating its ejection, suction, and filling properties in its ventricles, under different successive and concatenated phases through the continuous helical myocardium, which, in order to fulfill its mechanical function, has a support called the cardiac fulcrum [42].

The pressure in the circulatory circuit decreases from the aorta to the venous end. This drop in pressure causes the venous pressure to be very low, with an average value in the vena cava ranging between 0 and 2 mmHg [43,44] and therefore clinically expressed in centimeters of water. The low venous pressure at the entrance to both ventricles cannot create the thrust that forces blood into the ventricles, except through active suction of these chambers. The ventricles, formed by resistant muscles, do not expand with low venous pressure, much less with the contraction of the atria, which have very thin walls and lack an adequate structure to prevent the backflow of blood. Venous pressure is not the cause of ventricular expansion but its consequence. We must admit that the entry of blood into the ventricles is the result of suction due to the contraction of their walls occurring during PPMC in both ventricles. This concept is what we deduced from our research.

In the LV, the components of the three-dimensional reduction of the heart, three-dimensional reduction of the left ventricle by 15% in its longitudinal and radial axes (anteroposterior and transverse), together with the torsion-detorsion movement, interact synergistically to achieve torsion-ejection and subsequently ventricular detorsion-suction. The atrioventricular annulus contracts, the aortic annulus expands slightly, the mitral and aortic planes descend, and the outflow tract remains open. The basal annulus contracts towards the tip that remains fixed. The LVPPMC occurs after AV closure. During this phase, a drop in intraventricular pressure to negative values has been documented, evidencing suction, both in human clinical practice and in animal experiments. A fluid moves along a tube in response to a pressure gradient. Therefore, for flow to occur, there must be a pressure gradient, which in practice must exceed 10 mmHg due to energy losses in the system. When the vascular duct does not have this gradient, flow ceases. This is called the "critical closing pressure." Blood pressure fluctuates at an average mean of 90 mmHg. Pulmonary pressures have an average of 22/8 mmHg with a mean pressure 13 mmHg. On the other hand, the pressure difference between the pulmonary capillaries and the Left Atrium (LA) is 4-6 mmHg. Thus, a low-pressure gradient allows the same amount of blood to pass through the pulmonary circuit as is pumped through the general circuit, which has a gradient of 90 mmHg due to the complementarity between the pumping and suction energies. In addition, the power of the left atrium is only 1% that of the left ventricle, so no significant effects can be expected from it as a pump function. The LA distends in the face of LV suction deficit, but lacks flow propulsion. Obviously, this low gradient could not generate sudden ventricular filling without the need for active ventricular suction [45].

Electrophysiological Research on Cardiac Suction

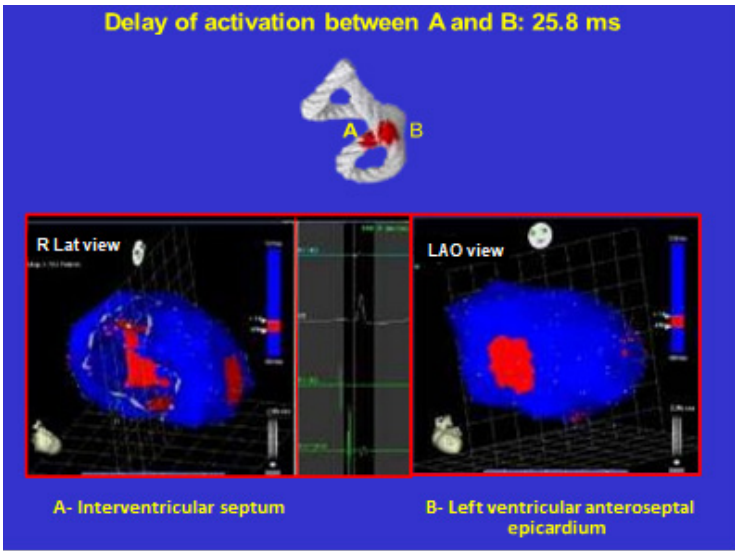

Figure 4: Transverse transmission of the impulse from the Interventricular Septum (A) to the left ventricular Anteroseptal Epicardium (B). As a result, the activation of the ascending and descending segments in unison produces, due to their opposite movements, a helical action with ventricular shortening, narrowing, and torsion.

The central point of this research on cardiac suction is the postulation that PPMC is an active phenomenon generated by a late myocardial contraction that causes the ventricle to elongate, separating the base from the apex. This concept presents two apparent "inconsistencies" from classical mechanical pathophysiology. In order to investigate and clarify these points of contention, we studied the activation sequence of the left ventricle using high-resolution three-dimensional mapping [28-34]. A very important finding from this research is that endocardial activation is completely finished when the surface QRS reaches only 60% of its duration. The rest of the QRS therefore corresponds to epicardial activation. This later stimulation (around 80-100ms) at the epicardial level, corresponding to the ascending segment of the apical loop, causes it to stiffen during PPMC through an active process of energy expenditure. According to the records obtained with three-dimensional mapping, the electrical impulse propagates through the helical myocardium in order to achieve two opposing forces that facilitate ventricular torsion (helical movement). During systole, transmission is longitudinal, producing shortening of the base- apex distance, and also radial (transverse), with narrowing of the chamber and twisting of the myocardium, determining ventricular torsion (Figure 4 and 5).

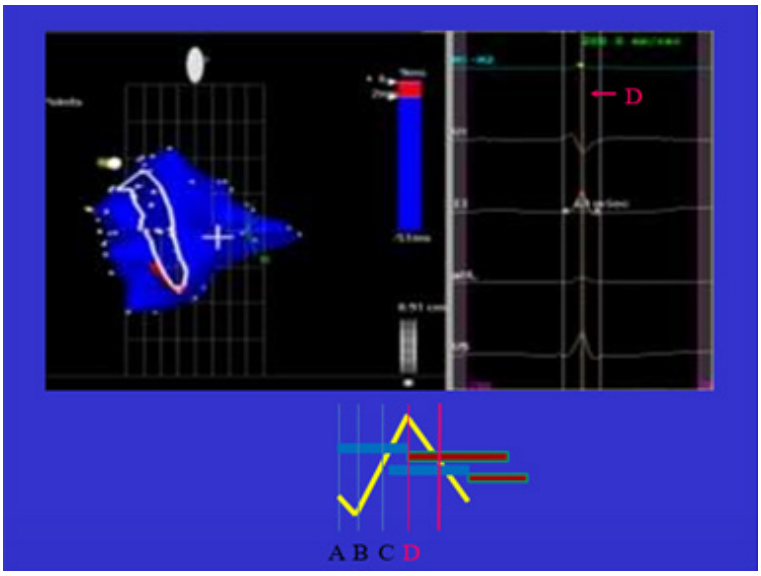

Figure 5: Continuation of the previous figure. Endocardial activation concludes in the area corresponding to the mitral annulus. Note that the entire endocardial activation "occupies" approximately 60% of QRS duration (line D in the right panel). Epicardial activation began earlier, but its completion occurs during the final part of the QRS. This entire sequence is consistent with the mechanical activation sequence described in previous article [1-4] and provides its electrophysiological substrate.

During the initial phase of PPMC, the ascending band contracts and the descending band repolarizes. This delayed contraction of the ascending segment allows, in PPMC, the corresponding mechanics to achieve the process of ventricular detorsion-elongation and suction, generating the conditions of pressure drop necessary to aspirate blood. The basal loop (contraction of the right and left segments) determines ventricular narrowing, while the contraction of the descending segment together with the ascending segment causes the shortening- torsion movement of systole [46]. All these physiological processes are necessary for the ejection phase. In the continuation of cardiac activity, the contraction of the apical loop ascending segment, by providing ventricular elongation, establishes during the PPMC process the generation of negative intraventricular pressure (suction phase) through a mechanism we call "suction" or "aspiration." It should be understood that in this process, the agonist muscle Favors the antagonist. Each benefits the other in order to restart the next cycle. Ventricular expansion, the last cardiac movement, occurs during the diastolic relaxation phase (diastolic filling). Similarly, when the mitral valve opens and wall stress increases with a decrease in wall thickness, the fibers lengthen, allowing fast ventricular filling. The high filling velocity at low pressures is explained by the phenomenon of suction. Thus, in the LV between systole (300ms) and diastole (400ms), the PPMC (100ms) takes place, representing a coupling between the two and causing cardiac suction [26,33]. This is a contraction with energy expenditure.

Protodiastolic Phase of Myocardial Contraction (PPMC)

The final part of the QRS corresponds in our research to the activation of the ascending segment. Thus, during PPMC, the contraction necessary to generate suction ("aspiration effect") occurs. With the onset of detorsion during this phase, the ascending segment progressively lengthens, generating negative intraventricular pressure with this segment still contracted (active process) due to residual energy from the torsion process. According to this research, diastole is divided into two very different phases. In the first phase, ventricular volume does not change; it is isovolumetric. The morphology changes and, with energy expenditure, causes the myocardial walls to contract, generating negative intraventricular pressure. This phase is what we call PPMC and lasts about 100ms. During the second phase, ventricular filling occurs with ventricular dilation due to blood repletion without energy expenditure over the remaining 400ms (Figure 6).

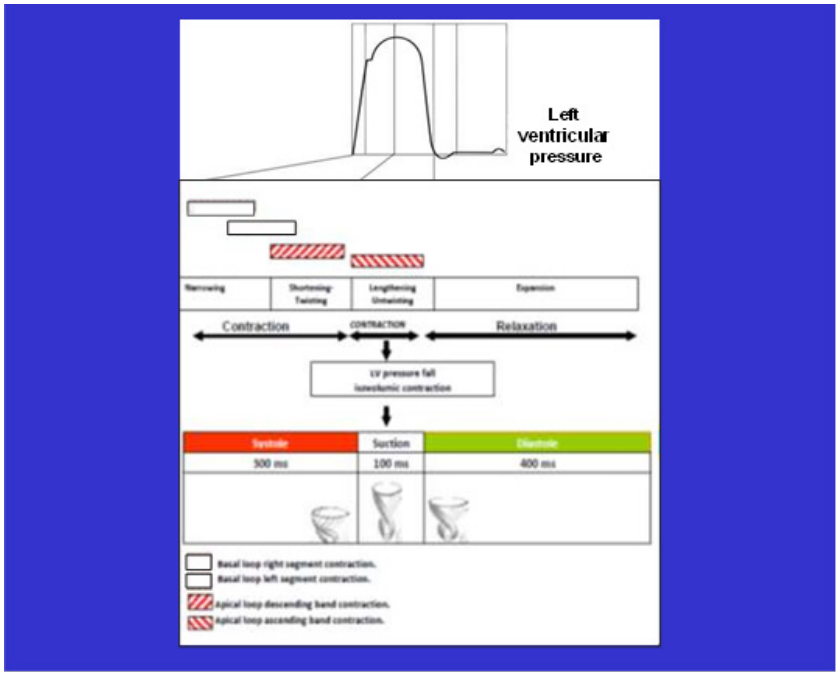

Figure 6: Effects caused by cardiac activation-contraction. Correlation with left intraventricular pressure.

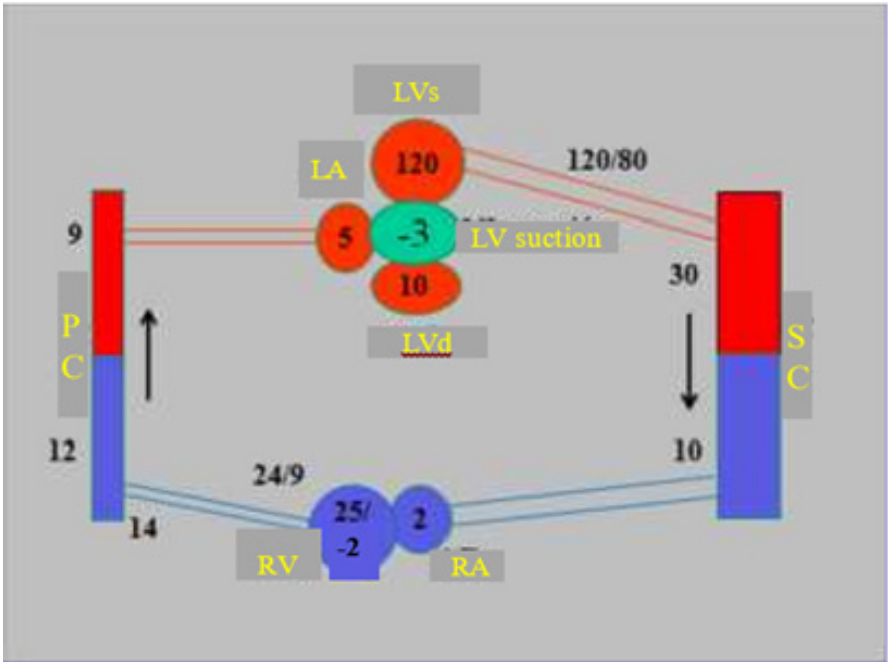

Figure 7: Diagram of the circulatory system with pressures along its path. Pressures are expressed in mmHg. References: **LV:** left Ventricle, Systole; **LA:** left Atrium; **LV:** left Ventricle, Diastole; **PC:** Pulmonary Capillary; **RV:** Right Ventricle; **RA:** Right Atrium; **SC:** Systemic Capillary.

In the traditional model, cardiac filling is determined solely by venous pressure. In reality, atrial pressure is too low to explain this situation. The last contracted areas of the ascending segment produce a suction effect to draw blood into the left ventricle, generating negative pressure. The high filling velocity at low pressures demonstrates that this is an active phenomenon. The results of this research on cardiac suction led us to consider that, in cardiac function, a contraction phase with a average duration between systole (300ms) and diastole (400ms), representing coupling a contraction phase with an average duration of 83ms in the LV and 30ms in the RV is inserted between both ventricles and producing PPMC, with ventricular contraction and energy expenditure [28, 29]. There is only one period in the circulatory cycle that can reach negative pressure in the ventricular chambers at a given moment. This phenomenon occurs during PPMC, when the pressure drops to -3 mmHg, according to our measurements taken in patients undergoing 3D-EAM and resynchronization (Figure 7) [31-34,47,48]. This phase is active and isovolumetric.

Between Aortic Valve (AV) closure and Mitral Valve (MV) opening, and therefore between Pulmonary Valve (PV) closure and Tricuspid Valve (TV) opening, there is a sharp drop in intraventricular pressure with energy expenditure that can reach negative values. It is during this phase that the muscular contraction of the ascending segment end at its insertion into the cardiac fulcrum-myocardial support- produces myocardial elongation-detorsion with the ventricular chambers closed. This contraction of the septum, because of its location in the anatomical interdependence of the ventricles, determines the postsystolic contraction of the ascending segment at the septal level involves the elongation of the ventricular wall with concomitant detorsion in both chambers, producing the aspiration phase of PPMC. This physiological action causes the drop in intraventricular pressure ("depression") to the point where it can reach negative values in both the RV and the LV.

The final part of the QRS corresponds in our research to the activation of the ascending segment. Thus, during the isovolumetric diastolic phase, the contraction necessary to generate suction ("suction cup effect") occurs. With the onset of detorsion during PPMC, the ascending segment progressively lengthens, generating negative intraventricular pressure with this segment still contracted (active process), an energy residue from the torsion process. After the semilunar valves close, the time taken by PPMC depends on the pressure drop required to open the atrioventricular valves. This involves not only the corresponding circuit with its set of pressures, but also the intrinsic muscular capacity of the myocardium to achieve the necessary detorsion in the generation of the intraventricular pressure drop. For this reason, normal PPMC values may have a margin of variation. With a wall half the thickness and hemodynamic values one-sixth of those corresponding to the LV, in addition to being less exposed to myocardial hypertrophy, the RV suffers less intensely from this situation of functional decline in PPMC. We have seen this in echocardiographic studies of patients with HFpEF who had myocardial hypertrophy. We also verified this in the animal research laboratory, where, with the annulment of the RV, LV suction takes control of this situation.

Our research has shown that the endocardium depolarizes completely during the first part of the QRS. Buckberg [49] also recorded that the mechanical contraction triggered by this electrical phenomenon begins about 50ms after it and persists for approximately 350ms. If the depolarization of the ascending segment begins an average of 25.8ms after the descending segment in our studies and its contraction persists for 350ms, the ventricular contraction state will be approximately 400ms. On the other hand, since ventricular systole lasts about 300ms, the remaining 100ms of contraction correspond to PPMC. In summary, during PPMC, the ascending segment remains contracted as a result of the depolarization that occurred during the QRS.

Left Ventricular Protodiastolic Contraction

The basal loop (contraction of the right and left segments) determines ventricular narrowing and the beginning of the cardiac cycle, while the contraction of the descending segment together with the ascending segment causes the shortening-torsion movement of LV systole. All these physiological processes are necessary for the ejection phase. Because it relates to a bed of greater resistance, the Aortic Valve (AV) opens after the Pulmonary Valve (PV), an asynchrony that, as we shall see, corresponds to the last period of left ventricular diastolic filling. In the continuation of cardiac activity, the contraction of the apical loop ascending segment at the end of systole, by providing ventricular elongation and detorsion, establishes the LVPPMC process that generates negative intraventricular pressure (suction phase) by means of a mechanism that we call "suction". The term suction designates the capacity of the ventricle to generate subatmospheric pressure (called "depression" by hydraulics) before filling begins, in the diastolic phase. Ventricular expansion, the last cardiac movement, occurs during the diastolic relaxation phase (diastolic filling), by means of the elastic recoil of the myocardium.

This model of the cardiac cycle is based on the fact that the right intraventricular pressure during the protodiastolic phase of right ventricular myocardial contraction (RVPPMC) represents the minimum pressure of the venous system, whereas the left intraventricular pressure in LVPPMC implies the minimum pressure of the arterial system (Figure 7). Both pressures during PPMC generate a suction mechanism to achieve diastolic filling. Thus, circulatory mechanics works in a complementary manner between the alternating suction and ejection phases of both ventricles. In this investigation, the interrelationship between the cardiac phases is critical for the correct interpretation of circulatory movement. The activation analyzed in our electrophysiological investigations supports the fact that between systole and diastole there is a phase of active suction coupling, with muscular contraction, energy expenditure and a drop of left intraventricular pressure. This effect draws blood into the ventricular chamber through a pressure difference relative to the periphery, responsible for 70% of the total filling volume being suddenly propelled into them, in only 20% of the total filling time, in period 1 of diastole [50]. As explained, this suction phase between systole and diastole lasts 83 ms and is active in its muscular contraction with intraventricular pressure dropping to below zero. The duration of mean systolic deformation between the systolic and post-systolic phases in echocardiographic studies is 88±7.1ms [4], a figure analogous to the activation times of the ascending segment in LVPPMC obtained during our investigation [32,51].

Why is there base-apex elongation in PPMC? During LVPPMC the ascending segment in its final part produces late contraction of the perivalvular zone, while the rest of the myocardium enters into repolarization. It seems contradictory that the contraction of the ascending segment through its stiffening determines ventricular elongation, but it can be explained by analyzing that the rest of the myocardium, simultaneously relaxed, allows an increase in the base-apex distance, because the contracted segment keeps the atrioventricular valves closed, leading the ventricle to a deformation in its morphology without volume change and with generation of an intraventricular pressure drop to a possible negative value. This physiological interplay during LVPPMC, in a closed chamber, rapidly decreases its intraventricular pressure and produces the consequent mitral opening with rapid ventricular filling ("suction" effect) (Figures 8 and 9).

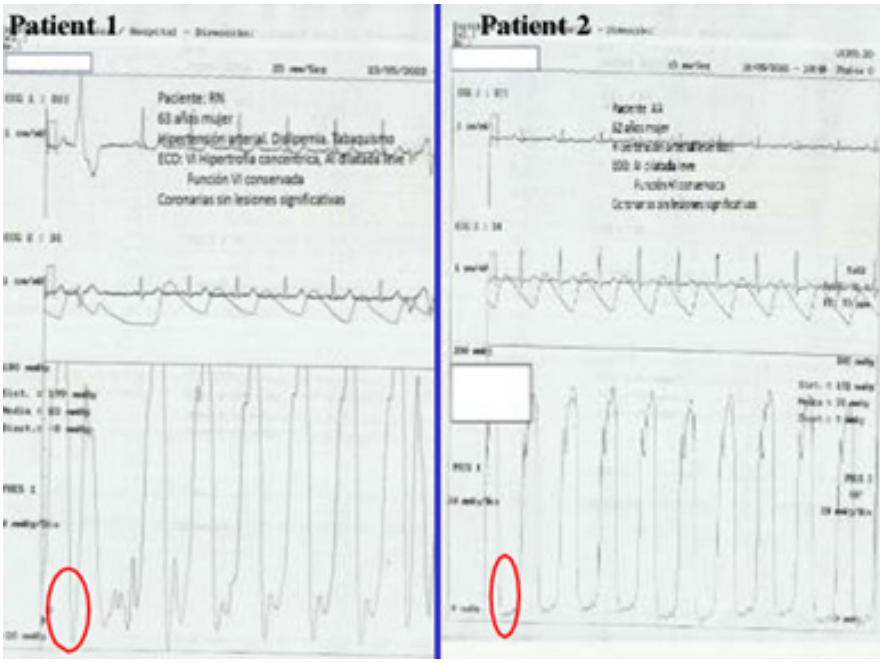

Figure 8: Left Intraventricular Pressure Curve During LVPPMC. Note the pressure drop to negative values (red circle).

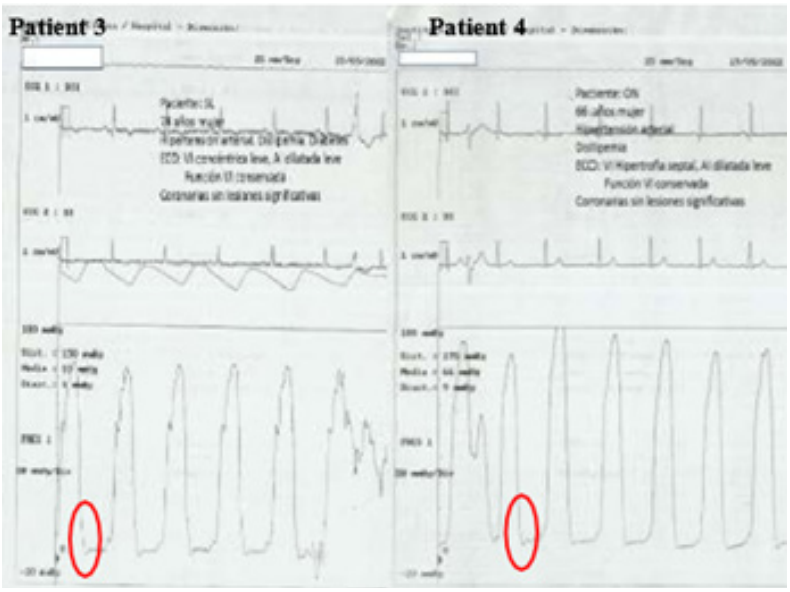

Figure 9: Left Intraventricular Pressure Curve During LVPPMC. Note the pressure drop to negative values (red circle).

The LVPPMC is produced by ventricular elongation-detorsion with contraction of the ascending segment in its terminal part. An essential question arises here: how does contraction produce opposite effects such as shortening-torsion in systole and lengthening-detorsion in suction? The explanation could be posed in relation to the fact that there is longitudinal predominance of the fibers in the final portion of the ascending segment, which become progressively oblique as they descend. Lengthening of this segment during LVPPMC causes a drop in intraventricular pressure since the atrioventricular valves are closed, while the rest of the myocardial fibers are relaxed. These closed valves also have a role in the elongation-detorsion interaction, since in this isovolumetric phase there is no change in volume, which generates a drop in intraventricular pressure. Let us recall that the helicoid arranged by the single myocardium harmonizes with the anisotropy of the directions adopted by the fibers [52]. The geometric properties of the cardiac fibers are of enormous importance in the capacity to generate, through electrical propagation, forces necessary for their function. This myocardial helicoid is composed of muscle layers with biased directions that allow the continuous myocardium to act as a multiplier belt generating a continuous force as the fibers slide over each other. According to classical physiology, contraction would occur “en bloc” during systole and relaxation homogeneously during diastole. Systole is synonymous with

cardiac contraction and diastole with relaxation. These have been the classical fundamentals. At this stage of knowledge, they should be considered more complex, since the contraction of a muscular sector of the myocardium determines the isotonic relaxation of the antagonists. As we have analyzed, the dissection of the myocardium reveals a structure with well-defined separation planes where the segments follow one another in continuity in a helical arrangement [29], which allows the execution of the successive and concatenated physiological movements of narrowing, shortening- torsion, lengthening- detorsion and expansion of the heart, consequence of the propagation of the electrical stimulus through its muscular trajectories according to the 3D-EAM study that we performed [53]. The interpretation is that the same thing occurs with the myocardium as with the rest of the anatomical muscles. Thus, the contraction of a group of fibers that make up a muscle determines the isotonic relaxation of the antagonistic fibers (Figure 10). In this aspect of the functional structure, the importance of anisotropy - understood as the directionally dependent property of the cardiac fibers- should be emphasized, as it allows to induce torsional movement.

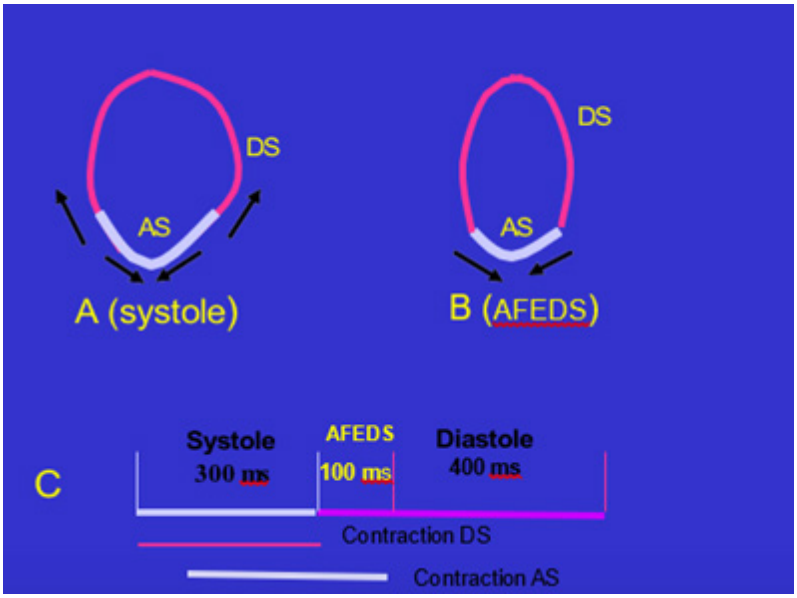

Figure 10.A: In systole the Descending (DS) and Ascending (AS) segments contract in opposite directions generating myocardial torsion. B: In the active LV Protodiastolic Phase of Myocardial Contraction (LVPPMC), the DS relaxes and the AS remains contracted, this interplay allowing to keep the atrioventricular valves closed with isometric myocardial deformation to generate an intraventricular pressure drop. C: Diagram showing the phases of the cardiac cycle and the duration of DS and AS contraction.

What is the function of the residual systolic volume? This volume represents 30% of the total diastolic volume. From the point of view of fluid mechanics, between systole and diastole we are faced with a closed chamber containing only blood, an incompressible fluid and, consequently, whatever the muscular contraction, the volume of the chamber cannot vary. Therefore, this phase is isovolumetric and muscular contraction, since it cannot produce a change in volume, creates a "depression" (pressure drop) in the chamber that favors subsequent filling in diastole. Under these conditions, the "depression" generated will depend on the capacity for muscular contraction and the geometry of the chamber that affects the distribution of pressures within it. For this pressure drop to occur, it is physically necessary that there is an incompressible fluid without the presence of any compressible flow, and that the geometry of the chamber and the volume of blood contained in it allow sufficient "depression" to be created ("suction" mechanism). There is a range of optimal residual systolic volume for suction, which is <25 ml/m2. If it is excessive, it will affect suction capacity and a significant muscle contraction will be needed to create the necessary "depression", whereas if it is lower, the interaction between the walls will hinder suction and therefore diastolic filling [3].

Right Ventricular Protodiastolic Contracción

The septum has a fundamental value in myocardial function since its mechanics is determinant in biventricular interdependence. In the RV, the longitudinal component predominates over the circumferential one. In fact, practically all methods for assessing RV function (except the three-dimensional volumetric method) are based on longitudinal parameters (tricuspid annulus plane systolic excursion-TAPSE-, tissue Doppler velocity, and longitudinal strain of its lateral wall) [1,54,55]. Even in the calculation of the fractional shortening area, the fundamental component is longitudinal. However, by means of cardiac magnetic resonance with myocardial tagging sequences using the DENSE technique, it has been possible to prove that there is a certain rotation in the RV. How can this be explained if there are no oblique fibers, since the RV is formed at the expense of the basal loop? It can be explained by the transmission of the torsion exerted by the LV on the RV, especially at the level of the interventricular septum. Some articles highlight the impact of the LV on the RV by this mechanism [56-59]. In this concept, the "interband" fibers [60] possibly have the function of dragging the RV accompanying the movement of the ascending segment during systolic torsion. This is what we see in cardiac surgery.

There is a very brief period at the beginning of systole when the base and apex rotate counterclockwise. This situation, called inertial state -in this case cardiac- has a physical explanation, since bodies have the property of trying to remain in their resting state. It involves the resistance of matter when its state of motion is modified, including changes in speed or direction of motion. Then, they differ in their sense of direction, being clockwise at the base and counterclockwise at the apex. As a consequence of the oblique arrangement of the myocardial fibers around the left ventricle, there is an opposite-rotation between the apex and the base of the heart, a situation that allows ventricular torsion (systolic contraction) and subsequent detorsion (PPMC, "suction cup effect") to be achieved. The rotation of the apex is considered positive while the base is negative. To calculate the twist, the echocardiographic algorithm performs an algebraic subtraction (adding the value of the positive rotation of the apex to the negative of the base) [61,62]. In our experience, in normal subjects it is around +19±9º, with apical rotation always predominating. With these studies we document the concept that the apex "rules". Although the terms twist and torsion are commonly used interchangeably, actually twist corresponds to the algebraic subtraction of the basal and apical rotations, while torsion is related to the twist divided by the base- apex distance at end-diastole [63]. In fact, torsion is twist normalized by the longitudinal diameter of the left ventricle.

This situation can be understood from the anatomical point of view, given that not all the fibers of the ascending segment become intraseptal. The most superficial fibers, skipping the anterior interventricular groove, instead of continuing their intraseptal path towards the end of the band at the aortic root, go to coat the free wall of the right ventricle and reach the anterior surface of the left ventricle after crossing the posterior interventricular groove. These fibers that we have called "interbands" [64], also mentioned as "aberrant" [65], are limited throughout their course by the ventricular base that includes the pulmonary, tricuspid and mitro- aortic valve annuli. Areas of septal contraction that are still active at the closure of the semilunar valves allow the RV to create a zone of depression (pressure drop) in its chamber, as the RV crescent-shaped free wall is relaxed. The intraseptal band, final segment of the continuous myocardium, would be responsible for this action, running between the anterior septal band and the descending segment. Echocardiographic studies corroborated that the last post-systolic deformation occurs later in the segments of the interventricular septum, creating a subatmospheric pressure or "depression" at the beginning of diastole in the RVPPMC, estimated to be about -2 mmHg. Figures 11 and 12 of our laboratory shows the pressure drop well manifested in the right intraventricular pressure curve during RVPPMC. In the case of suction, the invasive pressure recording demonstrating its drop is of indisputable value [66].

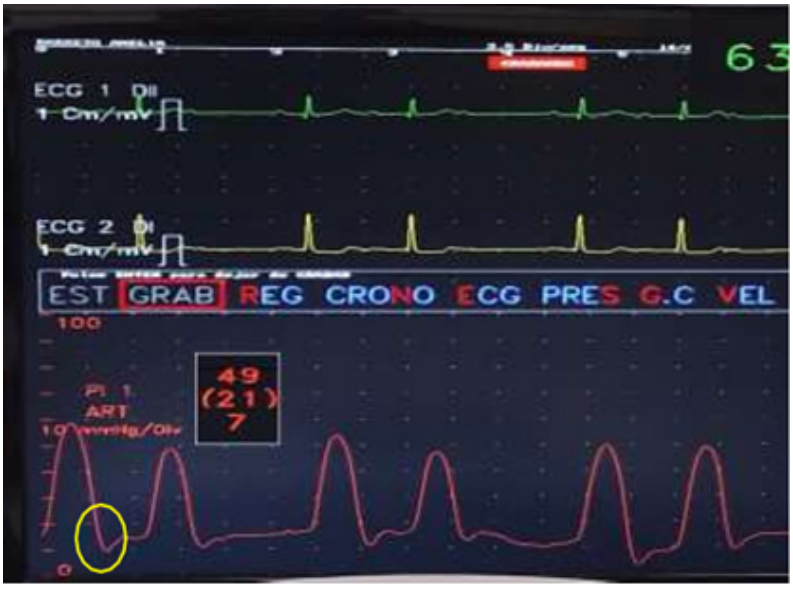

Figure 11: Right Ventricular recording showing the intraventricular pressure drop during RVPPMC in a patient (yellow circle).

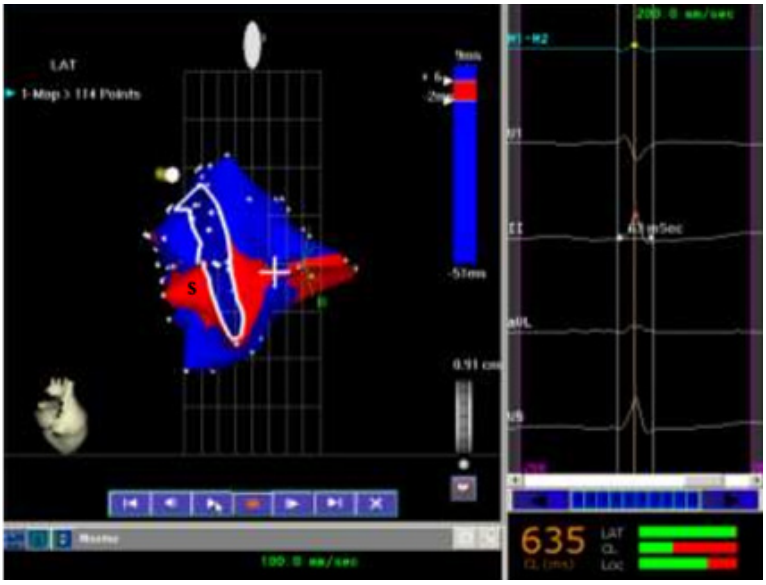

Figure 12: Propagation sequence map with 3D electroanatomical mapping in patients. As the PV closes, the blood volume within the RV remains constant. However, during this time, the interventricular septum at the level of the intraseptal band is still contracting. This causes the right intraventricular pressure drop with the consequent subsequent suction of the systemic circuit. Ref. S: *septum*.

The consequence is the corresponding active suction that occurs in the isovolumetric phase of RV diastolic relaxation that should more appropriately be called the Right Ventricular Protodiastolic Phase of Myocardial Contraction (RVPPMC). This suction is evidenced when, as the flow is tagged in the venous return, it is accelerated in the final sections of the vena cava [20]. This flow is slow during systole. Suddenly it accelerates to enter the right ventricular chamber. It is also supported by the fact that the right segment that forms the RV free wall is relaxed at that moment, so that the intraseptal contraction together with the relaxation of this wall would act in the same way that occurs between the contraction of the ascending segment in LV protodiastole and the rest of myocardial relaxation during LVPPMC (Figure 12). Thus, when the semilunar valves close, the septum is still contracting, producing a drop in RV intraventricular pressure and generating active suction with energy expenditure. Clinically, the duration of PPMC in the RV is less well investigated. There are physiological elements that give importance to this fact, such as the increase in velocity in the final segment of blood arrival to the RA. In ultasound measurements of patients without cardiac disease, we have found that this phase in the RV has an average duration of 30.8ms.

Negative Intraventricular Pressure and Suction Mechanism. Clinical and Experimental Research

Clinical Research

The most accurate estimate of ventricular functional state is obtained from the data of ventricular pressure-volume curves, but these have the disadvantage of invasive recording and are therefore restricted in practice to the experimental laboratory setting [19,67-69]. In patients undergoing a cardiac resynchronization procedure, we have been able to measure the left intraventricular pressure curve in order to demonstrate improvements in the suction mechanism during LVPPMC [70-72]. The hypothesis is that with left bundle branch block LV activation sequence is altered and therefore the mechanical sequence. This fact modifies the sequential activation of the segments with subsequent loss of the ventricular suction mechanism. Consequently, diastolic pressure increases [31].

Figure 13A shows the left intraventricular pressure curve corresponding to a patient with left bundle branch block in whom the resynchronizer has been turned off. In Figure 13B, in the same patient, the function of the device has been restored. It can be seen in the intraventricular pressure scale (in mmHg), to the right of each panel, that the diastolic pressure has decreased from 13 to -3 mmHg with ventricular resynchronization. Systolic pressure has also increased by 10 mm Hg. The same effect on intraventricular pressure is shown in Figures 14A and 14B in a patient before resynchronization and after resynchronization (Figure 13,14).

In conclusion, integrating all the information we have presented above, we could infer the following mechanisms: the normal ventricular activation sequence generates the mechanical phenomena already described that produce the high hemodynamic efficiency of cardiac contraction. At this point, we should remember that left ventricular activation is initiated in the endocardium (descending band). At the level of band crossing, it passes to the epicardium, where it takes a divergent path towards the apex and the basal zone. This late basal activation generates a protodiastolic persistence of contraction in this zone, giving rise to the suction phenomenon (Figure 15).

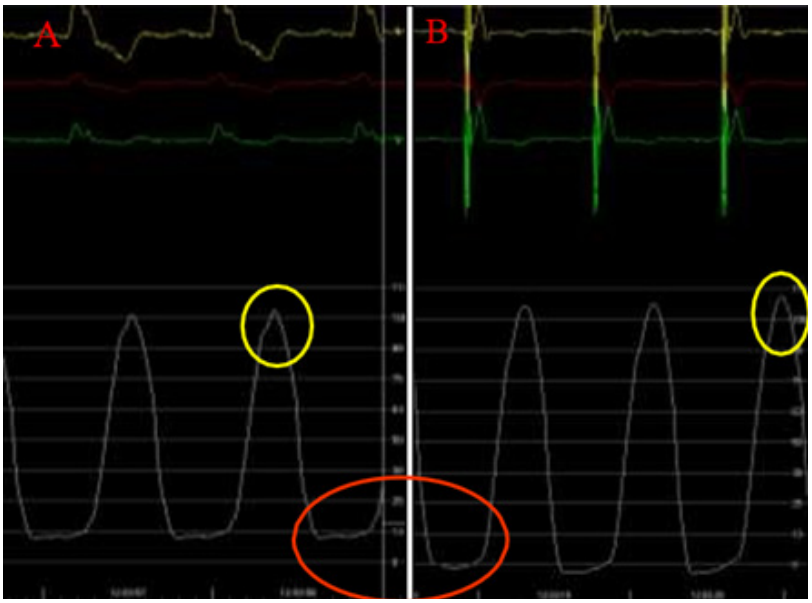

Figure 13: PLeft intraventricular pressure in a patient with resynchronization. A. *Resynchronizer* off.

B. In the same patient after resynchronization was restarted, it can be seen that: 1) the yellow circle details the increase in systolic blood pressure in B with respect to A; 2) in the red circle, attention is paid to the negativization of intraventricular pressure in B.

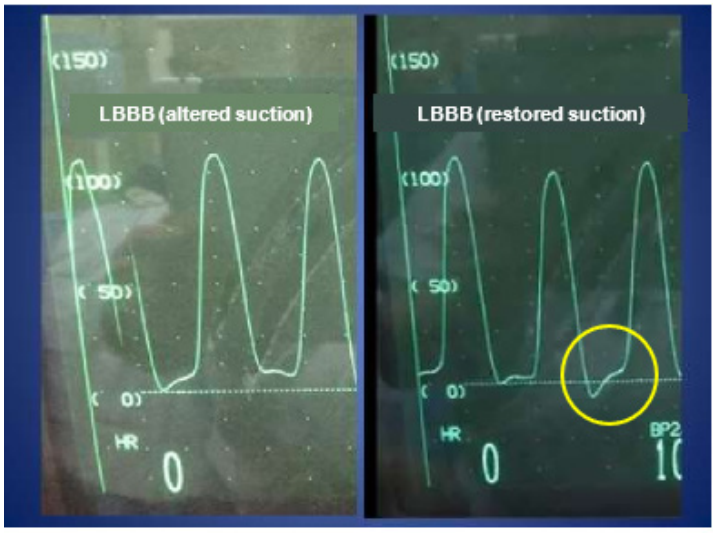

Figure 14: Negative left intraventricular pressure in B restored with ventricular resynchronization (see circle).

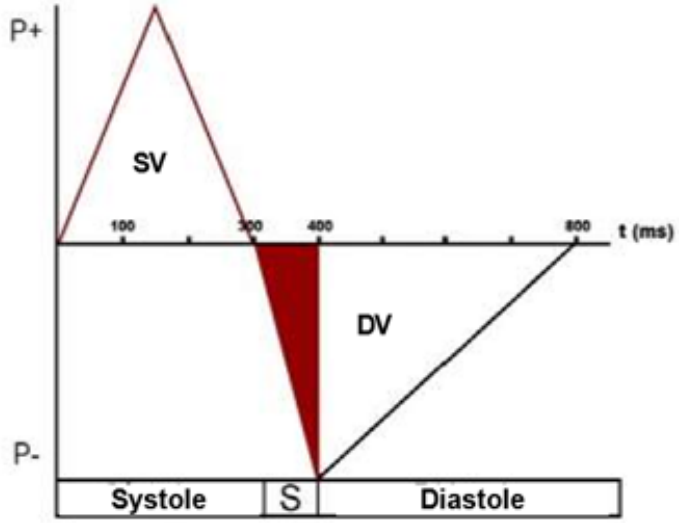

Figure 15: Cardiac Cycle. References. **P:** Pressure; **SV:** Systolic Volume; **DV:** Diastolic Volume; **T:** Time; **S:** Suction. The red-shaded area corresponds to the Protodiastolic Phase of Myocardial Contraction (PPMC).

Experimental Investigation of Left Ventricular Suction

The volumes handled by both ventricles are almost equal but these chambers do not have the same energy. Here is a point of support for understanding suction energy. The suction energy of the left ventricle is responsible for cardiac filling by compensating the right ventricle in order to draw blood into the heart. Based on this analysis we have used ligation of the right coronary artery in animals destined to euthanasia with normal circulatory apparatus, to achieve experimental right ventricular dysfunction. With hemodynamic deterioration already established, an atrio-pulmonary bridge, built prior to occlusion, was opened at 60 minutes. The function of the left ventricle in maintaining blood circulation, acting as single ventricle in circulatory support, was monitored. The underlying hypothesis was: in these conditions of right ventricular dysfunction, does the opening of an atrio-pulmonary bridge improve hemodynamic conditions through the left ventricular suction function? [68,69].

Material and Methods

The study was performed at Hospital Presidente Perón (Buenos Aires, Argentina). The research was previously approved by the Institutional Ethics Committee. Six mongrel adult male dogs with an average weight of 17kg and a body surface area between 0.56 and 0.96 m^2 (average 0.72 m^2) were used. All of them had euthanasia status due to tumor processes. Anesthesia was induced with alfadolone 0.05 ml/kg and gallamine 0.2 mg/kg. and was completed with ketamine hydrochloride at a dose of 10 mg/kg. The femoral vein and artery were cannulated for fluid infusion, central venous pressure control and mean arterial pressure. Controlled ventilation was carried out with intermittent positive pressure with a 100% oxygen-cycled ventilator, at a flow rate of 9liters per minute and positive airway pressure of 15 cm H20. Anesthetic maintenance was achieved with euflurane 0.5-2% and fentanyl 5mg/kg in a single dose. Median sternotomy and opening of the pericardium was performed, followed by heparin at a dose of 1 mg/kg. An atrio-pulmonary bridge was built with an 8 mm diameter woven tube, which was extended from the right atrial appendage to the trunk of the pulmonary artery by lateral clamping to make both sutures. The bridge remained occluded. Subsequently, a Swan-Ganz catheter was placed in the pulmonary artery, connected to a pressure transducer and amplifier with two recording channels. Through the superior vena cava a catheter was placed in the right atrium to record the respective pressure. Cardiac output was determined by thermodilution.

The following variables were recorded with the instrumentation described: Right Atrial Pressure (RAP), Pulmonary Artery Pressure (PAP), Pulmonary Capillary Pressure (PCP), Mean Arterial Pressure (MAP), Heart Rate (HR), and Cardiac Output (CO). These data enabled the calculation of the following parameters using the formulas detailed below:

a) Cardiac Index (CI)=CO/BSA= l/min/m^2 BSA= Body Surface Area.

b) Systolic Index (SI) = CI/HR= ml/beat/m^2

c) Left Ventricular Systolic Work Index (LVSWI) = (MAP-PCP) × SI x 0.0136 = g/beat/m^2

d) Right Ventricular Systolic Work Index (RVSWI) = (PAP-RAP) × SI x 0.0136 = g/beat/m^2

e) Systemic Vascular Resistance (SVR) = (MAP-RAP)/CO × 80 = dyn/sec/cm^{-5}

f) Pulmonary Vascular Resistance (PVR) = (PAP-PCP)/CO × 80 = dyn/seg/cm^{-5}

All these measurements were taken prior to occlusion of the right coronary artery by ligation at its origin (first measurement). Sixty minutes after occlusion a second measurement was performed. During this period, hemodynamic variables were recorded and

the RV was overloaded with physiological solution until RAP was three times its baseline value. After the second measurement, the atrio-pulmonary bridge was opened and 60 minutes later, the third measurement was taken. After having the atrio-pulmonary bridge in operation for 60 minutes, the experiment was terminated 120 minutes after occlusion of the right coronary artery. Hematocrit, pO2, pCO2 and pH were continuously monitored. The hearts were immediately removed and coronary angiography was performed to verify occlusion of the right coronary artery. The specimen was fixed in 10% aqueous formalin for histopathological study. The right ventricle was sectioned perpendicular to the apex-base axis, taking samples at different heights of the ventricular wall. A sample was also collected from the left ventricle in the posterior area near the tip. The material was processed in Autothecnicon and stained with hematoxylin-eosin, Periodic Acid Schiff (PAS) for glycogen and basic fuchsin technique for necrosis-ischemia. The statistical study was performed using analysis of variance for a completely randomized block design, Tuckey's test for multiple comparisons and Friedman's test for nonparametric method and post-hoc comparisons. Differences were considered significant for $p < 0.05$.

Results

Table 1 shows the hemodynamic values recorded at baseline, 60 minutes after occlusion of the right coronary artery and 60 minutes after opening of the atrio-pulmonary bridge.

Table 1: Hemodynamic values.

	Baseline	60' RCO	60' RA-PA	P value
RAP (mmHg)	3.66 ± 1.22	10.16 ± 3.06	3.00 ± 1.27	P < 0.05
PAP (mmHg)	6.41 ± 3.29	3.41 ± 1.43	6.25 ± 2.56	P < 0.05
PCP (mmHg)	5.00 ± 3.41	1.66 ± 2.25	4.83 ± 2.64	NS
MAP (mmHg)	91.60 ±14.38	51.00 ± 9.38	72.50 ± 9.87	P < 0.05
HR (lat/m)	121 ± 7.99	153 ± 25.00	115 ± 13.55	P < 0.05
CO (l/m)	3.43 ± 1.83	2.25 ± 1.04	3.29 ± 1.66	P < 0.05
CI (l/m^2)	5.22 ± 3.72	3.39± 2.08	4.95 ± 3.36	P < 0.05
LVSWI (g/lat/m^2)	53.30 ± 44.31	14.40 ± 7.34	40.80 ± 31.61	P < 0.05
RVSWI (g/lat/m^2)	1.61 ± 0.92	-1.97 ± 1.76	1. 57 ± 0.67	P < 0.05
SVR (dyn/seg/cm^{-5})	2.615 ± 1.581	1.605 ± 411.2	2.356 ± 1.800	NS
PVR (dyn/seg/cm^{-5})	49.90 ± 29.18	109 ± 77.81	48.9 ± 21.05	NS
SI (ml/lat/m^2)	41.50 ± 26.38	20.80 ± 8.97	45.10 ± 34.93	P < 0.05

*Note: **RCO:** Right Coronary Occlusion; **RA-PA:** Right Atrium-Pulmonary Artery Bridge; **RAP:** Right Atrial Pressure; **PAP:** Pulmonary Artery Pressure; **PCP:** Pulmonary Capillary Pressure; **MAP:** Mean Arterial Pressure; **HR:** Heart Rate; **CO:** Cardiac Output; **CI:** Cardiac Index; **LVSWI:** Left Ventricular Systolic Work Index; **RVSWI:** Right Ventricular Systolic Work Index; **SVR:** Systemic Vascular Resistance; **PVR:** Pulmonary Vascular Resistance; **SI:** Systolic Index.

Hematoxylin-eosin staining, both in the right and left ventricle, showed no alterations in fibrillar architecture, nor in their nuclei and transverse striations. Periodic Acid Schiff (PAS) staining of right ventricular slices showed marked glycogenetic depletion characterized by a complete lack of magenta granules. This finding was evident in almost the entire thickness of the ventricular wall, except in a thin strip of subepicardial parallel fibers and others isolated in the papillary muscles. These cells contained a few glycogen granules. The section of the left ventricle showed a visible glycogenic content in different regions of its thickness. The main finding in right ventricular sampling was the almost massive loss of intracellular glycogen demonstrated by the PAS technique, comparable to the early change, within 30 minutes, observed in experimental animals deprived of coronary circulation.

Discussion

Acute occlusion of the right coronary artery determines ventricular function impairment [72-74]. This assertion is perfectly demonstrated in our experience. In Table 1, in the period after acute occlusion of the right coronary artery, hemodynamic values show a decrease in right ventricular work, which falls from 1.61±0.92 to -1.97±1.76 g/lat/m^2 and cardiac output, with a drop from 3.43±1.83 to 2.25±1.04 l/m^2. The ventricular chamber increases its dimensions, distends, elevating RAP and lowering PAP. It should be noted that dilatation of the right ventricle has been a frequent finding in autopsies of acute right ventricular infarction. Pulmonary vascular resistance increases from 49.9 dyn to 109 dyn, due to the decrease in right ventricular systolic index (from 41.5 to 20.8 ml/lat/m^2) and lower right ventricular tissue oxygenation, which translates into low cardiac output. The time elapsed from right coronary occlusion to atrio-pulmonary bridge opening was 60 minutes. This interval is in agreement with previous studies that determine that the beating heart with regional ischemia due to acute coronary occlusion is irreversibly damaged after 40minutes [75,76]. In our experience, histology gave evidence of right ventricular ischemia in that period. The accumulated data reveal the inability of the right ventricle to behave as a simple conducting vessel. The volume overload performed at this stage did not offer favorable variants, but aggravated the right ventricular distension and its claudication with a greater drop in systolic index (Table 1). This overload works through the gradient between mean circulatory system pressure and RAP, but this effect is transient. The right ventricle does not act as a passive duct, but is distended. The higher the overload, the greater the dysfunction; the higher the end-diastolic pressure, the greater the tricuspid valve insufficiency and increased RAP.

At this stage of the knowledge, it is evident that there was no adequate pump function, decreasing ventricular work to a level incompatible with life. In all animals, right ventricular work showed a considerable decrease, and this fact was related to poor ventricular contraction and poor synchronism (biventricular circulatory interdependence), in which blood circulates in favor of a pressure gradient with a systolic index lower than 50% of the baseline value. This experimental model eliminates the action of the pericardium, which, if intact, attenuates the dilatation of the right ventricle following ischemic dysfunction [77]. In the presence of a dysfunctional right ventricle, in order to increase left ventricular preload and decrease right ventricular distension, the Fontan procedure was used in this study, which puts the right atrium in

communication with the pulmonary artery. Therefore, in animals, 60 minutes after acute occlusion of the right coronary artery and in the face of a significant decrease in RVSWI (with a drop in CO to 65% of the baseline value (from 3.43 to 2.25 l/m); in CI (from 5.22 to 3.39 l/m^2); in SI (from 41.5 to 20.8 ml/lat/m^2) and in LVSWI to 27 % its baseline value (from 53.3 to 14.4 g/lat/m^2), this situation allowed hemodynamic recovery at 60 min after atrio-pulmonary bridge opening by discharging the right atrium directly into the pulmonary artery [68,69].

Thus, flow was dependent on left ventricular function, allowing CO increase to 3.29 l/m ($p<0.05$); SI to 45.1 ml/lat/m^2 ($p<0.05$), LVSWI to 40.8 g/lat/m^2 ($p<0.05$); RVSWI to 1.57 g/lat/m2 ($p<0.05$), and the decrease in RAP (10.16 to 3 mmHg) ($p<0.05$) and PVR (109 to 48.9 dyn) (NS) (Table 1). The open atrio-pulmonary bridge led to an increase in CO, which reached 95% of its baseline value. In other words, the new situation transferred the driving force of the circulation exclusively to the possibility of left ventricular suction. From the experimental model we have used, it follows that the barrier imposed by the dysfunctional right ventricle can be bypassed with an atrio-pulmonary bridge, if pulmonary resistances are acceptable (indicative of good left cardiac function), making left ventricular suction work as the flow engine.

Conclusions

This experimental model represents a combination of concepts developed in this investigation, with the inclusion of active left ventricular suction, in accordance with clinical research work on the continuous helical myocardial stimulation and subsequent cardiac mechanics. These results confirm the research undertaken in this text in considering that the heart has three active phases in its function: systolic isovolumetric, systole and suction (Protodiastolic Phase of Myocardial Contraction). The fourth, corresponding to diastole, is passive [28].

Contributions of the Helical Heart Organization to Heart Failure with Preserved Ejection Fraction

Following Torrent Guasp's description of the myocardial band in the last third of the 20th century, we initiated a prolonged investigation encompassing studies of human, bovine, pig and anuran hearts including its anatomy, histology and biochemistry. Hemodynamic, electrophysiological and echocardiographic studies were also performed on patients, as well as physiological investigations in the laboratory with experimental animals. Among many findings, all of them led us to the importance of the negative intraventricular pressure that we have recorded in both the left and right ventricles, which occurs in a limited time after the closure of the aortic valve in the first ms of diastole, in cardiac and therefore circulatory function. The importance of this period (PPMC) lies in the fact that it allows the circulatory cycle to reach the negative pressure necessary to achieve the optimal gradient in the ventricular chambers.

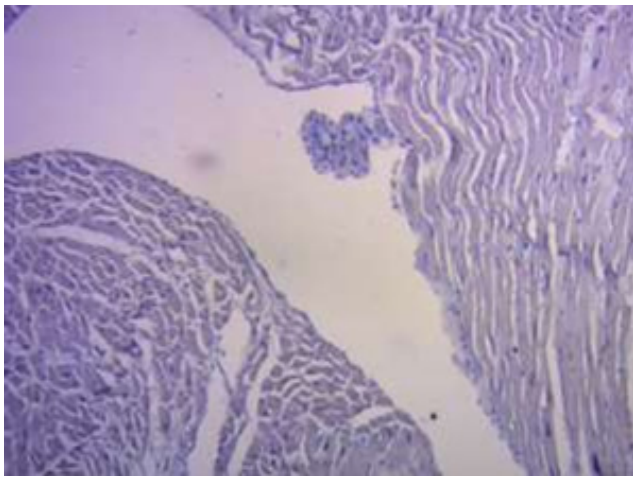

Figure 16: Hyaluronic acid stained with Alcian blue (15x) (adult human heart).

During this period, the pressure drops to -3 mmHg, according to our measurements taken in patients, as discussed in this article. Regarding Heart Failure with Preserved Ejection Fraction (HFpEF), this syndrome requires a pathophysiological understanding that allows interrelating the symptoms with the diagnostic instrumental findings, but for this to be possible it is essential to begin its understanding from cardiac anatomy and physiology. It must be considered that the myocardium, in its structure, is not globular and homogeneous, but rather a continuous muscle, coiled upon itself to form a helix supported by a fulcrum to generate its considerable power; that it is not only an active organ of ejection (positive pressure) but also of suction (negative pressure), which entails energy expenditure in the first 100ms of diastole; that its ventricles are complementary, not parallel; that it does not contract as a single unit but rather by integrating its parts in a concatenated manner, and that for this it needs an antifriction mechanism (hyaluronic acid) for the timely sliding of its overlapping muscle segments. The functional association between the venous Thebesian and Langer ducts, together with the considerable amount of hyaluronic acid found in our research in human and animal hearts, and knowing the lubricating role it plays in the rest of the body, could be crucial in understanding the dynamics of the helical heart. In this way,

ventricular torsion is correlated with a lubricating mechanism that facilitates the sliding of myocardial segments to prevent energy loss. Through these venous ducts and helical contraction, plasma fluid containing hyaluronic acid would be continuously propelled through a rich capillary network. In our research, we have found spaces with a capillary mesh and plasma fluid rich in hyaluronic acid between the cardiomyocytes (Figures 16 to 18).

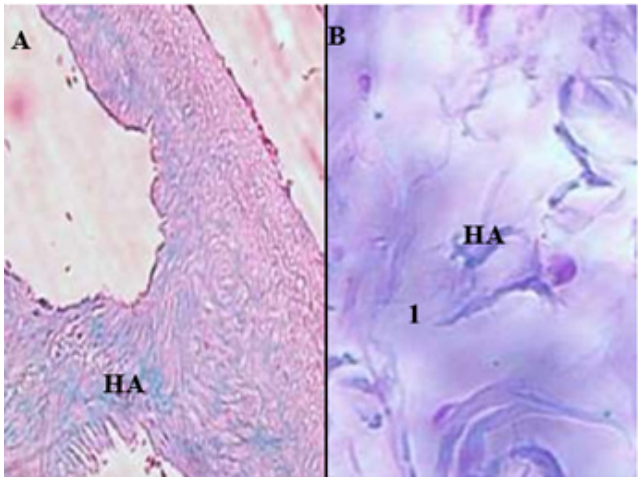

Figure 17: Histology of anuran (Rhinella Arenarum) myocardium stained with Alcian Blue. A: 10x magnification; B: 40x magnification. Ref. 1: cardiomyocytes; **HA:** Hyaluronic Acid.

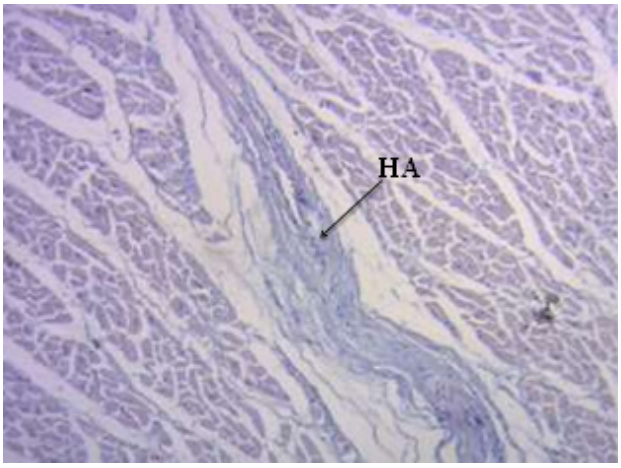

Figure 18: Contracted transverse vein with Alcian blue-positive edematous perivenous interstitium. Note the Alcian blue-stained Hyaluronic Acid (HA) in the interstitium between the cardiomyocytes (15x) (bovine heart).

Since an alteration in the ventricular suction mechanism could be an initial, even subclinical, stage of ventricular dysfunction, the objective of this analysis has been to identify whether there is a relationship between the parameters that determine the impairment of the LVPPMC phase and Heart Failure with Preserved Ejection Fraction (HFpEF). This should be classified as having an ejection fraction greater than 50%, the mechanisms underlying the onset and development of this heart failure being not well understood [78-82]. In this regard, the National Heart, Lung, and Blood Institute has stated that HFpEF is the greatest unmet need in the cardiovascular setting [80,83-89].

Is poor left ventricular suction the cause of this characteristic of heart failure?

Materials and Methods

A retrospective study was conducted on echocardiographic studies performed in the last six months. The study population consisted of three groups:

a) Group I: Ten (10) young patients (5 male, 5 female) without heart disease, with mean age 30.3±9.2 years and body surface area of 1.81±0.16 m^2.

b) Group II: Ten (10) adult patients (5 male, 5 female) without heart disease, with mean age 66.2±4.1 years and body surface area of 1.73±0.16 m^2.

c) Group III: Ten (10) patients (6 female, 4 male) with HFpEF, mean age 81.1±11.3 years and body surface area of 1.76±0.20 m^2.

In this study, patients provided their informed consent. The research was previously approved by the Ethics Committee. All patients were in sinus rhythm with no abnormalities in the electrocardiogram. The variables analyzed were: Cardiac Cycle (ms); Left Ventricular Systole (ms); LVPPMC (ms); Left Ventricular Diastole (ms); Relative Wall Thickness (RWT) (%); Left Ventricular Mass (LVM) (g/m^2); E/E´ ratio; Left Ventricular Ejection Fraction (%); Left Atrial Volume (LAV) (ml/m^2); Pulmonary Artery Pressure (mmHg); and End-Systolic Volume (ml).

Statistics

We defined cohorts C1, C2, and C3 according to whether they belonged to Group I, II, or III, respectively. For each variable, the values were plotted for each cohort, and the mean, standard deviation, minimum, maximum, median, and confidence interval for the mean was calculated. The difference between means was studied using Student's t-test for the difference of means in paired samples, with a confidence level of 95%. A p-value <0.05 indicated a positive test result, meaning that the means differed. Finally, confidence intervals were established for the difference between means of the indicators when comparing C1-C2 and C2-C3, in order to quantify their variation.

Results

Table 2 shows the results in the three groups with the echocardiographic variables studied. In this study, it was observed that in all patients with HFpEF (Group III) there was a longer LVPPMC time: 134±18.97ms, compared with the groups without heart disease (Groups I and II), which had a significantly shorter duration: 83±16.36ms and 83.10±18.45ms, (p < 0.01) and (Tables 3 and 4), respectively.

Table 2: Echocardiographic Values.

Variable	Group I	GI-GII	Group II	GI-GIII	Group III
		p – value		p – value	
Cardiac cycle (ms)	783 ± 129	0.19	855 ± 97	0.829	865 ± 148
LV Systole (ms)	346 ± 44	0.01	300 ± 27	0.003	423 ± 99
LVPPMC (ms)	83 ± 16	0.987	83 ± 18	0.0009	134 ± 18
LV Diastole (ms)	354 ± 111	0.029	471 ± 78	0.001	333 ± 82
RWT (%)	0.33 ± 0.03	0.111	0.36 ± 0.03	0.0001	0.50 ± 0.05
LVM (gr/m2)	67.3 ±13.33	0.2831	72.5 ± 15	0.004	106.3 ± 25
E/E' Ratio	6.34 ± 1.46	0.1454	7.5 ± 1.53	0.004	16.13 ±6.47
LVEF (%)	61.80 ±3.46	0.8827	61.5 ± 4.9	0.3328	63.6 ± 4.88
LAV (ml/m2)	19.2 ± 4.08	0.032	25.2 ± 5.79	0.002	43.9 ± 14.6
PAP (mmHG)	22.7 ± 6.77	0.006	22.5 ± 5.64	0.045	32.9 ±15.89
LV End-systolic Volume (ml)	32.8 ± 7.84	0.094	27.20 ±8.48	0.746	25.5 ±12.65

***Note: MS:** Milliseconds; **LV:** Left Ventricular; **LVPPMC:** Left Ventricular Protodiastolic Phase Myocardial Contraction; **RWT:** Relative Wall Thickness; **LVM:** Left Ventricular Mass; **LVEF:** Left Ventricular Ejection Fraction; **LAV:** Left Atrial Volume; **PAP:** Pulmonary Artery Pressure. The p-values between GI and GII are those obtained by Student's t-test for the difference of means in paired samples, with a confidence level of 95%, comparing Group I with Group II. The p-values between GI and GIII are those obtained by the test comparing Group I with Group III. Values with p < 0.05 indicate a positive test result and are interpreted as meaning that the compared means differ. Values with p ≥ 0.05 indicate a negative test result and are interpreted as meaning that the compared means coincide. The lower the p-value, the greater the probability that the compared means differ.

Table 3: Ratio of percent left ventricular cardiac cycle, systole and diastole duration with the protodiastolic phase of myocardial contraction.

Phase	Group I	Group II	Group III
Systole / LVPPMC ratio (%)	23	27	31
Diastole /LVPPMC ratio (%)	23	17	40
Cardiac Cycle / LVPPMC ratio (%)	10	9	15

Table 4: Protodiastolic phase of myocardial contraction duration in each patient with heart failure with preserved ejection fraction for a normal investigated value of 83 *ms*

Patient	1	2	3	4	5	6	7	8	9	10
Duration(*ms*)	130	140	160	120	110	160	150	110	140	120

Concomitantly, an increase of LVM was also found in Group III with an average of 106 g/m^2 compared with the other groups (67 and 72 g/m^2, respectively). Also, RWT increased from 0.33% and 0.36% in groups I and II to 0.49% in group III, and LAV reached 43 ml/m^2 for a value in the control groups of 19 and 25ml/m^2. In this analysis (Table 2), it is clear that in Group III, LVM, E/E', PAP, and LAV are significantly increased. In terms of total cardiac cycle duration, systole, and diastole, the cohorts are basically the same (p >0.05 for all comparisons) except for VIPPCM, which is longer in patients with HFpEF (p<0.01). The mean values obtained when comparing C1-C2 and C2-C3 to study whether they differ or coincide are summarized in Table 5.

Table 5: Comparison of C1-C2 and C2-C3 cohorts.

Comparison	Result		Interpretation of the indicator/Impact on Diagnosis
C1-C2	Coincide	CC	Neither age nor disease alter it Scarcely significant
C2-C3	Coincide		
C1-C2	Coincide	CD	Age does not alter it, but disease does Very significant
C2-C3	Differ		
C1-C2	Differ	DC	Age alters it, but not disease
C2-C3	Coincide		Scarcely significant
C1-C2	Differ	DD	Age alters it and also disease
C2-C3	Differ		Significant

Discussion

There is a significant increase in the time to LVPPMC in Group III (patients with HFpEF) compared with the group without heart disease (Groups I and II). Furthermore, the tissue deformation curve in these cases loses its steep slope and becomes irregular, requiring a longer time to generate the pressure difference necessary to open the mitral valve (Figures 19 and 20). This variable correlates with the E/E' ratio, as in Group I this value was 6.34±1.46 and in Group II 7.50±1.53, compared with Group III, which reached a value of 16.13±6.47 ($p < 0.01$) (Table 2). An abnormal effect on the negative pressure generated in this phase can be interpreted, as the process is slowed down with increased time to open the mitral valve.

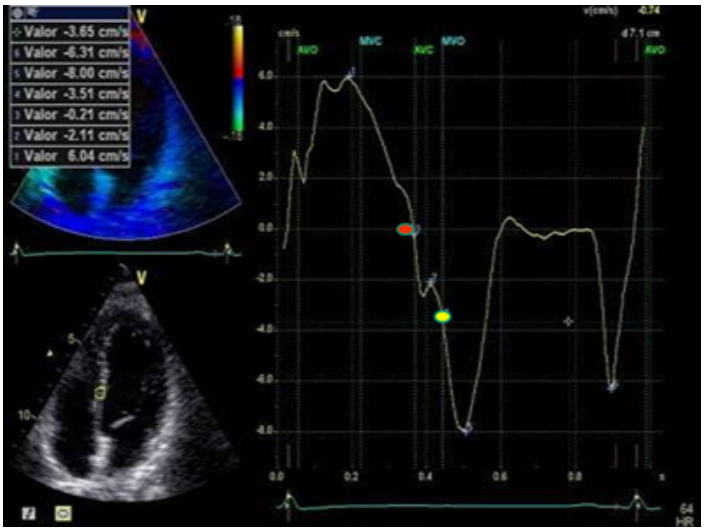

Figure 19: Left Ventricular Protodiastolic Phase of Myocardial Contraction curve in a normal patient. The red dot indicates the phase onset and the yellow dot shows the end. Duration: 80ms; LVMI (left entricular mass index): 67 g/m^2; RPT (relative wall thickness): 0.33%.

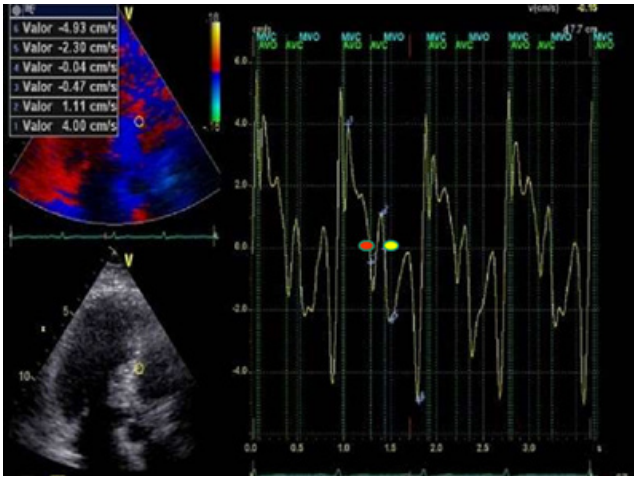

Figure 20: Left Ventricular Protodiastolic Phase of myocardial contraction curve in a patient with Heart Failure with Preserved Ejection Fraction (HFPEF). The red dot indicates the start of the phase and the yellow dot shows the end.Duration 160 ms; LVMI (left ventricular mass index): 106g/m^2; RPT (Relative Wall Thickness): 0.49%.

Figures 19 and 20, showing tissue deformation obtained by echocardiography correspond to LVPPMC. The first (Figure 19) belongs to a patient without cardiac pathology, in which the tissue deformation curve in this phase of the LV is shown, with a duration of 80ms. Figure 20 depicts the same phase of the LV in a patient with HFpEF. The difference in the LV tissue deformation curve in PPMC between patients is clear. In the patient with abnormality, the slope is fractured, with a duration that greatly exceeds normal values, at 160ms. This data correlates with the measurements of Left Ventricular Mass (LVM) and Relative Wall Thickness (RWT) in these same patients, since in normal patients the values are 67g/m2 and 0.33%, respectively, compared with 106 g/m2 and 0.49% in the patient with HFpEF.

We also observed that the duration of diastole itself (passive filling phase without energy expenditure) remained largely unchanged in all the groups (354ms in Group I; 471ms in Group II and 333ms in Group III), which confirms that the alteration of the suction mechanism that occurs in LVPPMC is primarily involved in the dysfunctional process. The increase in LVM, RWT, and LAV in Group III, all of which are significant, are measurements that correspond to an increased PAP to 32 mmHg in Group III compared with 22 =mmHg in Groups I and II. These concepts would explain why pulmonary wedge pressure ≥15 mmHg or left ventricular end-diastolic pressure ≥16 mmHg is often found in HFpEF. The possible interpretation is that as its mass increases, the left ventricle does not achieve adequate detorsion in a normal time to generate a pressure drop with a suitable slope to allow mitral valve opening. In terms of flow, when the inflow to the left ventricle decreases by 1 cc per cardiac cycle due to suction deficit and the right ventricle continues to pump blood into the pulmonary system, dyspnea appears. This is understandable, since at 1 cc per beat, every hundred beats represent 100 cc, which are held in the lungs. Consensus statements on heart failure highlight concentric left ventricular hypertrophy as a characteristic of this disease [90]. Other characteristics include reduced ventricular wall distensibility, and ventricular and aortic valve stiffness. In addition, excessive myocardial fibrosis is also mentioned, due to an increase in type 1 collagen in the extracellular matrix and an inflammatory process with increased fibroblasts and cytokines.

Regarding the increase in LAV, we must understand that the atria are compensatory volume chambers that prevent the ventricles from becoming overloaded. This increase in LAV in patients with HFpEF should be considered a consequence of LV suction deficit, probably as a mechanism to reduce the increase in wall tension and prevent a significant increase in atrial pressure. This observation, present in all patients with this pathology, is clinically accompanied by both exertion and rest dyspnea. In the LV, EF and end-systolic volume are normal in all groups, implying that the altered values corresponding to LVPPMC indicate the moment in the cardiac cycle where the pathophysiological alteration is located. The duration of the total cardiac cycle, LV systole, PPMC, and diastole were measured in the three groups. The results (Table 3) are consistent with the contributions of research. It shows that in patients with HFpEF, the duration of LVPPMC is prolonged in relation to the duration of the total cardiac cycle, systole, and diastole. This would demonstrate the possibility that patients with HFpEF may experience their problem in LVPPMC, as it requires a longer time to achieve adequate intraventricular pressure to open the mitral valve (Table 4).

Conclusions

Based on the results obtained, it can be interpreted that the mechanism of HFpEF is primarily due to ventricular suction dysfunction, which is excessively prolonged during LVPPMC compared with control groups. This would result in increased filling pressures in the cardiac chambers, with the resulting dyspneic symptoms that characterize these patients.

Structural Bases of Left Ventricular Diastolic Containment in the Suction Mechanism

There is evidence from current functional anatomy to microscopy. The irregular helical anatomical description of Torrent Guasp's ventricular myocardial band mimics in its torsion the supporting microscopic connective structure of the heart, a condition reinforced in his study. Lengthening resides both in the sarcomere structure as in the muscle cell components that make up the cytoskeleton. The sarcomere expands laterally and increases its diameter. This lateral enlargement extends the Z discs. Thus, it becomes the storage mechanism of part of the contraction energy that could be used as expansion energy [1].

Connective tissue is here involved. The outer surface of the muscle cells is covered by collagen and elastin connective fibers which have stress-strain properties arranged in a network. This network structure returns muscle cells to their original configuration by preventing excessive stretching of the sarcomeres in order to achieve suitable suction during the PPMC. The fibrous cytoskeleton should be understood as the sum of the fibrous interweaved constituents essential for the preservation of ventricular geometry [16]. The collagen scaffold coordinates the muscle fibers by collecting them in bundles of increasing structures, to keep an optimal stretching with the aim of achieving an effective subsequent contraction. This fibrous cytoskeleton is formed by a grid-shaped mesh that individually enfolds the sarcomeres which are gathered in bundles of connective structures called straps or cords, twisting helically around their own axis (Figure 21).

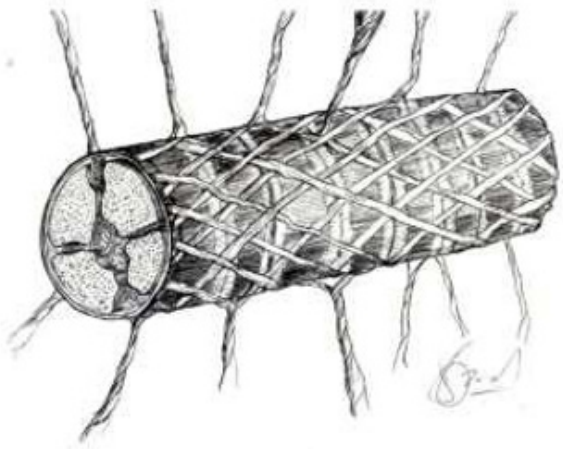

Figure 21: Collagen cytoskeleton consisting of a grid-shaped mesh surrounding the sarcomere..

In normal conditions, myocardial sarcomeres undergo length changes ranging from 1.85micrometers during contraction to 2.05micrometers in the resting period. During systole, sarcomere shortening is only 12%, but with this small percentage the left ventricle empties by 70%. Due to this efficacy, ejection is achieved at a speed of 200cm/s and pressure of 120 mmHg, allowing a left ventricular three-dimensional reduction of 15% in its longitudinal, anteroposterior and transverse axes. The helical arrangement of muscle fibers (macro and microscopic) enables this efficiency, resembling, in the words of Torrent Guasp, a "heart plunger" [24,35]. This connective tissue skeleton, with a similar arrangement to that of helically twisted stay cables of suspension bridges, has suggested the idea of systolic energy storage, which when released in the last stages of the suction process allow the effect of a suction pump. Mammalian hearts placed in a buffered solution are self-driven due to the strap structure. In contrast, there is no such impulse in the frog heart because it lacks these straps that act as interfiber fixing elements. Paradoxically, an invertebrate such as the squid, draws water through a hollow chamber wrapped in a muscular structure achieving with its ejection the effect of jet propulsion. This can be done due to the connective tissue straps present in the muscles.

Left ventricular recoil elevates the right ventricle favouring its rapid and accelerated filling. The whole heart motion contributes to its filling. As a result of this mechanism the increased contractility of the left side enhances the efficiency of the right side. In conclusion, as a result of the helical ventricular elastic recoil, suction is an active ventricular process. During the PPMC the ascending apical loop segment contracts. Suction in this phase is explained by a "suction cup" mechanism. As the ventricular walls that exert suction give in and dilate, the "suction cup mechanism" becomes unsteady, and through this concept, a different assessment of heart failure and its clinical severity can thus be established. Likewise, mitral valve opening which increases wall stress and decreases wall thickening lengthens the fibres allowing fast ventricular filling. The high filling velocity with low pressures would be explained by the suction phenomenon. This active mechanism of the ventricular myocardial band on the diastolic effect opens a wide perspective for surgical ventricular repair techniques both for shape and volume and the consequent left ventricular function.

The force generated by systolic contraction exerts a compression on the heart muscle elastic elements of such magnitude that even without internal diastolic filling the ventricular tendency is to expand. This negative pressure determines a suction pump mechanism. The negative intraventricular pressures determining this effect were first described in 1930 [1]. For this dynamic suction pump to be effective, the elastic recoil process must have a limit that allows a subsequent effective systole. Therefore, the possibility of sarcomere lengthening is engraved both in the muscle structure proper as in the heart´s fibrous cytoskeleton. The arrangement of the muscle straps, similar to stay cables on a suspension bridge, have suggested the idea of systolic energy storage, which once released in the diastolic process would allow the effect of a ventricular suction pump.

Acknowledgements

None.

Conflicts of Interest

None.

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