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Ventricular Interaction: Series vs Direct Mechanisms

by

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ABSTRACT

Diastolic ventricular interaction has been studied extensively, but because of the difficulty in separating the series and direct components in the intact system, the relative contributions of series-vs-direct interaction is not well understood. Although it is clear that the pericardium and the septum play a major role in direct interaction, this relationship has not been adequately quantified. In order to address these issues, we have designed a canine right-heart bypass model in which the series (RV output, or LV venous return) and direct (pericardial and septal) components of ventricular interaction can be independently controlled. Using this model we were able to separate the series and direct components of ventricular interaction, determine the relationship between RV output (LV venous return) and external constraint, and determine the pericardial and septal contributions to the direct mechanism.

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Over the past three years, I have considered my experience as a graduate student under the supervision of Dr. Tyberg both a privilege and a pleasure. Initially, when I began working in Dr. Tyberg's lab I was somewhat intimidated because the research environment was a new experience for me, and I was unsure that my background in was substantial enough. Over the next several months, however, my confidence grew. Through my experience in competitive athletics and physical eduction, I had learned the importance of team work and found that the research environment in Dr. Tyberg's lab was really no different. This experience gave me the opportunity to develop working relationships, mentorships, and in many cases friendships, with an outstanding team of individuals.

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List of Abbreviations

DVI	direct ventricular interaction
IVC	inferior venae cavae
LV	left ventricle
PA	pulmonary artery
P_{LVED}	left ventricular end-diastolic pressure
P_{RVED}	right ventricular end-diastolic pressure
P_{PER}	pericardial pressure
P_{LVTM}	left ventricular transmural pressure (calculated as $P_{LVED} - P_{PER}$)
P_{LVTM}*	left ventricular transmural pressure (calculated as $P_{LVED} - (1/3\ P_{RVED} + 2/3\ P_{PER})$)
RV	right ventricle
SV	stroke volume
SVC	superior venae cavae
VI	volume index
VI_{LVED}	left ventricular end-diastolic volume index
VR_{LV}	left ventricular venous return

Chapter 1: Introduction

Since the right and left ventricles (RV and LV) function in series, share a common septum and are enclosed in a relatively non-distensible pericardium, changes in function of one ventricle can affect that of the other. Diastolic ventricular interaction involves two components. Interaction via RV output (equal to LV venous return) is termed series interaction, and that via the septum and/or pericardium is termed direct interaction. Diastolic ventricular interaction has been studied extensively[6,9,13,18,21,25,30,42,44,58] and many features have been clarified. However, there remains considerable uncertainty regarding the individual contributions of series and direct interaction to the hemodynamic consequences of various interventions and, as well, the relative contributions of the septum and pericardium to direct interaction. Normally, series interaction is considered the dominant physiologic mechanism. However, an increase in RV end-diastolic pressure (P_{RVED}) will usually be associated with an increase in pericardial pressure and a change in the transseptal gradient so that the effects of direct ventricular interaction may be substantial.

Our lab has shown in previous studies that direct ventricular interaction plays an important role in determining the hemodynamic response to interventions such as acute pulmonary embolism.[3-5] After pulmonary embolization with the pericardium closed, these studies demonstrated that volume loading decreases LV end-diastolic volume and stroke work while, with

the pericardium open, volume loading increases LV end-diastolic volume and stroke work. Although series interaction is clearly important, these studies demonstrated that there is a substantial contribution of direct interaction to the hemodynamic responses to acute pulmonary embolism.

The relative contributions of series-versus-direct ventricular interaction were not addressed in our previous work and, in the intact heart, the question has remained difficult to resolve because most interventions affect both mechanisms. For example, pulmonary artery constriction increases RV end-diastolic pressure but also decreases LV venous return (VR_{LV}). We therefore, used a canine right-heart bypass model in which both VR_{LV} (the series component) and P_{RVED} (a determinant of direct interaction) could be varied independently to separate the series and direct components of ventricular interaction. Using this model, we were thus able to, assess the series effects at constant P_{RVED} and the direct effects at constant VR_{LV}. By independently altering LV venous return at constant RV end-diastolic pressures we were first able to determine the relationships between LV venous return and external constraint; second, to determine the required increase in RV output to maintain a given LV end-diastolic volume, when RV end-diastolic pressure is increased; and third, to determine the required increase in RV output to increase LV end-diastolic volume, at different RV end-diastolic pressures. By applying the interventions while the pericardium was closed and opened we were also able to separate and quantify the pericardial and septal contributions to direct interaction.

Chapter 2: Ventricular Interaction: Series vs Direct Mechanisms

2.1) Diastolic Ventricular Interaction

The right and left ventricles (RV and LV) are arranged in series, share a common interventricular septum, and are enclosed in a pericardium. Therefore, changes in the function of one ventricle can affect the function of the opposite ventricle indirectly or directly by altering its loading conditions and shape. This relationship is referred to as ventricular interaction. Diastolic ventricular interaction involves two components. The series component reflects the changes in LV filling which occur due to alterations in LV venous return. The direct component occurs when changes in RV end-diastolic pressure compress the LV or allow it to expand; the septum is displaced as a function of the transseptal pressure gradient (P_{LVED} - P_{RVED}) and the LV free wall is displaced as a function of transmural pressure (P_{LVED} -pericardial pressure, P_{PER}).

Diastolic ventricular interaction can be understood more clearly by using a schematic (Fig 2.1) first proposed by Tyberg et al[61] and later modified by Shabetai.[46] In this figure, the series and direct arrangement of the right and left ventricles are illustrated. The RV and LV are represented as distensible, water-filled balloons separated by a common septum, contained within the pericardium which is represented as a rigid water-filled box. The pressures in each chamber and the pericardium are represented as the height of the

columns connected to each corresponding cavity. In the control condition (A) the pericardium is lax, exerting little pressure on the heart. During volume loading (B) the more distensible chambers (atria and RV) are enlarged. The increased RV volume, in the presence of the relatively non-distensible pericardium, results in a leftward septal shift (due to the decreased gradient across the septum). This figure implies that, when the contents of the pericardium reach a certain critical volume, any further increases in volume will result in an increase in pericardial pressure. This pressure will be added to the pressure necessary to distend the LV, and thus, to maintain the same volume, pressure must increase, constituting a shift in the pressure-volume relationship.

Tyberg et al[61] also illustrated this hypothesis graphically (Fig 2.2). These plots suggest the mechanism by which an increase in RV volume can result in an upward shift of the LV end-diastolic pressure-volume relation. If RV volume is increased (from 1 to 2, panel A), this increased volume of the intrapericardial contents results in an increase in pericardial pressure (panel B). Assuming that there is no concomitant change in LV volume, this additional pressure increment must be added to the pressure measured in the LV, resulting in an upward shift of the LV pressure-volume relation (from solid to dotted curve, panel C).

The above hypothesis suggests that the upward shifts in the pressure-volume curves, as the result of increased RV volume, may be caused by changes in pericardial pressure secondary to increased pericardial volume

(heart volume). In order to determine the magnitude that the pericardial contents enlarge to raise pericardial pressure by a specific amount, Junemann et al[22] quantified the effect of the pericardium on LV diastolic pressure-volume relations in anesthetized closed-chest dogs. Pericardial effusion and volume loading were used as methods to increase pericardial volume. The original volume of the pericardium was defined as the heart volume measured when the LV transmural pressure was 6 mm Hg. The best-fit equation for the pericardial pressure-volume curve was used to calculate the amount of increase in pericardial volume necessary to increase pericardial pressure by a certain amount. This study demonstrated that saline infusion, which increased the sum of RV and atrial volumes by 1 LV volume, was found to shift the LV diastolic pressure-volume curve upward by 4 mm Hg. To increase the LV pressure-volume curves upward by 20 mm Hg, the sum of RV and atrial volumes had to be increase by approximately 2 LV volumes. They concluded that under conditions which increase heart or pericardial volume acutely (ie, congestive heart failure with volume loading or pericardial effusion), the pericardium shifts the LV diastolic pressure-volume relation upward by a significant amount.

2.2) Series Mechanism

Since the RV and LV are connected as two pumps in series, the output of the RV effects input of the LV. Changes in RV stroke volume travel through

the pulmonary vasculature, and within a few cardiac cycles reaches the LV resulting in alterations in LV filling and stroke volume. This indirect relationship resulting from the series arrangement of the two pumps is referred to as delayed or series interaction.

In the intact circulation, volume loading increases RV stroke volume and end-diastolic pressure thus resulting in both series and direct effects. Under normal physiological conditions, series interaction is thought be the dominant mechanism. The increased RV stroke volume to the LV (series component, which tends to increase LV preload) is greater than the effect of septal shift and increasing pericardial constraint (direct component, which tends to decreased LV preload). Thus, the net effect of volume loading under normal physiological conditions is an increase in LV end-diastolic volume and hence the stroke volume, maintaining the balance between the outputs of the RV and LV. Thus, under normal conditions, the series component plays a more important role during volume loading in the intact circulation.

However, this is not always the case. For example, during acute pulmonary embolism[3-5] and acute RV infarction[16,39] volume loading has been shown to decrease LV end-diastolic volume and stroke work. With interventions which acutely increase RV end-diastolic volume and pressure (ie, pulmonary embolism and RV infarction), direct interaction becomes the dominant mechanism because RV stroke volume cannot increase proportionally due to the deteriorated RV myocardium or cannot travel through the pulmonary

vascular system due to increased pulmonary vascular resistance. In these situations, blood becomes backed up in the right heart which further increases direct interaction and decreases LV preload and stroke volume. Belenkie et al[3-5] have shown that direct interaction plays a very important role in determining the hemodynamic response to acute pulmonary embolism and pulmonary artery constriction. In these studies, with the pericardium closed during severe pulmonary embolism, volume loading was shown to decrease LV end-diastolic volume as well as stroke work. However, after the pericardium was opened, LV end-diastolic volume increased during volume loading after embolism and was associated with increased LV stroke work.

2.3) Direct Mechanism

Direct ventricular interaction occurs through the shared septum[1,5,6,9,10,16,25,27,32,37,57,63] and this interaction is enhanced by the presence of the pericardium.[4,13,17,21,27,35,47,48,55,56] Several studies have examined the mechanisms involved in direct interaction, with septal positions and transseptal pressure gradients, in addition to the pericardium, being identified as important factors. Conditions which elevate RV end-diastolic pressure while decreasing or maintaining LV end-diastolic pressure result in a reduced end-diastolic transseptal gradient and a leftward septal shift. When the P_{RVED} increases approaching P_{LVED}, the septum becomes flattened, and if the transseptal

pressure gradient is reduced sufficiently, the septum may even become convex toward the lumen of the LV.[12,30]

This can be appreciated utilizing a static equilibrium analysis of the ventricles and the pericardium at end-diastole (Fig 2.3, Tyberg[60]). Although the heart is obviously a dynamic organ, at end-diastole when velocity is zero, the viscous and inertial effects can be ignored. When analyzed in terms of static equilibrium, the sum of all forces must equal zero. Considering first the left side of the figure, RV pressure must be exactly opposed by the sum of the transmural pressure and the pressure applied to the epicardium by the pericardium. Due to the compliance of the RV, transmural pressure is low; therefore, P_{RVED} equals pericardial pressure over the RV. An elevation in P_{RVED} would result in a rightward shift of the RV freewall until pericardial pressure increased sufficiently to re-establish the equilibrium. The pericardium is relatively non-compliant under acute conditions, thus an increase in pericardial pressure over the RV would increase in pericardial pressure over the left side in a similar manner (RV pericardial pressure = LV pericardial pressure).

An increase in RV end-diastolic pressure would not only affect the position of the free wall and pericardial pressures, but also exerts an effect on the interventricular septum. In general, the septum acts as a compliant membrane between two fluid-filled chambers. At end-diastole, the position of the septum relative to the two ventricles is determined by the transseptal pressure gradient (P_{LVED} - P_{RVED}). Since the transseptal pressure gradient is

decreased by factors which elevate P_{RVED} (while P_{LVED} is maintained or decreases), as P_{RVED} is increased the septum shifts leftward at end diastole decreasing LV volume. Thus, with an increase in right-heart pressures, the LV is essentially "squeezed" between the leftward shifting septum and the relatively non-distensible pericardium.

2.3.1) The role of the pericardium

The pericardium encloses all four cardiac chambers and under acute conditions is relatively non-distensible, which allows for tight coupling between the chambers. Lee et al[28] and Wiegner et al[64] examined the mechanical properties of isolated canine pericardium, and found that following a rapid increase in stress, creep averaged less than 1% in a 30 minute test period, and over a more prolonged period averaged less than 2% per hour. Le Winter and Pavelec[29] compared the influence of the pericardium on LV end-diastolic pressure-segment relations in dogs studied 7 to 9 days and 34 to 50 days after surgical induction of chronic volume overload. In this study, pericardectomy was shown to shift the pressure-diameter relation rightward in the dogs studied following 7 to 9 days of volume overload, but no change was demonstrated following pericardectomy in dogs after chronic volume load for 34 to 50 days. These studies suggest that the pericardium cannot expand significantly in response to acute stresses, but can expand to a considerable degree over the course of days to weeks.

The total pericardial volume consists of the chambers of the heart together with the pericardial fluid. Pressure-volume studies of the pericardial space have shown that a small volume of fluid may be infused with little or no change in the intrapericardial pressure, but additional amounts of fluid can result in a dramatic rise in pressure. The curve relating total volume of the pericardium to the pressure within it has been described by Holt et al[20] who defined the pericardial pressure-volume curve in a dead dog (Fig 2.4). As illustrated, as the volume of the pericardium is increased from zero, there is little or no change in pressure to a certain point. Over physiological ranges of volume and pressure, a small amount of fluid is present between the pericardium and the heart and the pericardium exerts very little stress on the epicardium.[32,33,61] The flat early portion of the curve is probably important in allowing for normal changes in cardiac volume, such as those associated with respiration, straining, and changes in posture. At higher cardiac volumes, however, as excessive amounts of fluid rapidly accumulate, the constraining effect of the pericardium becomes greater.[32,33,54,61] After the pericardium reaches a certain volume, any further small increases in volume result in a nearly perpendicular rise in pericardial pressure. This exponential relationship suggests that the pericardium is relatively stiff and its reserve volume is relatively small.

Several studies suggest that direct ventricular interaction is dependent to a great degree on the presence of the pericardium.[3,4,6,17,21,32,35,47,48,54,55]

Moulopoulos et al, with the pericardium opened, suggested that RV filling affected the LV end-diastolic pressure volume-relation only at relatively high RV end-diastolic pressures. Bemis et al[6], using isolated hearts, closed the pericardium and demonstrated that the RV affects LV filling and geometry over the whole range of end-diastolic pressures, although they concluded that the interaction observed was independent of the pericardium. Maruyama[32] observed (post-mortem canine hearts) that ventricular interaction was enhanced with an intact pericardium. Spadaro et al,[54] studied the effects of the RV and the pericardium on the LV diastolic pressure-volume relation in isolated canine hearts. This preparation allowed the investigators to control LV end-diastolic volume directly and determine accurately the LV diastolic pressure-volume relations with the pericardium closed and opened. The presence of the pericardium in this preparation resulted in a parallel upward shift of the pressure-volume relation. They concluded that the pericardium affects the LV diastolic pressure-volume relation even at low RV filling pressures, and that the intensity of this effect is clearly augmented at increasing RV diastolic pressures. Thus an important interaction between the RV and LV exists, particularly when the pericardium is closed. Spotnitz and Kaiser[55] also demonstrated that the pericardium influences LV filling pressures even at small volumes. Glantz et al,[17] in open-chest dogs, studied the relationship between LV and RV pressures with the pericardium closed and opened. They varied diastolic pressure by infusing or withdrawing blood or by increasing RV afterload with transient pulmonary

artery occlusion. This study demonstrated that, with the pericardium closed, RV pressure was a more powerful predictor of LV pressure than LV dimension. They concluded that the pericardium has a substantial effect on LV end-diastolic pressure, even at normal diastolic pressures. Janicki and Weber[21] showed that the coupling between the ventricles was greater with the pericardium intact, especially at greater end-diastolic volumes. In their study, as RV end-diastolic volume was increased, significantly greater changes were observed in P_{LVED} with the pericardium closed. Santamore et al,[41] using arrested canine hearts (in vitro and in situ) with the pericardium intact, examined mechanical coupling between the ventricles at increased levels of pericardial pressure. At low initial pericardial pressure, the mechanical coupling between the ventricles occurred as the result of ventricular-to-ventricular interaction. Raising the pericardial pressure significantly increased the mechanical coupling between the ventricles and this increased coupling occurred through an increase in ventricular-to-pericardial-to-ventricular coupling, while ventricular-ventricular coupling was unaltered.

2.3.2) The role of the septum

The septum, being the common wall between the two ventricles, is one structure by which mechanical events in one ventricle are able to influence the behaviour of the other. At end-diastole, the position of the septum relative to the two ventricles is determined by the end-diastolic transseptal pressure

difference, commonly referred to as the transseptal pressure gradient (equal to P_{LVED} minus P_{RVED}). It is through changes in the transseptal pressure gradient that the interventricular septum, by altering its shape and/or position mediates ventricular interaction.

In clinical and experimental studies, increased RV volume has been shown to shift the LV end-diastolic pressure-volume curve to the left and to displace the interventricular septum.[6,8,13,19,21,30,32,37,38,59] As early as 1914 it was shown by Henderson[19] that, in order to maintain a constant LV area while RV end-diastolic pressure was increased, the LV end-diastolic pressure must also increase. Bemis,[6] Elzinga,[13] and Janicki and Weber[21] used isolated beating hearts in which the right and left volumes and pressures could be independently controlled. In these studies, distension of either ventricle during diastole was shown to alter the compliance and geometry of the opposite ventricle. They all demonstrated that ventricular interaction was great enough to be physiologically significant. In normal dogs, Little et al[31] observed that caval occlusion promptly decreased RV end-diastolic pressure and increased end-diastolic septal-lateral dimension. A sudden release of the caval occlusion resulted in the opposite effect. Sudden pulmonary artery constriction increased RV end-diastolic pressure and decreased LV septal-lateral dimensions. Even in the absence of the pericardium, they demonstrated that alteration in RV end-diastolic pressure has a significant effect on the LV end-diastolic pressure volume-relation. Increasing LV volume has been shown to have the opposite

effect resulting in rightward displacement of the septum and increased LV septal-to-freewall and reduced RV septal-to-freewall dimensions.[36,42]

In a clinical investigation, Thompson et al[59] examined diastolic ventricular septal motion in patients with mitral stenosis to determine if the position (and therefore motion) of the septum was determined by the transseptal gradient during diastole. They found that the position of the septum was better correlated with transseptal gradient than with LV or RV intracavitary pressure, and thus concluded that the position of the septum in patients with mitral stenosis was determined by the instantaneous transseptal gradient.

The material properties of the septum also play an important role in direct ventricular interaction.[31,61] Maughan et al[34] suggested that the effect of alterations in RV pressure on the LV end-diastolic pressure-volume relation depends on the relative elasticity (or slope of the pressure-volume relation) of the septal component of the LV compared to the elasticity of the component of the LV made up by the free wall. This model predicts that, if the interventricular septum is very stiff in relation to the LV free wall, then changes in the RV pressure would have little influence on the LV pressure-volume relation. If, on the other hand, the interventricular septum is very compliant and the LV free wall very stiff, then the RV pressure would have a large effect on the LV and-diastolic pressure-volume relation. Thus, increasing septal compliance increases the coupling between the ventricles, whereas decreasing septal compliance decreases the coupling between the ventricles. Disease states that

decrease septal compliance would therefore be expected to decrease septal interaction. This concept is supported by several studies. Santamore et al[44] developed a theoretical model which indicated that the magnitude of ventricular interaction was related to the relative compliances of the LV and RV freewalls, septum, and the pericardium. They verified this theoretical analysis in post-mortem canine hearts, and demonstrated that increasing septal compliance enhanced the coupling between the ventricles, and a decrease in the septal compliance resulted in the opposite. Little et al[31] studied the effect of RV pressure on LV end-diastolic pressure-volume relation before and after chronic RV overload. They demonstrated that alterations in RV end-diastolic pressure-volume relation, independent of the pericardium, is reduced following septal hypertrophy. This implies that the effect of alterations in RV end-diastolic pressure on the LV end-diastolic pressure-volume relation depends on the relative compliance of the interventricular septum and LV free wall, not simply on the ratio of the interventricular septal surface area to the LV surface area. These results are consistent with the model proposed by Maughan et al.[34]

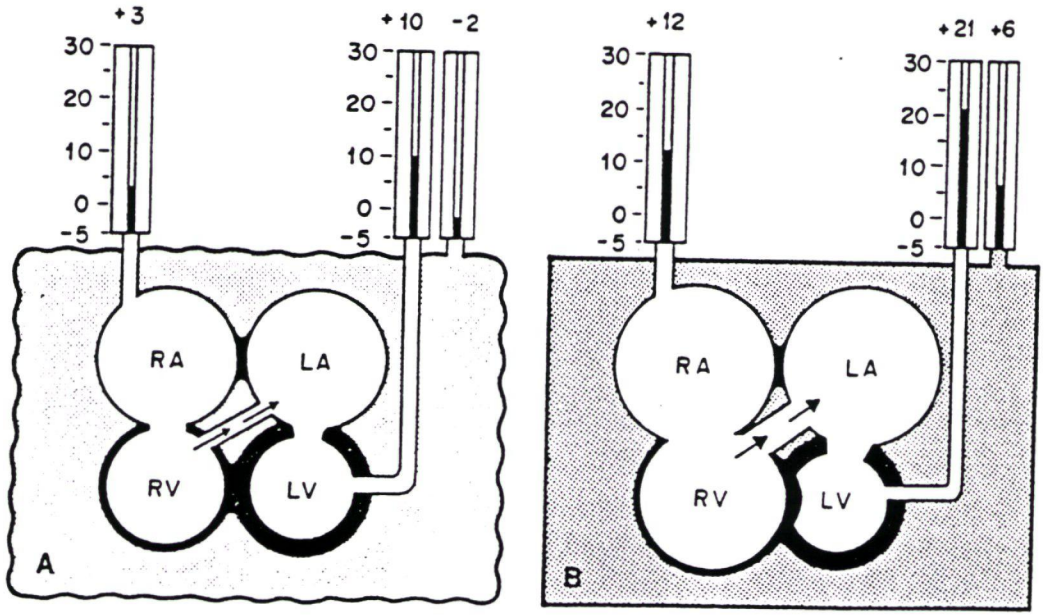

Figure 2.1: Schematic Hydraulic Model of Series vs. Direct Interaction

This figure represents a hydraulic model of the series and parallel arrangement of the right and left sides of the heart which was first introduced by Tyberg et al,[61] and later modified by Shabetai[46]. The RV and LV are represented as distensible, water-filled balloons, separated by a common septum, and contained in a rigid fluid-filled box (the pericardium). *Panel A:* Control. Under normal conditions, the filling pressure is higher in the LV than in the RV and the pericardium is lax. *Panel B:* Volume Overload. With volume loading, intracavitary pressure increases and the more distensible atria and RV expand. Since the pericardium is relatively non-distensible, pericardial pressure also increases reducing the transseptal gradient and shifting the septum leftward.

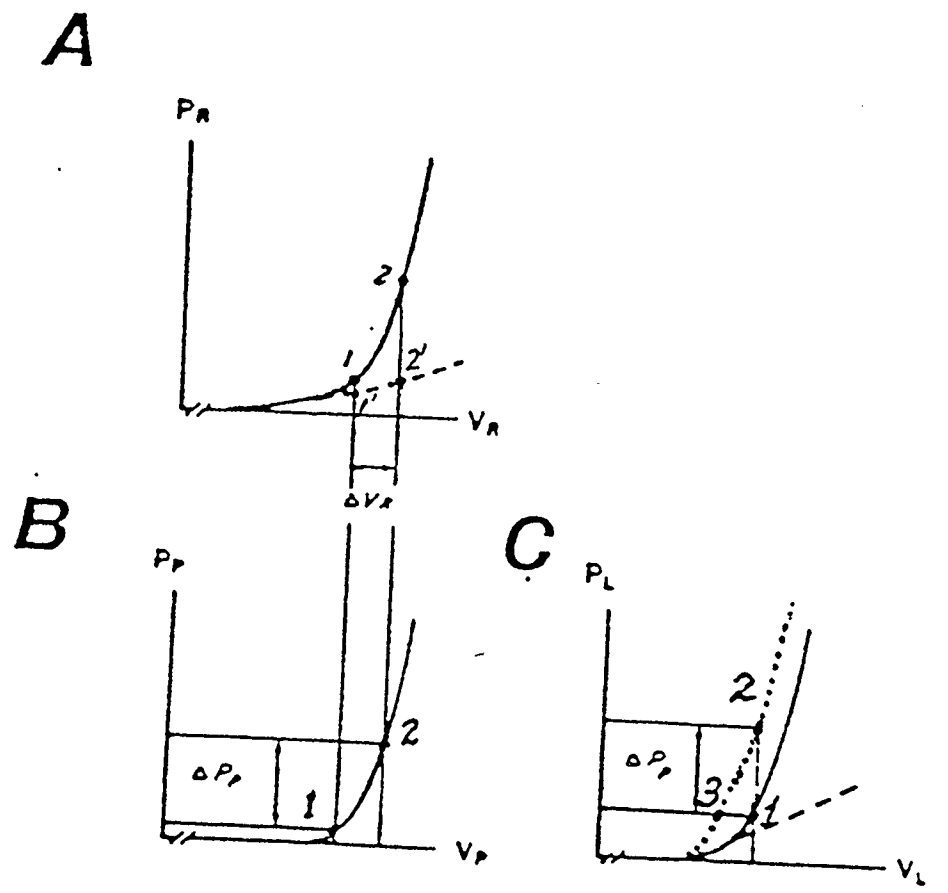

Figure 2.2: RV, LV, and Pericardial Pressure-Volume Relationships

This figure shows plots of RV (panel A), LV (panel C) and pericardial (panel B) pressure-volume curves with the pericardium closed (solid lines) and opened (dashed lines). The dotted curve in C represents the leftward shifted curve due to the increase in RV volume. (from Tyberg et al[61])

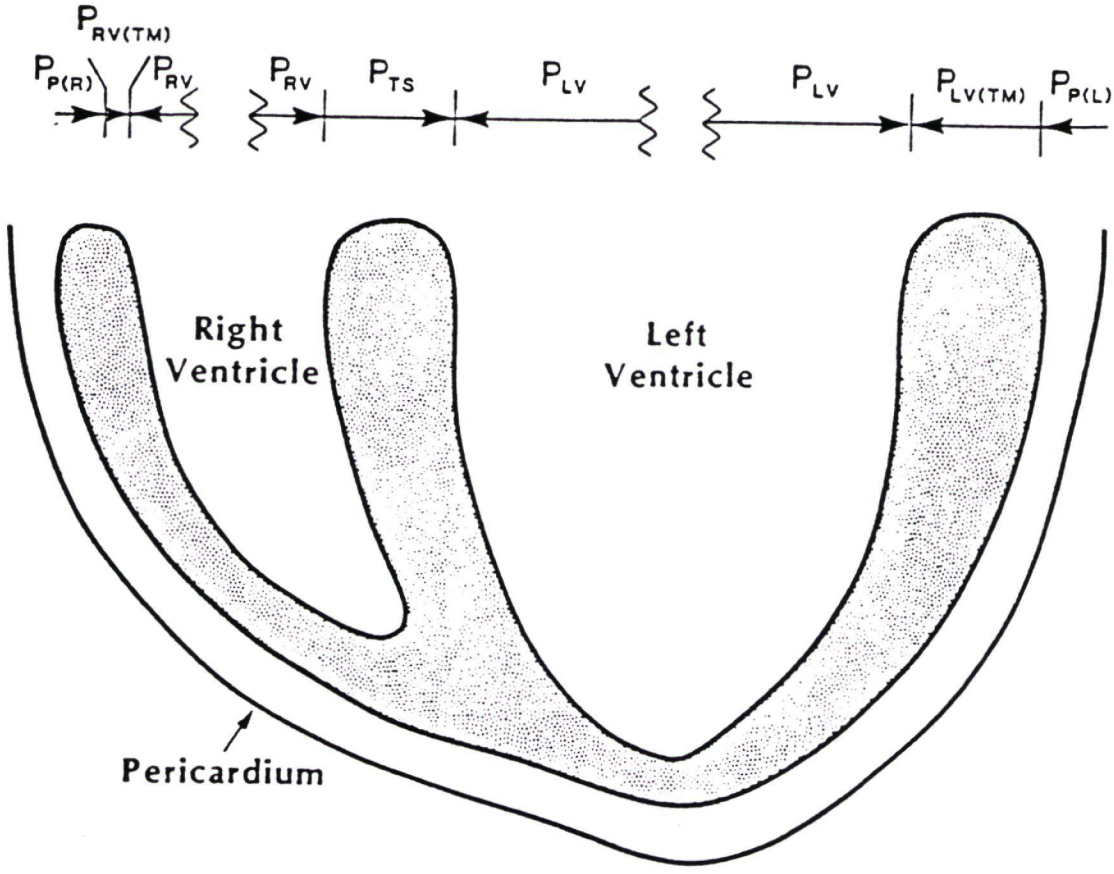

Figure 2.3: Static Equilibrium Analysis

This figure represents a static equilibrium analysis of the ventricles and the pericardium. The balance of forces at the RV freewall, the interventricular septum, and the LV freewall is represented at the top of the figure from the left to the right, respectively. (from Tyberg[60])

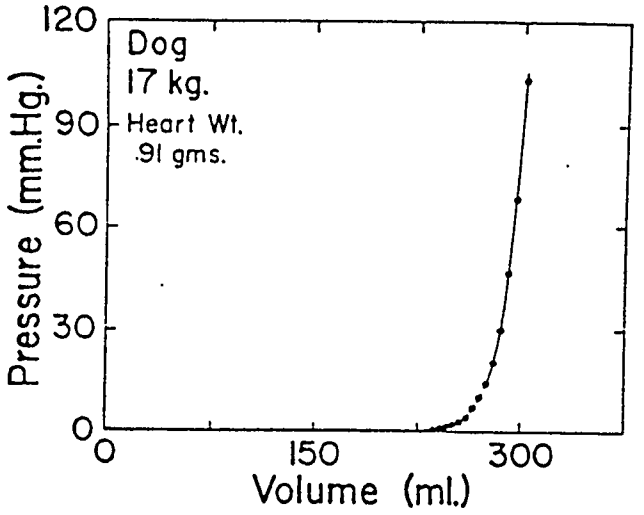

Figure 2.4: Pericardial Pressure-Volume Curve In A Dead Dog

This figure illustrates a pericardial pressure-volume curve from a dead dog which demonstrates that the pericardium is relatively nondistensible. As the volume of the pericardium is increased from zero, there is little or no pressure within the pericardial space. However, after the volume reaches a critical point, further small increases in volume cause a nearly perpendicular rise in pericardial pressure. (from Holt et al[20])

Chapter 3: Historical Overview

3.1) Review of History

At the turn of the century, the concept that the pericardium may constrain the normal heart under certain conditions was first suggested by Barnard,[2] who published a series of very elegant experiments designed to address this issue. By subjecting strips of pericardium to traction Bernard demonstrated that the pericardium was virtually inextensible. He further evaluated the concept of pericardial constraint by raising the pressure in an excised feline heart (pericardium intact) with a bicycle pump until the heart and pericardium ruptured. He observed that the pericardium gave way from the great vessels at a pressure of 1.25 to 1.75 atm, but the fundus of the pericardium did not rupture until a pressure of 2 atm was reached (a pressure sufficient enough to rupture the thick rubber tube in the preparation). The isolated heart without the pericardium could only withstand about half this pressure. Barnard further emphasized this concept by demonstrating that a post-mortem canine heart, full of saline (pressure of 20 cm H_2O), could double its volume upon removal of the pericardium. From these results, Barnard concluded that the pericardium exerts a significant restraining influence on the heart.

Another comprehensive study of the constraining influence of the pericardium was done by Evans and Matsuoka.[14] They examined the effect of various mechanical conditions on the gaseous metabolism of the heart and demonstrated that the metabolism is proportional to the diastolic volume or length of its fibers and that removing the pericardium resulted in a drop of venous pressure and a concomitant increase in gaseous metabolism. Thus, at elevated volumes the efficiency of the heart was greater for a given cardiac output if the pericardium was intact that if it was removed.

Kuno,[26] in 1915, published a series of experiments designed to clarify the function of the pericardium and to test the hypothesis that the pericardium prevents over-distension of the heart. The experiments were conducted using the Starling heart-lung preparations as well as open-chest dogs. The basic design was the same, however, in that observations were made both with the pericardium opened and after it had been resutured. Kuno observed that, when the pericardium was opened, venous pressure fell and this was accompanied by increased blood pressure and output. Kuno also found that the heart's maximum limit was approximately 25% larger after removal of the pericardium, and that this increased work involved damage to the heart in the form of hemorrhage into the muscle. He concluded that the pericardium had a protective role in limiting the dilation of the heart and so protecting it from damage.

Wilson and Meek[65] examined the effect of the pericardium on cardiac distension. In anesthetized dogs they raised venous pressure by infusing saline and, using X-ray images, they demonstrated that even at low venous pressures (from -4 to 0 cm H_2O) the pericardium constrains the heart, as demonstrated by the fact that, without the pericardium, the heart was larger at the same venous pressure.

Despite the considerable understanding that was present nearly one hundred years ago, the advancement of concepts pertaining to the role of the pericardium in ventricular interaction was intellectually stalled. Conflicting views regarding the quantitative effect of pericardial constraint on LV diastolic function remained controversial for quite some time. This difference in views was largely the result of the methods used to measure pericardial pressure. Resolution of this controversy was dependent on the magnitude of pericardial pressure, and the magnitude, dependent on the method of measurement.

Much of the misconception relating to the role of the pericardium was due to the often-quoted studies performed by Kenner and Wood.[23] These investigators performed a detailed series of experiments on pericardial dynamics in dogs, measuring pericardial pressure using an open catheter within the pericardial space. Using a balloon-tipped catheter, they constricted the pulmonary artery producing an increase in mean right atrial pressure to 26 cm H_2O, yet pericardial pressure did not rise. Similarly, with partial aortic occlusion, left atrial pressure rose to nearly 20 mm Hg and again pericardial

pressure did not change. Although they produced significant increases in end-diastolic pressure and the heart appeared enlarged, they were not able to measure a significant increase in pericardial pressure. Thus, the opinion developed that the pericardium did not constrain even an over-filled heart, and that pericardial pressure was similar to intrathoracic pressure. This led to the common measurement of LV transmural pressure as the difference between LV intracavitary pressure and esophageal pressure.

It was not until Smiseth et al[51] demonstrated that it is necessary to use a device similar to a balloon transducer to measure the physiological external constraint to the heart that the commonly held views were questioned. Smiseth et al, in an attempt to properly determine the better method of measuring pericardial constraint, compared pericardial pressure measured with an open-end catheter (liquid pressure) to that measured with a flat liquid-containing balloon (surface pressure), similar to the one Holt et al[20] used twenty-five years earlier. They also calculated pericardial pressure by determining the difference in LV end-diastolic pressure with the pericardium closed versus opened from LV pressure-diameter loops for comparison. In this study, pericardial pressure measured by the flat balloon was similar to the calculated pericardial pressure at all pericardial liquid volumes. Pressure recorded by the open-ended catheter, however, was significantly lower than the calculated pressure unless there was at least 30 ml of liquid in the pericardium. Thus, it was demonstrated that measuring pericardial pressure using an open-ended catheter significantly

underestimates pericardial constraint, and measuring pericardial pressure using a flat liquid-containing balloon is more accurate.

3.2) Recent Approaches

Essentially, three different types of approach have been used to study ventricular interaction over the recent years. Because of the difficulty in separating direct and series interaction, the first method has been to eliminate the series contribution to ventricular interaction by using isolated[13,17,33,45] or arrested[40,58] hearts, in which the ventricles were no longer coupled in series. Elzinga et al[13] eliminated the series component of ventricular interaction in feline hearts by interrupting the normal series-pump arrangement with an elaborate system of pumps and reservoirs. By eliminating the series component, these investigators were able to examine the direct relationship between the two ventricles. They observed that when atrial pressure was increased on one side of the heart, output from the other side decreased, and in spite of constant left atrial filling pressure, LV end-diastolic pressure increased. This effect was much more pronounced with the pericardium intact than removed. Santamore[42] examined the alterations in the pressure-volume relations and ventricular geometry in isolated, beating canine hearts. It was observed that changes in LV volume altered the RV end-diastolic pressure-volume relation. Increased LV volume resulted in an increase in RV pressure, whereas, decreased LV volume

resulted in the opposite. Thus, increased RV volume was shown to alter the LV pressure-volume relation and vice versa. Bemis et al[6] also used isolated canine hearts and closed the pericardium to evaluate the influence of RV filling pressure on LV pressure-volume dimensions. This experimental model allowed the investigators to vary RV pressure and volume while LV inflow, blood pressure and heart rate were held constant. Increased RV filling pressure was associated with decreased LV septal-to-freewall and increased anteroposterior dimensions, and was accompanied by a substantial increase in LV filling pressure. As with the other studies, this resulted in decreased LV diastolic compliance and alteration in the pressure-volume relation. Although the above preparations allowed for precise control of the ventricular pressures and volumes they were not physiologic in that the hearts were removed from the circulatory system and often were arrested.

A second approach has been a statistical one involving analysis of beat-to-beat changes over a number of cycles in response to manipulations such as caval occlusion or pulmonary artery constriction.[31,49] Little et al[31] used such an approach in which RV and LV end-diastolic pressure was altered by sudden caval and pulmonary artery occlusion and release. Because of pulmonary transit time, rapid changes were produced in RV pressure while LV pressure initially remained relative constant, then slowly decreased. This approach was used to examine the effect of chronic RV pressure overload on diastolic ventricular interaction in dogs without a pericardium. These investigators

concluded that alterations in RV pressure on LV end-diastolic pressure-volume relations was reduced following pulmonary artery banding (which caused septal hypertrophy) independent of the pericardium. Thus, the effects of alterations in RV pressure on LV pressure-volume relations is influenced by the material properties of the septum. Slinker et al[49] used a statistical analysis of transient changes in LV and RV pressures and diameters following pulmonary artery and caval occlusions to separate and quantitate the series versus direct interaction effects on LV size at end-diastole. They concluded that, in open chest dogs with the pericardium closed, direct interaction was 1/3 as important as series interaction at end diastole and, with the pericardium opened, that direct interaction was 1/5 as important as series interaction.

Using a third approach, Slinker and coworkers [50] have studied ventricular interaction in a dog model in which they separated direct from series interaction by occluding both venae cavae while simultaneously withdrawing blood from the RV and analysing the change in LV end-diastolic pressure on the next beat. However, they did not have independent control of ventricular volume and, with the pericardium opened, they were unable to remove volume fast enough to decrease RV end-diastolic pressure substantially.

3.3) Quantification of Interaction Gain

Direct ventricular interaction can be quantified by determining the RV-to-LV end-diastolic pressure gain, which is the ratio of the change in the end-diastolic pressure in one ventricle produced by change in the pressure in the other ventricles. RV-to-LV pressure gains from several studies have demonstrated coupling between the ventricles and have demonstrated that this interaction is strengthened with the pericardium intact. In arrested canine hearts, Maruyama et al[32] reported RV-to-LV pressure gains of 0.38 and 0.44 with the pericardium intact and 0.28 after pericardectomy. Bemis[6] closed the pericardium and examined LV filling pressure during incremental changes in P_{RVED}. Data were obtained over a range of P_{LVED} of 0.8 to 18.4 mm Hg and P_{RVED} from 0 to 10 and occasionally 15 mm Hg. They found that the change in RV-to-LV pressure gain averaged 0.45 and that interaction between RV and LV filling occurred over the entire physiological range of transmural pressures. Janicki and Weber[21] with isolated canine hearts, found that ventricular interaction between the ventricles was consistently greater with the pericardium closed, and that this relationship was stronger at larger end-diastolic volumes. They fixed LV end-diastolic volume at end-diastolic pressure of 5, 10, 15 and 20 mm Hg and then varied P_{RVED} incrementally by 5 mm Hg from 0 to 20. RV-to-LV pressure gains calculated from their data were 0.26 with the pericardium closed and 0.13 with the pericardium opened. Slinker et al[50] calculated pressure gains

using multiple linear regression analysis of data obtained during venae cavae constriction and/or pulmonary artery constriction. They separated the two components of ventricular interaction by combining venae cavae occlusion and rapid withdrawal of blood from the RV. With this model, they were able to reduce RV end-diastolic volume by 10 - 15 ml on the next beat without changing pulmonary venous flow. They quantified direct RV-to-LV pressure gain with the pericardium closed and reported values of 0.32 at an P_{LVED} of 5, 0.23 at a P_{LVED} of 10 and 0.28 at a P_{LVED} of 15. Little et al,[31] in chronically instrumented normal dogs with the pericardium removed, demonstrated an RV-to-LV pressure gain of 0.43 following caval occlusion. Caval occlusion and pulmonary artery constriction resulted in an RV-to-LV pressure gain of 0.47. Dauterman et al[11] calculated pressure gains in patients undergoing cardiac catherization using balloon obstruction of the inferior venae cava (decreased P_{RVED} to zero from baseline) and demonstrated RV-to-LV gains of 0.53 - 0.62. Despite different techniques and experimental models, there is substantial agreement among these studies.

3.4) A Novel Approach

Understanding the contributions of the direct and series components of ventricular interaction has been limited by the inability to control each component independently in the intact system. We have designed a canine

right-heart bypass model which enables us to assess the series and direct components independently and, as well, to quantitate the pericardial and septal contributions to direct interaction. Our method allows us to separate and control independently the series and direct mechanisms of ventricular interaction in the beating heart in an in situ system and study these interactions over a wide range of ventricular pressures and volumes. By establishing LV end-diastolic pressure-volume relations while each component was varied independently, we are able to define pressure-volume curves reflecting changes in the series components at constant P_{RVED}s and demonstrate the independent effects of increasing P_{RVED}. By independently altering LV venous return at constant RV end-diastolic pressures, we are able to determine the relationship between LV venous return and external constraint. This model also enables us to collect data with the pericardium closed and open; thus, by studying the effects with the pericardium closed and opened, we are able to quantitate the septal and pericardial contributions to direct ventricular interaction.

Chapter 4: Methods

4.1) Animal Preparation

After premedication with 0.75 mg/kg morphine sulphate, 11 dogs weighing 19-29 kg were anaesthetized, initially with sodium thiopental (10 - 15 mg/kg intravenously), and then maintained with fentanyl citrate (50 μg/kg intravenously over 5 minutes followed by 20 to 50 μg/kg/hr). Additional boluses were administered and infusion rates were adjusted as necessary. The animals were ventilated with a 70% nitrous oxide - 30% oxygen mixture using a constant-volume respirator (model 607, Harvard Apparatus Inc., Natick, Mass.).

LV and RV pressures were measured with 8F micromanometer-tipped catheters with reference lumens (model PR279, Millar Instruments, Houston, Texas) inserted through the femoral artery and the RV cannula, respectively. Aortic pressure was measured with a fluid-filled catheter introduced through the femoral vein. An electrocardiographic lead and a signal generated by the ventilator to indicate end-expiration were also recorded.

A midline sternotomy was performed with the dog in the supine position. The ventral surface of the pericardium was incised transversely along the base of the heart, and the heart was removed from the pericardium for instrumentation. A flat, liquid-containing balloon was sutured loosely to the anterolateral surface of the LV to measure pericardial pressure.[3] Septum-to-LV

free wall and LV anteroposterior diameters were measured by sonomicrometry (Triton Technology, San Diego, Calif.).[5]

The animal was then prepared for right-heart bypass (Fig 4.1). The venae cavae were cannulated and drained to a reservoir where the blood was filtered and heated. The circuit was primed with fresh blood from a donor animal. A roller pump (Sarns Inc., Ann Arbor, Mich.) was used to pump blood from the reservoir to the pulmonary artery, the flow (ie, VR_{LV}) being measured with an ultrasonic flow probe (Transonic Systems Inc., Ithaca, N.Y.) positioned on the pulmonary artery cannula. An 11-mm cannula which drained into a height-adjustable reservoir was inserted into the right atrium to drain the coronary sinus flow and to control RV pressure. The azygous veins were tied off and the heart was then returned to the pericardial sac, the edges of which were loosely reapproximated with several individual sutures, taking care to avoid decreasing the pericardial volume.

Conditioned signals (model VR16, PPG Biomedical Systems, Lenexa, Kan.) were recorded on a personal computer (IBM Corporation, Armonk, N. Y.). The analog signals were passed through anti-aliasing low-pass filters with cutoff frequencies of 100 Hz and were sampled at a frequency of 200 Hz. The digitized data were subsequently analyzed on a personal computer using a software package developed in our laboratory (CVSOFT®, Odessa Computer Systems Ltd., Calgary, Alta.).

4.2) Experimental Protocol

The right-heart bypass model used in this study allowed for independent control of VR_{LV} and P_{RVED}. The series mechanism of ventricular interaction was controlled by adjusting pump output (ie, VR_{LV}) and the direct mechanism (ie, P_{RVED}) was controlled by changing the height of the RV reservoir. Baseline VR_{LV} was adjusted so that P_{LVED} was approximately 8 mm Hg.

The height of the RV reservoir was adjusted to maintain P_{RVED} at 0 mm Hg and, to change series interaction without changing DVI, VR_{LV} was first decreased by reducing the pump output until aortic pressure decreased to approximately 60 mm Hg and then increased incrementally until P_{LVED} was at least 20 mm Hg. This required approximately 4 minutes. VR_{LV} was then returned to the control rate. To assess the effects of increasing degrees of direct interaction, the height of the RV reservoir was then raised to maintain P_{RVED} at 5 mm Hg. VR_{LV} was then varied over a similar range as described above. The procedure was then repeated with P_{RVED} maintained at 10 and 15 mm Hg.

To assess the pericardial contribution to DVI, the pericardium was opened and the entire protocol was repeated.

4.3) Data Analysis

Only data collected at end-expiration were analyzed. LV transmural pressure was calculated using two methods: first, P_{LVTM} as P_{LVED} minus LV pericardial pressure (P_{PER}, balloon pressure) and, secondly, P_{LVTM}* as P_{LVED} minus the sum of 2/3 of P_{PER} and 1/3 of P_{RVED}.[35] The product of the LV minor-axis diameters (anteroposterior × septum-to-free wall diameter) was used as an index of LV area and, hence, volume (VI_{LVED}). Stroke volume (SV) was calculated as VR_{LV}/beat. End-diastolic pressure-volume curves ($(P\text{-}VI)_{LVED}$) were plotted for each animal and the curves fitted to second-order equations. Normalized data from each animal were combined for analysis. Baseline LV volume (VI_{LVED} = 100%) was defined as the volume observed at an P_{LVED} of 5 mm Hg with the pericardium removed (P_{PER} = 0) and P_{RVED} = 0 mm Hg (ie, P_{LVTM} = P_{LVTM}* = 5 mm Hg). Other values of VI_{LVED} were expressed as percentages of the above-defined baseline value in order to compare data from different animals. To assess the relationship between VR_{LV} and external constraint, these data were summarized by recording the VR_{LV} at each level of P_{RVED} at volumes of 94, 100, and 106%. VR_{LV}/beat equals 100% was defined as the VR_{LV}/beat when the VI_{LVED} was 100%, P_{RVED} was 0, and when the pericardium was closed. LV end-diastolic pressure-volume curves at VI_{LVED} = 94, 100, and 106% were then plotted at different P_{RVED}s to assess RV-to-LV end-diastolic pressure gain (ie, the ratio of the change in LV [which is the vertical shift in the curve at the nominal

value of VI_{LV}] to the change in RV pressure). Pressure gains were calculated as the slopes of the linear regressions for each constant P_{RVED} curve.

4.4) Statistical Analysis

To determine if the opening of the pericardium decreased DVI, two-way repeated-measures analysis of variance was used to compare the linear regressions of the RV-to-LV diastolic gains at VI_{LVED} of 94, 100, and 106% (Fig. 5.5) with the pericardium closed and opened. A *p* value of less than 0.05 was considered significant.

To determine if the relationship between VR_{LV} and different degrees of external constraint (the upward shift in the curves, Fig 5.3) were significant we used two-way repeated-measures analysis of variance to compare the effect of P_{RVED} on VI_{LVED}. To isolate which groups were significantly different from the others we used a multiple comparisons procedure (Student-Newman-Keuls Method). Also, to further determine if a greater change in VR_{LV} was required to change VI_{LVED} from 100 to 106% then from 94% to 100%, we compared the slopes of the respective portions of the curves using two-way repeated-measures analysis of variance. A *p* value of less than 0.05 was considered significant.

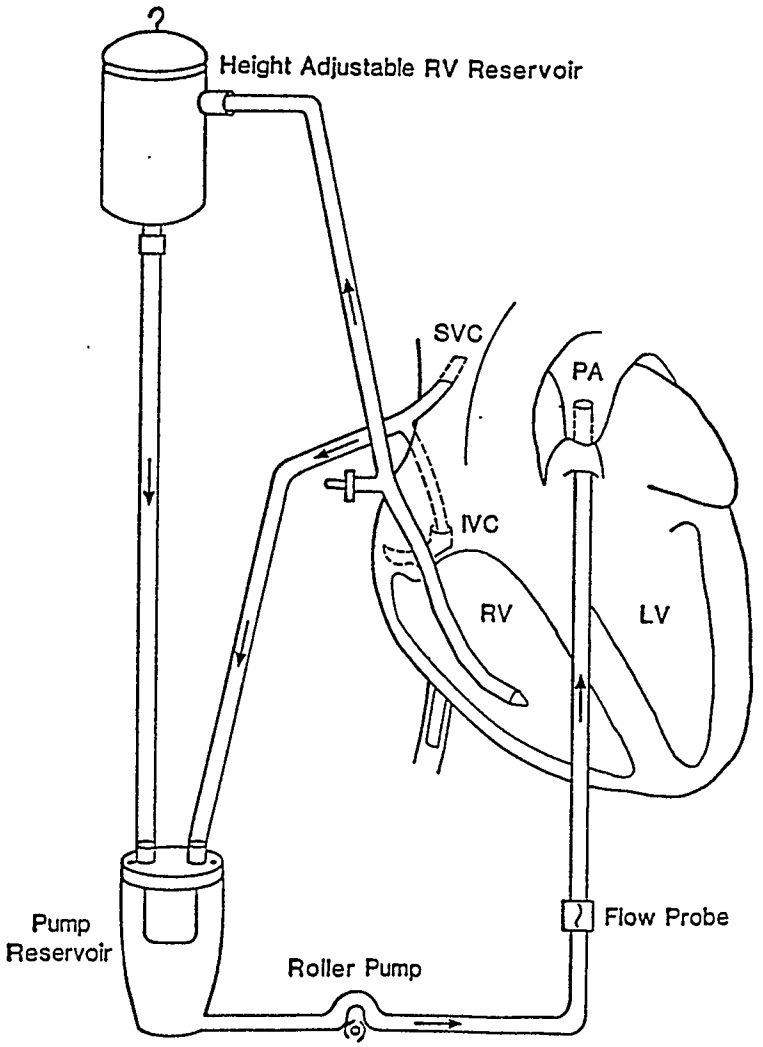

Figure 4.1: A Schematic Diagram Of The RV Bypass Model.

The venae cavae (SVC, IVC) were cannulated and drained to the pump reservoir; the pump returned systemic venous blood to the pulmonary artery, simulating RV output. Pulmonary artery (PA) flow was measured with an ultrasonic flow probe. A cannula was used to drain coronary sinus flow into a height-adjustable RV reservoir. Thus, the series component was controlled by adjusting the pump output (equal to LV venous return) and the direct component (P_{RVED}) was altered by adjusting the height of the RV reservoir.

Chapter 5: Results

5.1) Introduction

The series contribution of ventricular interaction was characterized by plotting the end-diastolic pressure-volume relations ($(P\text{-}VI)_{LVED}$) at constant P_{RVED}s of 0, 5, 10, and 15 mm Hg and the direct component by characterizing the shifts in these curves when P_{RVED} was altered.

5.2) Independent Effects of Increasing VR_{LV} and P_{RVED}

Fig 5.1 illustrates $(P\text{-}VI)_{LVED}$ relations (intracavitary and transmural) from one experiment with the pericardium closed. While P_{RVED} was maintained at 0, 5, 10, and 15 mm Hg, VR_{LV} was varied over a wide range to define each curve. As VR_{LV} was increased (panel a), VI_{LVED} increased along a single curve for each P_{RVED} reflecting the series component. When P_{RVED} was increased the $(P\text{-}VI)_{LVED}$ curves shifted upward and to the left reflecting the direct component of ventricular interaction. Plots of LV transmural pressure versus volume (calculated both ways, panels b and c) eliminated the effects of direct interaction (pericardial and septal) and the curves became superimposed. There was no difference between the P_{LVTM} and P_{LVTM}* curves with the pericardium closed.

Figure 5.2 illustrates the degree to which pump output had to be increased to maintain VI_{LVED} constant with increasing P_{RVED}. Each symbol represents data (from Fig 5.1) which has been segregated by similar stroke volumes (VR_{LV}/beat). As P_{RVED} was increased from 0 to 15 mm Hg, it can be seen that substantial increases in VR_{LV} were required to maintain a constant VI_{LVED}. From each experiment, these data were summarized and data from all dogs were combined (Fig 5.3). To determine the relationship between VR_{LV} and different degrees of external constraint, we calculated the required VR_{LV} to maintain representative small (94%), normal (100%), and increased (106%) VI_{LVED}s, at different levels of P_{RVED}. Figure 5.3 shows VR_{LV}/beat (in percent) plotted as a function of VI_{LVED}, at P_{RVED}s of 0, 5, 10, and 15 mm Hg. This figure illustrates that increases in external constraint (P_{RVED}) resulted in a progressive upward shift of these curves, thus more VR_{LV} was required to maintain the same volume as P_{RVED} was increased. Also, the slopes of these curves increased as VI_{LVED} became larger, as illustrated by the steeper slope from 100 - 106% than from 94 - 100%.

5.3) Contributions of the Pericardium and Septum to DVI

After the pericardium had been opened (Fig 5.4, panel a), there were still upward and leftward shifts in the $(P\text{-}VI)_{LVED}$ relations but the shifts were smaller. To evaluate the proportion of DVI that was due to the septum, we plotted P_{LVTM}*-

VI_{LVED} curves (Fig 5.4, panel b). This calculation eliminated the remaining P_{RVED}-mediated shifts in the curves and the curves became superimposed indicating that the remaining DVI was septum-mediated.

The combined RV-to-LV end-diastolic pressure gain plots from all animals are shown in Fig 5.5 at normalized VI_{LVED}s of 94, 100, and 106%. With the pericardium closed, RV-to-LV pressure gains were 0.52 at 94%, 0.57 at 100%, and 0.52 at 106% VI_{LVED} (closed circles, top 3 panels). With the pericardium opened, the respective pressure gains were 0.31, 0.34, and 0.23 (open circles, top 3 panels), the difference being statistically significant ($P< 0.005$). When the pericardium-opened contributions of P_{RVED} (via the septum) to P_{LVED} were taken into account,[35] the slopes of the pressure gains were not different from zero (open circles, bottom 3 panels) indicating that the remaining interaction could be explained by the septum. Comparison of the P_{LVTM}* data (bottom 3 panels) revealed no significant difference between the pericardium-closed versus pericardium-opened data ($P=0.25$).

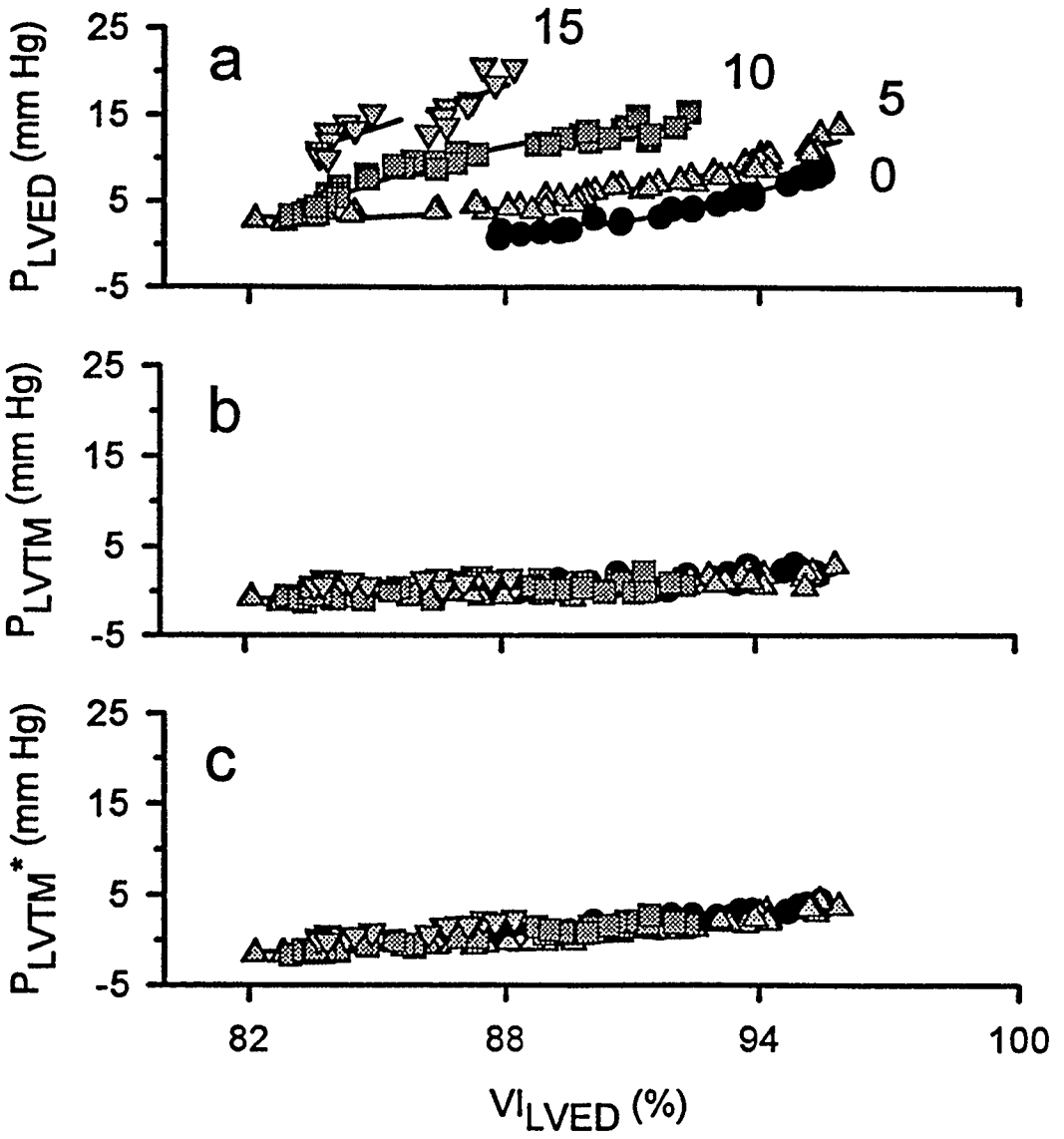

Figure 5.1: End-Diastolic Pressure-Volume Curves, Pericardium Closed

This figure illustrates $(P\text{-}VI)_{LVED}$ curves in a single dog with the pericardium closed with P_{RVED} held constant at 0 (circles), 5 (triangles), 10 (squares), and 15 (inverted triangles) mm Hg. *Panel a:* At each P_{RVED}, as VR_{LV} increased, VI_{LV} increased along a single curve representing series interaction. *Panel b:* Using LV transmural pressure ($P_{LVTM} = P_{LVED} - P_{PER}$) there was no shift in the curves indicating that DVI had been eliminated. *Panel c:* Using a measure of LV transmural pressure accounting for RV pressure [$P_{LVTM}^* = P_{LVED} - (2/3\ P_{PER} + 1/3\ P_{RVED})$] there was no further change, implying that P_{PER} and P_{RVED} were similar.

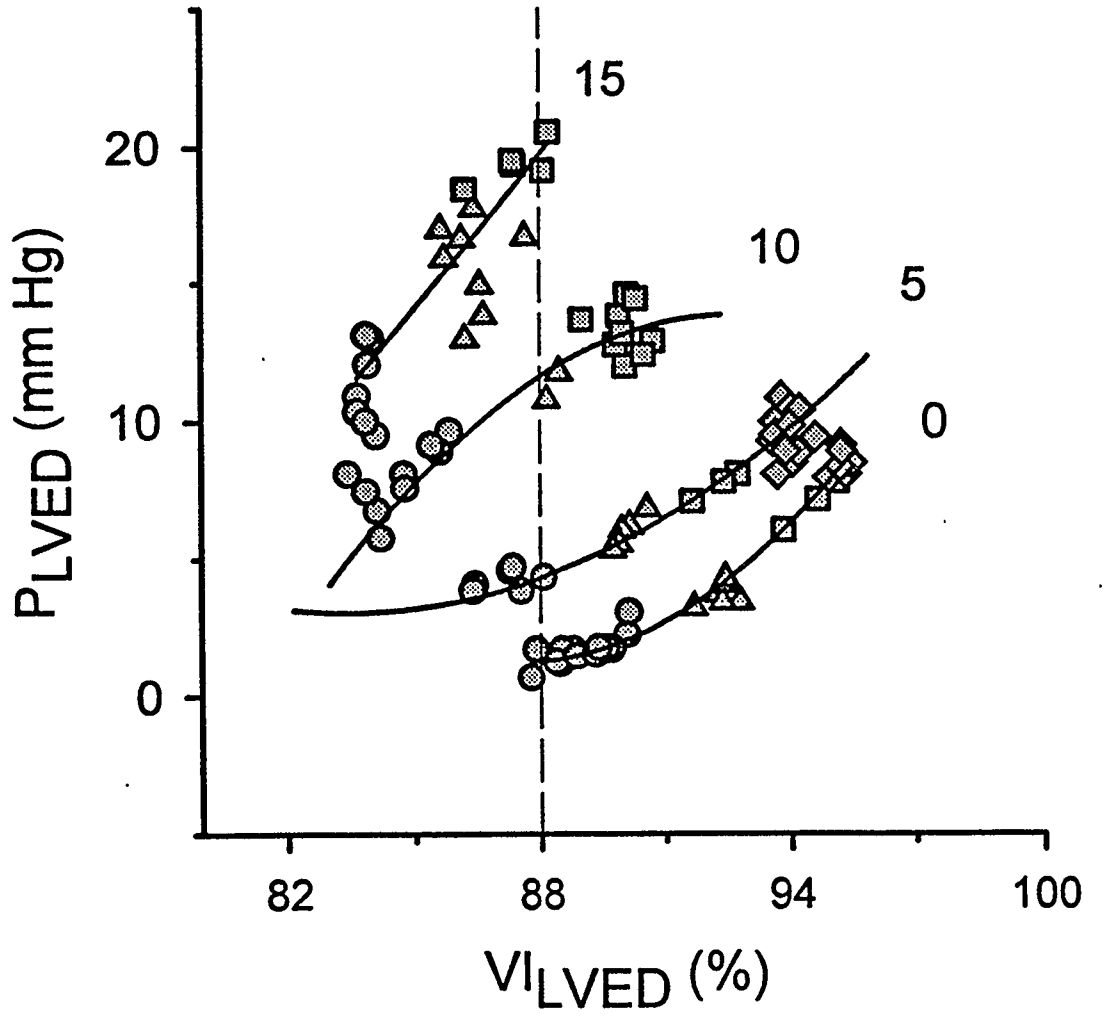

Figure 5.2: End-Diastolic Pressure-Volume Curves, Sorted By Stroke Volume

This figure represents $(P\text{-}VI)_{LVED}$ curves at P_{RVED}s of 0 - 15 mm Hg (same data as Fig 5.1) with the data points segregated according to stroke volume (VR_{LV}/heart rate) (circles = 10 - 20 ml/beat; triangles = 30 - 40 ml/beat; squares = 50 - 60 ml/beat; diamonds = 70 - 80 ml/beat). To maintain a given volume (eg, VI_{LVED} = 88%) stroke volume had to be increased from 10 - 20 ml/beat at a P_{RVED} of 0 and 5 mm Hg to 30 - 40 ml/beat at a P_{RVED} of 10 mm Hg to 50 - 60 ml/beat at a P_{RVED} of 15 mm Hg.

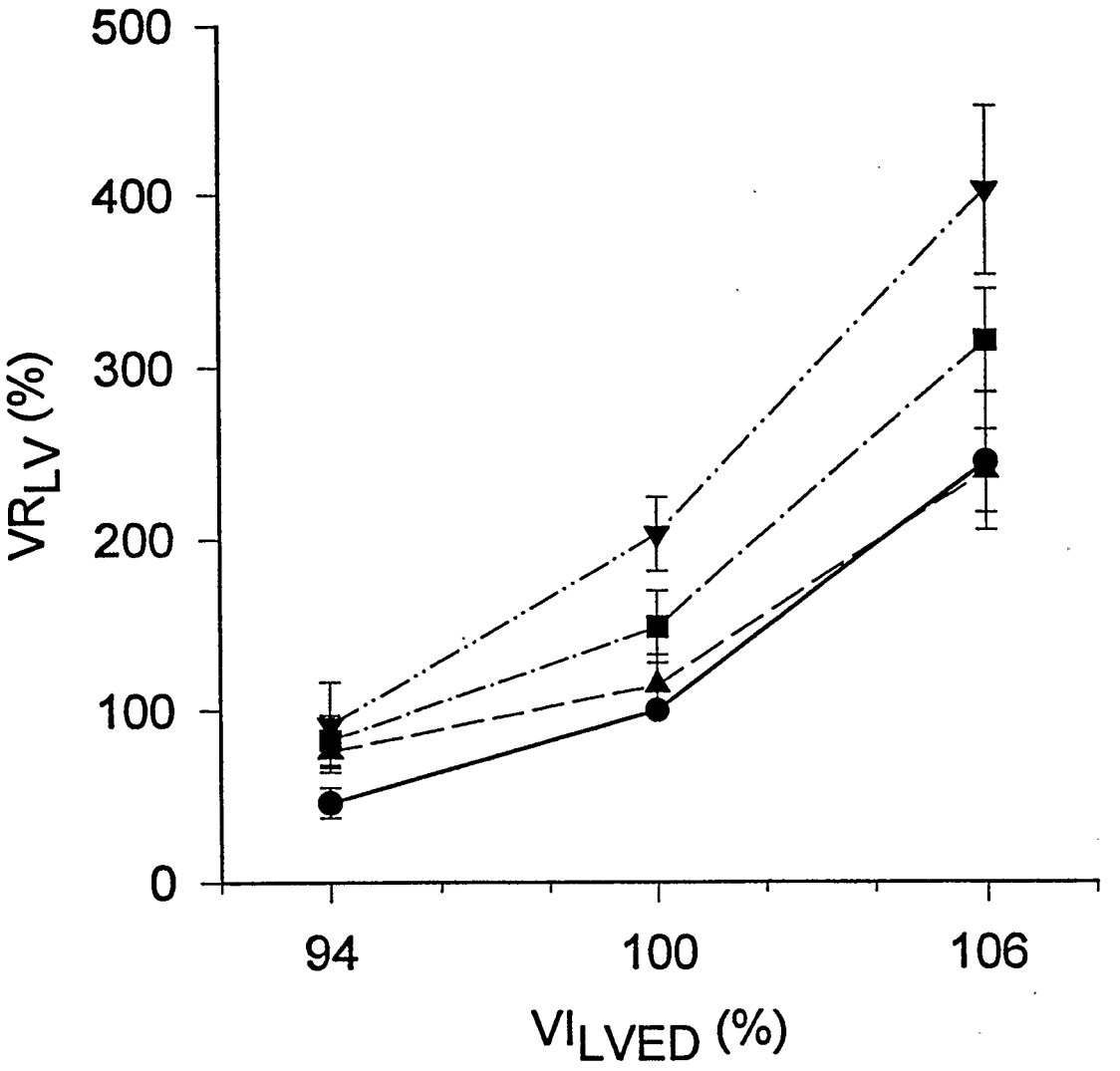

Figure 5.3: Relationship Between VR_{LV} and External Constraint

To determine the relationship between LV venous return and external constraint we calculated the VR_{LV} required to maintain representative small (94%), normal (100%), and increased (106%) LV volumes at P_{RVED}s of 0 (circles), 5 (triangles), 10 (squares), and 15 (inverted triangles) mm Hg. As P_{RVED} was increased, more VR_{LV} was required to maintain the same LV volume and, at the same degree of external constraint (P_{RVED} held constant), a greater increase in VR_{LV} was required to increase LV volume index from 100 - 106% than from 94 - 100%.

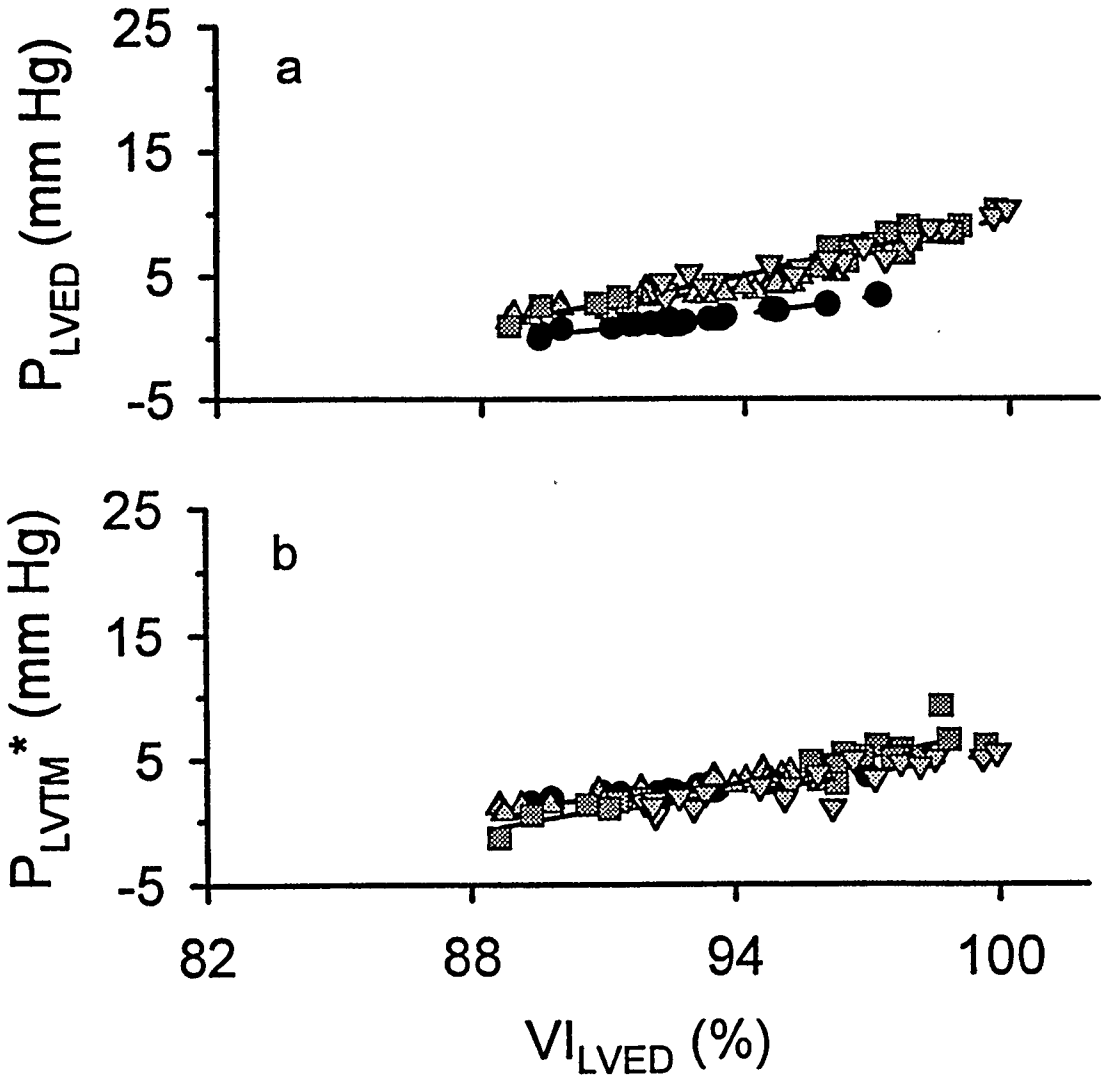

Figure 5.4: End-Diastolic Pressure-Volume Curves, Pericardium Open

This figure illustrates $(P\text{-}VI)_{LVED}$ curves in a single dog after the pericardium had been opened while P_{RVED} was maintained at 0 (circles), 5 (triangles), 10 (squares), and 15 (inverted triangles) mm Hg while VR_{LV} was varied over a wide range. *Panel a:* Opening the pericardium eliminates the pericardial contribution to DVI but some leftward and upward shift remained. *Panel b:* After accounting for the different RV and pericardial pressures, however, all the points fall on the same curve suggesting that the interaction observed is septal mediated.

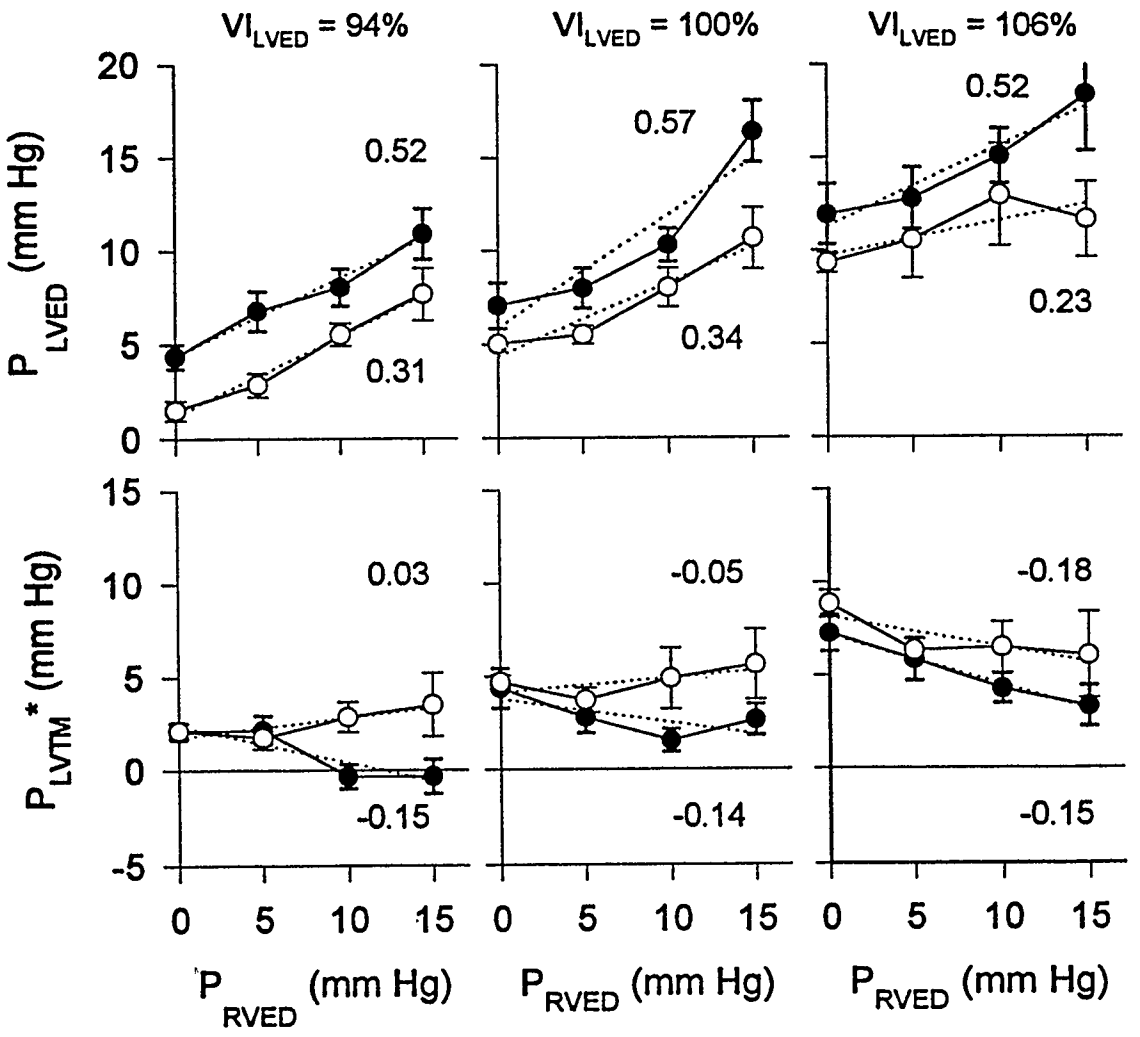

Figure 5.5: RV-to-LV End-Diastolic Pressure Gain Plots

This figure illustrates RV-to-LV pressure gain plots at VI_{LVED}s of 94, 100, and 106%. *Top panel*: With the pericardium closed (closed circles), RV-to LV pressure gains indicated the sum of the pericardial and septal effects and were similar (0.52 - 0.57). The opening of the pericardium (open circles) resulted in a statistically significant reduction in the pressure gain ($p<0.05$) indicating the remaining septal effects. *Bottom panel*: When the septal effect was eliminated[35], the RV-to-LV pressure gains were zero as expected. There was no statistical difference between the P_{LVTM}* curves with the pericardium closed or open.

Chapter 6: Discussion

6.1) Introduction

Understanding the interplay between the direct and series components of ventricular interaction has been limited by the inability to control each component independently. In this study our right-heart bypass model allowed us to manipulate the series and direct components independently and, thus, we were able to demonstrate predictable and quantitative relationships between the two mechanisms. As P_{RVED} was increased, more VR_{LV} was required to maintain the same LV volume and, at the same degree of external constraint (P_{RVED} held constant), a greater increase in VR_{LV} was required to increase the LV volume index from 100 to 106% than from 94 to 100%. Also, by opening and closing the pericardium, we were able to discriminate between the pericardial and the septal contributions to direct ventricular interaction. Shifts in these curves when P_{RVED} was increased reflect the results of changes in direct interaction. The difference in these relations with the pericardium closed and opened, reflect the combined contributions of the pericardium plus septum versus the contributions of the septum alone.

6.2) Series vs Direct Interaction

The effects of altering series and direct components of ventricular interaction are clearly illustrated by the LV end-diastolic pressure volume curves ($(P\text{-}VI)_{LVED}$, Fig 5.1) when these components were altered independently. As shown in panel a, when VR_{LV} was increased (while holding P_{RVED} constant), P_{LVED} and VI_{LVED} both increased monotonically along a single curve, reflecting changes in series interaction. When P_{RVED} was increased incrementally, the $(P\text{-}VI)_{LVED}$ curves shifted upward and to the left, reflecting increased direct interaction. Thus, the position along a given $(P\text{-}VI)_{LVED}$ curve is determined by series interaction (ie, an increase in VR_{LV} resulted in an increase in LV end-diastolic volume) and the upward and leftward shifts in these curves are caused by increasing DVI. Constraint to LV filling may be due to increased pericardial or RV pressure. As P_{RVED} is increased, the reduced transseptal gradient causes the septum to shift leftward and, since transmural P_{RVED} is small, pericardial pressure also increases; this results in increased constraint to LV filling around the whole ventricle. As constraint to LV filling increases (ie, increased P_{RVED} and P_{PER}), intracavitary P_{LVED} must increase to maintain the same end-diastolic volume (ie, to maintain the same transmural pressure). This requires increased VR_{LV} as illustrated in Fig 5.2 in which the points on each curve have been sorted according to stroke volumes (VR_{LV}/beat). In order to maintain a given VI_{LVED}, as P_{RVED} was increased, VR_{LV} also had to increase. For an example, at an end-

diastolic volume index of 88%, VR_{LV}/beat increased from 10 - 20 ml/beat at a P_{RVED} of 0 and 5 mm Hg to 30 - 40 ml/beat at P_{RVED} of 10 to 50 - 60 ml/beat at a P_{RVED} of 15 illustrating the potential substantial negative effects of increasing direct interaction. To determine the relationship between VR_{LV} and different degrees of external constraint, we calculated the required VR_{LV} to maintain representative small, normal, and increased LV end-diastolic areas at different P_{RVED}s. To illustrate the importance of this interaction, to maintain a normal (Fig 5.3, VI_{LVED} = 100%) LV end-diastolic volume when P_{RVED} was increased from 0 to 15 mm Hg, VR_{LV} had to be doubled (the shifts in the curves were statistically significant). This demonstrates the antagonism of the series and direct mechanisms of ventricular interaction in that, as P_{RVED} is increased, more VR_{LV} is required to maintain the same LV volume index. Also, a greater change in VR_{LV} was required to change the LV volume index from 100 to 106% than from 94 to 100%, as reflected by statistically significantly steeper curves from 100 to 106%. This shows the effect of the curvilinear end-diastolic pressure-volume relation in that, at the same degree of external constraint, a greater increase in VR_{LV} was required to increase the VI_{LVED} from 100 to 106% than from 94 to 100%. Thus, the series and direct components of ventricular interaction can be assessed relative to each other in this model and our data quantify these interactions, in support of the generally accepted conceptual framework of ventricular interaction.

6.3) Pericardial and Septal Contributions to Direct Interaction

The end-diastolic pressure-volume curves with the pericardium closed versus opened clearly show that, while there is less interaction with the pericardium open, some direct interaction is still present. As proposed previously by Mirsky and Rankin,[35] the effective external pressure of the LV is a function of RV pressure and pericardial pressure, each weighted according to the respective surface areas over which they apply. Since the LV free wall constitutes approximately 2/3 of the LV surface and the interventricular septum 1/3, the effective external pressure equals $2/3(P_{PER}) + 1/3 (P_{RVED})$. Our data support this algorithm. With the pericardium opened, P_{LVTM} curves (Fig 5.4) demonstrated leftward and upward shifts at P_{RVED} of 5, 10, and 15 mm Hg that were less than those seen in $(P\text{-}VI)_{LVED}$ (Fig 5.1) but still substantial. However, when the RV contribution was accounted for all the points fell on the same curve. With the pericardium closed, P_{LVTM}-VI_{LVED} curves demonstrated little or no shift (Fig 5.2, panel b) and the remaining shift was not consistently reduced by calculating P_{LVTM}* (Fig 5.2, panel c). This is consistent with the fact that, when the pericardium was closed, RV and pericardial pressures were similar, as has been shown before.[3,52,53,62] These data strongly suggest that, when P_{RVED} and P_{PER} are different, both should be considered when calculating LV transmural pressure.

Others have reported that opening the pericardium substantially reduces DVI and that, with the pericardium opened, septal-mediated DVI is remains. Little et al[31] examined the effect of P_{RVED} on LV end-diastolic pressure-volume curves before and after chronic RV pressure overload in dogs with the pericardium opened. In normal dogs, caval occlusion promptly decreased P_{RVED} and increased the end-diastolic LV septal-lateral dimension and release of the occlusion had the opposite effect. Pulmonary-artery constriction increased P_{RVED} and decreased LV septal-lateral dimensions. Even in the absence of the pericardium, it was demonstrated that alterations in P_{RVED} have a significant effect on the LV end-diastolic pressure-volume curve. Glantz et al[17] demonstrated that the pericardium had a substantial effect on P_{RVED} at normal diastolic LV pressures. Using open-chest dogs with the pericardium closed and opened, they varied diastolic pressures by infusing or withdrawing blood or by pulmonary-artery constriction. They demonstrated that P_{RVED} was the most important determinant of P_{LVED} (more important than LV dimensions) with the pericardium closed. After opening the pericardium, the effect of RV pressure was reduced but still significant. Kieser et al,[24] in a preliminary report of patients undergoing open-heart surgery, calculated the difference between pulmonary capillary wedge and central venous pressures as an estimate of LV preload, before and after pericardectomy. Their results suggest that substantial LV constraint may be present even after pericardectomy, presumably due to the remaining constraint of the pericardium and mediastinal structures and the

open-but-unexpanded chest. These data all suggest that there may be substantial septum-mediated DVI with the pericardium removed and further, that both external pressures acting on the LV (P_{PER} and P_{RVED}) should be considered when evaluating DVI, especially when there is cause to suspect that P_{PER} is different from P_{RVED}.

6.4) RV-to-LV End-Diastolic Pressure Gain

End-diastolic pressure "gain" is the ratio of the change in the end-diastolic pressure in one ventricle produced by change in the pressure in the other ventricle (ΔP_{LVED} vs ΔP_{RVED}). With the pericardium on, RV-to-LV pressure gain was approximately 0.5 at 3 representative LV end-diastolic volumes indicating the sum of the pericardial and septal effects (Fig 5.5, top panel, solid symbols). After the pericardium was opened, the gain decreased to approximately 0.3 but was still clearly present. As indicated earlier, the remaining gain represents the residual direct interaction due to the shared septum. Thus, when the septal effect was theoretically eliminated (calculated by subtracting 1/3 of the value of P_{RVED} from P_{LVED}, [35]), RV-to-LV pressure gains became zero as expected (bottom panel). Thus, the results from our study indicate strong coupling between the pericardium and the ventricles, and also suggest that the septum exerts a degree of coupling in the absence of the pericardium.

Calculated RV-to-LV interaction gains from several studies also demonstrate strong coupling between the ventricles and have shown that this interaction is strengthened with the pericardium closed (Table 6.1). Despite widely differing techniques and experimental models, there is substantial agreement between these studies and our results.

6.5) The "Natural" End-Diastolic Pressure-Volume Curve

We have demonstrated that each $(P\text{-}VI)_{LVED}$ curve generated using our protocol represents series interaction and the shifts between the curves represent direct interaction. Under normal physiological conditions, however, both the series and direct mechanism operate simultaneously. For example, volume loading simultaneously increases both cardiac output (VR_{LV}) and LV constraint (P_{RVED} and P_{PER}). Thus, the "natural" end-diastolic pressure-volume curve described during volume loading represents a composite of these curves reflecting simultaneous alterations in both mechanism. Boettcher et al[7] defined such a curve in the intact dog (Figure 6.1). Compared to the curves defined in this model, the pressure-volume curve defined in their study is very steep (in their study, volume loading doubled heart rate while end-diastolic diameter and stroke volume did not change). This is consistent with the concepts that the steepness of the curve described during volume loading in an intact animal reflects a simultaneous increase in both the series and direct effects. In

addition, in the intact animal the curve becomes even steeper because the tachycardia induced by volume loading tends to decrease end-diastolic volume.

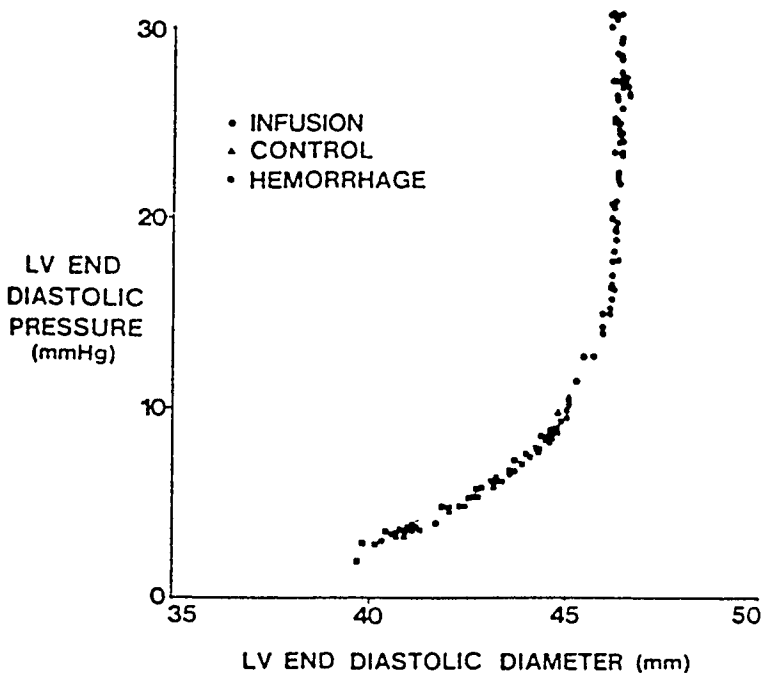

Figure 6.1: End-Diastolic Pressure-Diameter Curve In An Intact Dog

This figure represents an LV end-diastolic pressure-diameter curve in an intact dog. P_{LVED} and diameter decreased with hemorrhage (squares) and returned to the same control level with reinfusion (triangles). With subsequent volume infusion (circles) P_{LVED} increased substantially while LV end-diastolic diameter was essentially unchanged. (from Boettcher et al[7])

Table 6.1: RV-to-LV Pressure Gains

Author	PER +	PER -
Bemis et al[6]	0.45	
Dauterman et al [11]	0.53 - 0.62	
Janicki & Weber[21]	0.26	0.13
Glantz et al[17]	0.97	0.47
Little et al[31]		0.43 - 0.47
Maruyama et al[32]	0.38 - 0.44	0.28
Santamore et al[43]		0.14
Slinker et al[50]	0.23 - 0.32	
Mean	0.47	0.32
Baker et al	0.52 - 0.57	0.23 - 0.34

PER +, pericardium closed; PER -, pericardium opened.

Chapter 7: Conclusions

7.1) Evaluation of the Method

Three different types of approaches have been used to study ventricular interaction. Because of the difficulty in separating the direct and series components, one approach has been to eliminate the series contribution to ventricular interaction by using isolated[13,17,33,45] or arrested hearts,[40,58] in which the ventricles were no longer coupled in series. The contributions of direct versus series interaction were evaluated as the pressure or volume in one ventricle was held constant while the pressure-volume relation of the other ventricle was determined. These models allowed for precise control of the ventricular pressures and volumes but were not physiologic because the hearts were removed from the circulatory system and often were arrested. A second approach has been a statistical one involving analysis of beat-to-beat changes over a number of cycles in response to manipulations such as caval occlusion or pulmonary artery constriction.[8,50] This approach did not allow the direct description of ventricular pressure-volume relations. Using a third approach, Slinker et al[50] have studied ventricular interaction in a dog model in which they separated direct from series interaction by occluding both venae cavae while simultaneously withdrawing blood from the RV and analysing the change in P_{LVED} on the next beat. However, they did not have independent control of

ventricular volume and, with the pericardium opened, they were unable to remove volume fast enough to decrease P_{RVED} substantially.

Our method allowed us to separate and control independently the series and direct mechanisms of ventricular interaction in the beating heart in an in situ system and study these interactions over a wide range of ventricular pressures and volumes. This model also allowed us to collect data with the pericardium closed and open; thus, we were able to quantitate the pericardial and septal contributions to direct ventricular interaction.

Clearly, this model only describes the results of acute hemodynamic changes. The results cannot be assumed to reflect what might occur in chronic disease states. Under such conditions the pericardium may expand[15] and increases its unstressed volume; other changes also occur such as chamber size and wall thickness. It should also be noted that RV pressure was not consistent throughout diastole; although it was accurately maintained at 0, 5, 10, and 15 mm Hg at end-diastole, it was lower during early diastole. Finally, the RV was not loaded physiologically. The pulmonic outflow tract was obstructed and a variable degree of tricuspid incompetence was caused by the cannula.

7.2) Conclusions

In summary, we have devised a right-heart bypass model in which series and direct interaction can be independently controlled. We demonstrated that the position of each $(P\text{-}VI)_{LVED}$ curve reflects direct interaction and the position along each constant-P_{RVED} curve is a function of series interaction. LV end-diastolic volume is augmented by VR_{LV} and diminished by pericardium and septum-mediated constraint. At a given LV end-diastolic volume, more VR_{LV} is required to offset increasing external constraint. Further, as the LV enlarges, for each level of external constraint, increasingly more VR_{LV} is required to increase LV end-diastolic volume. Also, the pericardium has a significant effect on direct ventricular interaction in this model. Opening of the pericardium resulted in a reduced but still significant RV-to-LV gain. After accounting for P_{RVED}, the gain was reduced to zero. This suggests that the residual DVI observed after the pericardium was opened was septum-mediated.

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