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Inertia-Driven Mitral and Aortic Valves: The Isovolumic Myth

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ABSTRACT

Background: For the past century, the Wiggers Diagram has been universally taught as defining the phases of the cardiac cycle. However, the concepts underlying this diagram have never been fully and directly tested on intact, beating hearts.

Methods: In vivo datasets from sheep recorded left ventricular and aortic pressures and flows along with simultaneous 4-D coordinates of 30 miniature strategically placed radiopaque markers. This allowed hemodynamic synchronization with tracking of key anatomical landmarks every 16.7 msec to test Wiggers' concepts.

Results: The Wiggers Diagram is not supported as there were no consistent isovolumic periods; the mitral valve closed anywhere during the rising phase of left ventricular pressure, and aortic valve closure and mitral valve opening were *simultaneous* at the end of the systolic pressure drop.

Conclusions: The Wiggers Diagram describes valve opening and closing solely in terms of pressure differences which can be transmitted almost instantaneously through incompressible blood in the ventricle. However, pressure differences do not open and close the valves; *it is inertial flow through the valves.* The present study redefines the description of the interaction between the left ventricle and its valves and shows that the periods of isovolumic contraction and relaxation are mythical concepts.

Introduction

In his landmark paper, published a century ago, Dr. Carl Wiggers proposed what became the standard definition of the eight phases of the cardiac cycle, encapsulated in the classic, universally-taught Wiggers Diagram[1].

During the first phase, Wiggers suggested that "*At the beginning of ventricular systole, the a-v valves have been partly floated into apposition, probably in consequence of the sudden cessation of a jet when the peak of the intra-auricular pressure curve is reached about the middle of auricular systole. The first elevation of intraventricular pressure firmly closes these valves…*" During the second phase he proposed that "*As soon as intraventricular exceed intra-aortic pressure the semilunar valves open and a comparatively large volume of blood is ejected.*" During the fourth phase, he proposed that the cusps of the aortic valve floated toward a position of closure as systole waned, and "*not until such closure has been effected, however, does a steep decline of intraventricular pressure, such as one might logically associate with a relaxation process in muscle take place.*" For the fifth phase, he wrote "*following closure of the semilunar valves and until the a-v valves have opened, the ventricle relaxes without any flow of blood either from or into its cavity*" and that "*the time interval existing between the complete closure of the semilunar valves and the opening of the a-v valves represents the isometric relaxation phase.*"

These proposals were based on Wiggers' years of careful pressure measurements in beating hearts, but while his interpretations above required validation with studies of leaflet and cusp positions and ventricular flows, he did not have access to such direct measurements. His proposals were thus important, sophisticated conjectures that could not be fully tested at that time and, indeed, although presently universally taught, have never been fully and directly tested in intact, beating hearts.

In the present study we directly test these conjectures utilizing datasets obtained from the beating hearts of closed-chest sheep. In these experiments, high frequency sampling of left ventricular and aortic pressures was recorded along with the simultaneous 4-D coordinates of 30 miniature radiopaque markers. The markers were arrayed to silhouette the left ventricle and track key specific anatomical landmarks of both the aortic and mitral valves, including the leaflets and cusps, every 16.7 msec. This method has been used extensively in prior, widely cited publications[2-15], as well as more detailed assessments in the book "Mitral Valve Mechanics" [16]. Our analysis of these data allows simultaneous measurement of the instantaneous relationships between pressures, motions, and flows in the relevant regions and thereby directly test the validity of Wiggers' widely taught concepts. Our present findings do not support these concepts.

Methods

This study reports the findings of our current analysis of datasets arising from experiments in ovine subjects that were approved by the Stanford Medical Center Laboratory Research Animal Review Committee, accredited by the Association for Assessment and Accreditation of Laboratory Animal Care International, and conducted according to Stanford University Policy. The methods involved are described in detail in publications arising from this work[2,3], as well as a freely downloadable book describing in detail the mechanics of the mitral valve[16], and thus will only be summarized here.

Eight sheep had surgical implantation of thirty miniature radiopaque tantalum markers at the locations shown in Figure 1. Three sub-epicardial markers were placed around the left ventricular equator at anterior (#3), lateral (#4), and posterior (#5) sites. An additional sub-epicardial marker was placed at the left ventricular apex (#1), alongside an indwelling Konigsberg high frequency micro-manometer to measure left ventricular pressure.

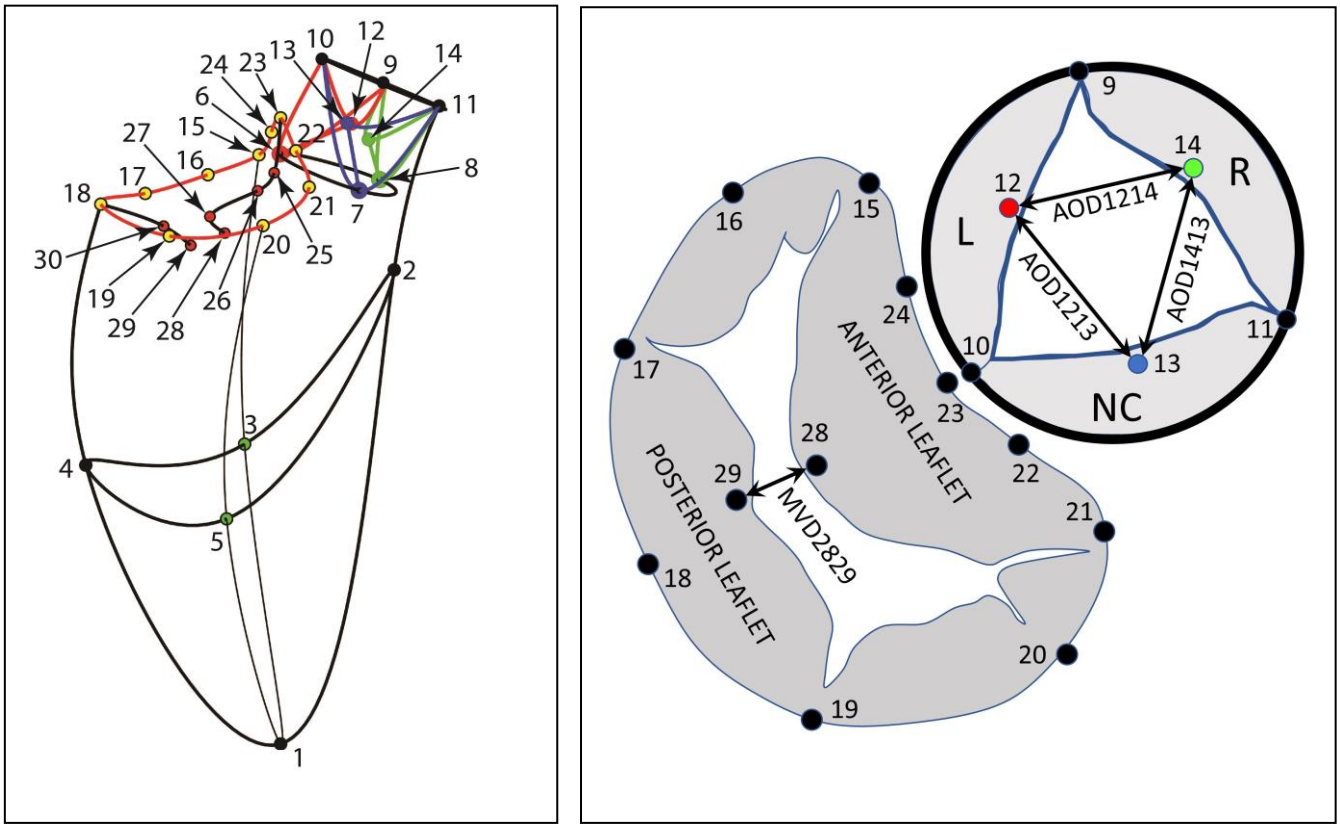

Figure 1: Mitral valve annulus marker placement: Left Panel: Implantation sites for the 30 radiopaque markers employed in this study. See text for anatomical locations. Right Panel: Enlarged schematic showing mitral and aortic valve marker locations.

On cardiopulmonary bypass, through a left atriotomy, a ventricular marker was placed at the high left ventricular septum (#2) and ten markers sutured to the mitral annulus at the aorto-mitral "saddlehorn" junction (#23), left fibrous trigone (#15), anterior commissure (#16), lateral annulus (#18), posterior commissure (#20), right fibrous trigone (#21), and sites in-between (#17, #19). Markers were also sutured to the central meridians of the anterior (#23, #25-28) and posterior (P2, #29, #30) leaflets of the mitral valve. These miniature markers do not affect leaflet motions; we have shown that loading the leaflets with even ten times the number of the markers used in this study does not alter maximum leaflet opening velocities[17].

Nine markers were sutured to the aortic valve apparatus *via* a transverse aortotomy 5 mm above the top of the aortic commissures; three at the nadir of the belly of each cusp on the annulus (Left #6 (coded red in the present paper) , Right #8 (green), and Non-Coronary #7 (NC, blue)); three at the top of each commissure NC(blue) to Left (red) #10; Left (red) to Right (green), #9; and NC (blue) to Right (green), #11); and three at the central edges of the cusps Left #12 (red), Right #14 (green), and NC #13 (blue).

After closing the atriotomy and aortotomy, the animals were weaned off cardiopulmonary bypass, the micro-manometer leads exteriorized, and the animal recovered in the animal cardiac surgical intensive care unit.

In Figure 1, the mitral valve annulus markers (#15-24) along with central anterior leaflet A2 (#28) and posterior leaflet P2 (#29) edge markers and the distance between these pair of markers (MVD2829) are shown. Also shown are three aortic valve markers located on the Left Cusp (L,#12, red), Right Cusp (R,#14, green), and Non-Coronary Cusp (NC,#13, blue) and at the top of each commissure NC to L, #10; L to R, #9; and NC to R, #11; along with the distances between the aortic cusp marker pairs (AOD1213, AOD1214, AOD1413).

One week later, the animals were taken to the cardiac catheterization laboratory where simultaneous biplane videofluoroscopic and hemodynamic data (including aortic pressure just distal to the aortic valve) were acquired at end-expiration with the hearts in normal sinus rhythm. Figure 2 shows an example of biplane videofluoroscopic data from a sheep heart.

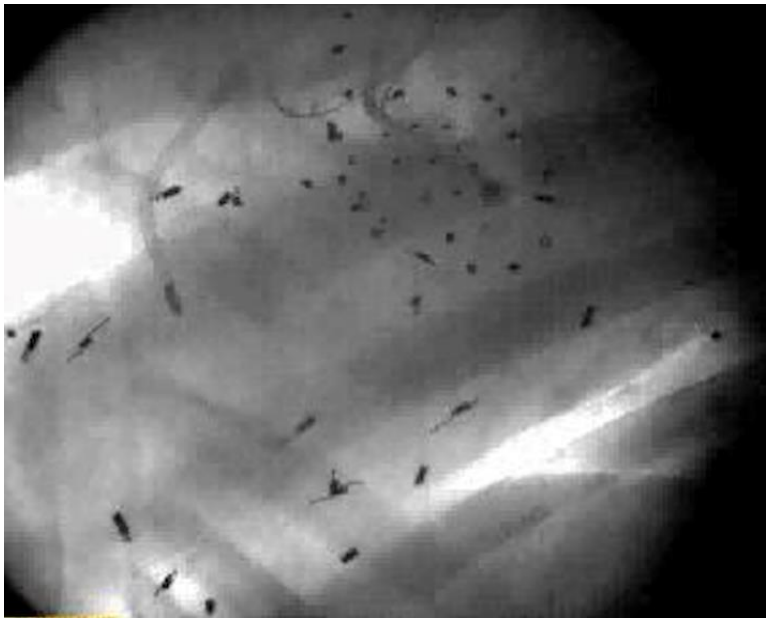

Figure 2: X-ray image showing Tantalum markers in a beating sheep heart. *This picture shows an example of biplane videofluoroscopic data from a sheep heart displaying one frame from a stereo x-ray pair used to measure the 3D coordinates of the markers every 16.7msec.*

At the end of the experiment, aortic root angiography was used to confirm aortic valve competence. The present report analyzes data from the five technically successful runs from this experiment.

Data Analysis

The 4-D coordinates of all 30 markers were reconstructed using biplane videofluorography with a spatial resolution of 0.1 mm[18] and temporal resolution of 16.7 msec (60 frames/sec) for three consecutive beats in each heart.

Left ventricular instantaneous inflow and outflow was estimated by a multiple tetrahedral space-filling approach that yields changes in left ventricular volume (V) at each frame (f) (*i.e.* flow into and out of the left ventricular chamber) as previously validated with aortic ultrasonic flowmeters[19]. Left ventricular flow, *i.e.*, left ventricular volume change ΔV (mL) at each frame (f), was computed using a second order centered finite difference method.

Distances between marker pairs were computed from the norm of the 3D vector constructed between them.

Results

Figure 3 graphically displays the results from a representative heart. These data, along with frame-by-frame analysis of the computer animations, were used to characterize each of the three beats analyzed in each of the five hearts, 15 beats in all.

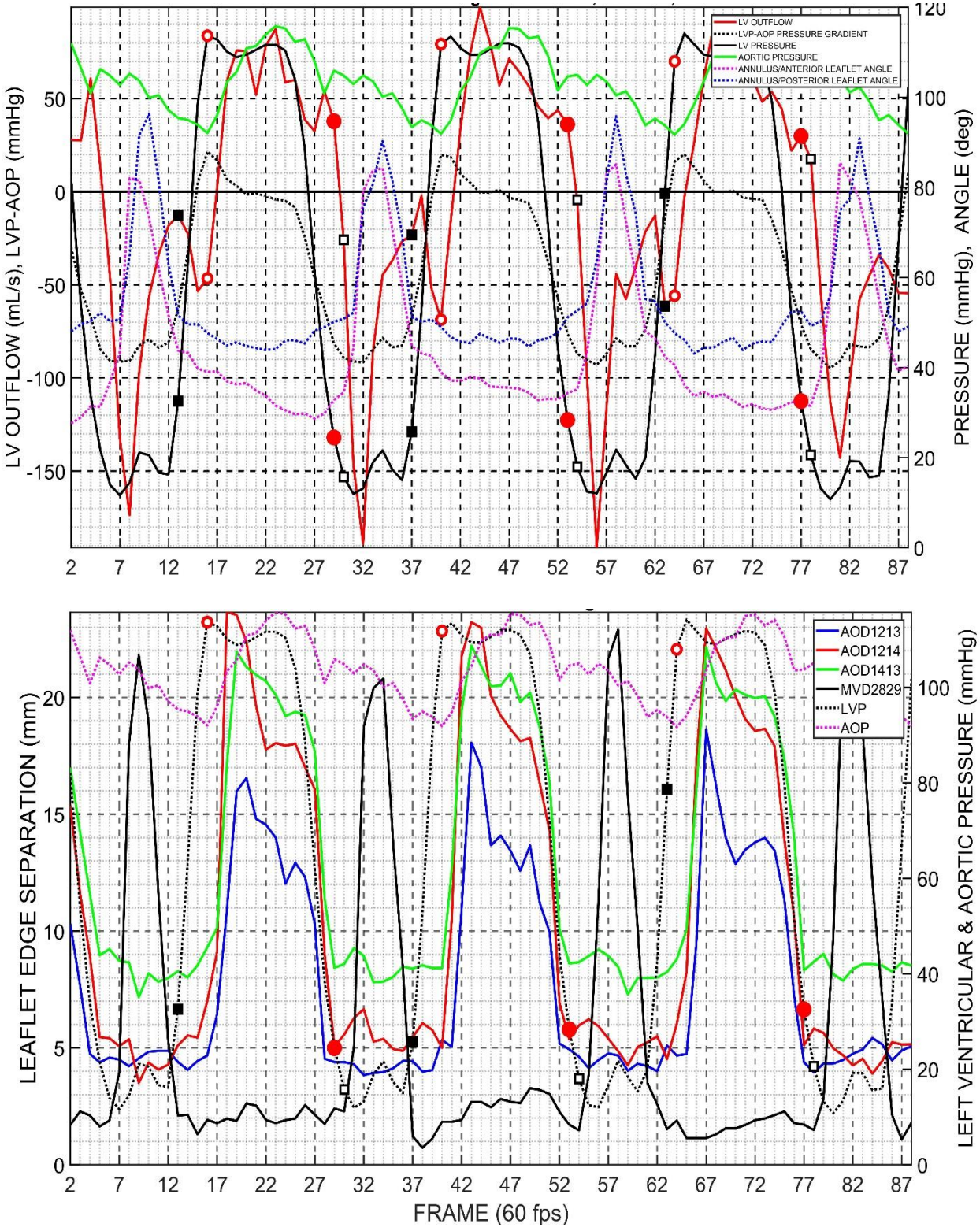

Figure 3: Data from a representative heart in this study. *Black squares, mitral valve. Red circles, aortic valve. Open symbols, initiation of valve opening. Closed symbols, time of valve closure. Top Panel shows left ventricular pressure (LVP), aortic pressure (AOP), left ventricular flow (positive, outflow; negative, inflow), LV-Aortic pressure difference (LVP-AOP), annulus/anterior mitral leaflet angle, annulus/posterior mitral leaflet angle. Bottom Panel shows left ventricular pressure, aortic pressure, distance between mitral valve markers on the anterior and posterior cusp edges, distance between aortic valve markers on the Left-Non Coronary) cusps, Left-Right cusps, Right-NC cusps.*

In Figure 3 top panel, the left ventricular pressure (LVP) is solid black line. Aortic pressure (AOP), solid green line. Left ventricular flow (positive, outflow; negative, inflow), solid red line. LV-Aortic pressure difference (LVP-AOP), dotted black line. Annulus/Anterior mitral leaflet angle (18-23-28), dotted magenta line. Annulus/Posterior mitral leaflet angle (23-18-29), dotted blue line. In the bottom panel, Left ventricular pressure, dotted black line. Aortic pressure, dotted magenta line. Distance between mitral valve markers on the anterior and posterior cusp edges (MVD2829), solid black line. Distance between aortic valve markers on the Left-NC (Non Coronary) cusps (AOD1213), solid blue line; Left-Right cusps (AOD1214), solid red line; Right-NC cusps (AOD1413), solid green line.

The Group mean maximum left ventricular pressure was 118 ± 7 mmHg (range 109-129) and minimum left ventricular pressure was 11 ± 5 mmHg, (range 3-15 mmHg), both normal values. Mean heart rate was 142 ± 15 beats/minute, (range 124-161), roughly twice the normal resting rate for sheep, but not unusual in this experimental setting. Stroke volumes were 11 ± 2 mL (range 9-14 mL) and cardiac output was 1.8 ± 0.2 L/min (range 1.5-2.0 L/min) both low values, but typical for those recorded under these experimental conditions.

An important finding in this study is that the aortic valve closed in all 15 beats at low left ventricular pressures (group mean LVP 28 ± 6 mmHg; range 18 to 35 mmHg) in the last third of the "isovolumic relaxation" (IVR) interval and that *there was no statistically significant difference between the time the aortic valve closed and the initiation of mitral valve opening* (group mean 10±19 msec; range 17 to +33 msec; p=0.06 NS from 0). In the 12 beats where LV inflow and outflow could be computed, the final closure of the aortic valve occurred immediately before rapid left ventricular flow deceleration during IVR. Group mean flow at the time of aortic valve closure was 0.4±23 mL/sec, ranging from -28 to +38 mL/sec, with mean flow at valve closure being about one-fifth of the maximum systolic outflow during the associated systole (mean 19±15%; range 0 to 43%).

Statistically, for the group, the mitral valve closed (MC) before the aortic valve started opening (ASO) during so-called "isovolumic contraction", IVC (ASO-MC interval 29 ± 34 msec, p=0.005 from 0) at a group mean left ventricular pressure of 59 ± 41 mmHg (range 8-109 mmHg). But differences in individual hearts were more revealing than this lumped statistical behavior. Final mitral closure occurred in 8 of the beats analyzed during the first third of IVC (supporting the traditional view of mitral closure, as in Figure 2), 1 beat closed in the middle third, but *6 beats exhibited mitral closure in the last third of IVC at left ventricular pressures exceeding 100 mmHg. In 4 of these 6 beats, both the mitral and aortic valves were open at the same time and in 3 the aortic valve was opening before the mitral valve had closed.* At the time of mitral valve closure, group mean left ventricular outflow had ceased (0.00 ± 0.51 mL/frame, range -1.02 to +0.75 mL/frame) then quickly reversed with a group mean initial inflow at the initiation of aortic valve opening of -0.31 ± 0.71 mL/frame (range -1.3 to 0.71).

From initiation of closing to fully closed required 37 ± 36 msec (range 0-100 msec) for the mitral valve and 66 ± 18 msec (range 50-100 msec) for the aortic valve. From initiation of opening to fully opened required 57 ± 8 msec (range 50-67 msec) for the mitral valve and 60 ± 15 msec (range 50-100 msec) for the aortic valve.

Discussion

For more than a century, the periods of "isovolumic contraction" (IVC) and "isovolumic relaxation" (IVR) have been defined based on presumed (not measured) valve opening and closing times. The present study demonstrates, for the first time, by direct, high-resolution, simultaneous temporal and spatial measurements of aortic and mitral valve opening and closing in relation to instantaneous left ventricular pressures and volumes, that these IVC and IVR periods are not consistently isovolumic,

as left ventricular volume changes were observed throughout these periods. In this paper we will continue to use the terms IVC and IVR, however, in deference to their historic role as a shorthand notation for the periods of rapidly increasing left ventricular pressure (IVC) and rapidly decreasing pressure (IVR) but recognize that these terms must be eventually dissociated from their role as acronyms for these misleading phrases.

Wiggers' postulate that the first elevation of intraventricular pressure firmly closes the mitral valve is not supported by the present results. Mitral valve closing was observed everywhere along the rising left ventricular pressure curve, from pressure elevation onset all the way up to peak systolic pressure.

Wiggers' proposal that "*As soon as intraventricular exceed intra-aortic pressure the semilunar valves open and a comparatively large volume of blood is ejected*" is somewhat supported by this work, but the valve was not fully open at this time, it was just starting to open and, due to the inertial lag in blood flow after pressure difference reversal, the aortic cusps didn't fully open for another 60 msec after this pressure crossover, with the result that the "comparatively large volume of blood" is actually ejected well after aortic valve opening, closer to mid-systole.

Wiggers' suggestion that the steep decline of intraventricular pressure during isovolumic relaxation is preceded by closure of the aortic valve is not supported by the present results. The steep decline of intraventricular pressure in these hearts *always* took place before the aortic valve closed, with aortic valve closure always occurring in the final third of the LV pressure drop in all beats studied, in direct contradiction to this concept.

Wiggers' statements "*…following closure of the semilunar valves and until the a-v valves have opened, the ventricle relaxes without any flow of blood either from or into its cavity*" and "*the time interval existing between the complete closure of the semilunar valves and the opening of the a-v valves represents the isometric relaxation phase*" are in conflict with the results of the present analysis in two ways: (1) in these hearts there was *no interval between closure of the aortic valve and opening of the mitral valve* during isovolumic relaxation; and (2) a considerable outflow of blood occurred throughout isovolumic relaxation, with flow being, on average, 0.94 mL/frame when the aortic valve just begins its closing motion as left ventricular pressure starts to fall, and continuing outflow of 0.07 mL/frame when the aortic valve finally sealed shut.

Why are the results of this study, particularly those having to do with isovolumic periods and valve closures, so incompatible with current textbook views of how the left ventricle interacts with the mitral and aortic valves? The problem is that the textbooks describe valve opening and closing solely in terms of pressure difference (*i.e.*, only the left side of Newton's Second Law, (*F=ma*), but pressure differences across the valves do not open and close the valves; *it is flow through the valves*. Discussing valve performance only in terms of pressure difference neglects *the inertia of the mass of the flowing blood,* and pressure differences (which can be transmitted almost instantaneously through the ventricle due to blood's incompressibility) lead to flows that are governed not only by these pressure differences, but, very importantly, by *inertial mass*. This problem has long been known. More than 30 years ago Beyar and Sideman wrote "*…to determine the opening of the aortic valve and the termination of isovolumetric contraction one must also consider the kinetic energy (dynamic pressure) and the acceleration term (associated with Newton's Second Law).*"[20] More recently, Pasipoularides wrote "*Central pulsatile blood flows are… dominated by inertial effects and almost all the driving phasic pressure gradient goes into acceleration or deceleration, i.e., into overcoming blood inertia.*"[21] and Jensen, et al. demonstrated the inertial effects associated with the closing of isolated porcine mitral valves.[22] Detailed leaflet tracking has only been analyzed more recently with medical imaging modalities [23-25],

whereas simultaneous tracking of mitral and aortic valve leaflets with untethered miniature markers in beating hearts has not been analyzed until now. To the best of our knowledge, this is the first study where aortic cusp positions, mitral valve leaflet positions, and left ventricular pressures and volumes could all be measured simultaneously and directly in the beating heart to reveal the impact of inertial blood flow on the aortic cusps and mitral valve leaflets throughout the cardiac cycle.

The present study makes clear that understanding the left ventricle as a pump is going to require understanding the importance of inertial mass in the movement of the blood through its chambers. As noted in Results, 6 of the 15 beats analyzed exhibited mitral closure in the last third of IVC at left ventricular pressures exceeding 100 mmHg. *In 4 of these 6 beats, both the mitral and aortic valves were open at the same time and in 3 the aortic valve actually opened before the mitral valve closed.* This can only happen through inertial effects. Depending on the temporal relationship between left atrial and left ventricular force development, A-wave-driven left ventricular inflow drives mitral valve leaflet opening while, simultaneously, LV-driven outflow drives aortic cusp opening. Thus, for a very brief moment, an inertially-supported flow condition can exist allowing *both valves to be open at the same time.* This moment lasts no more than about 33 msec when left ventricular blood flow patterns adjust, in accordance with Newton's Second Law, to turn the inflow through the mitral valve into mitral regurgitation, thereby closing the mitral leaflets, while, at the same time, continuing to drive the aortic cusps further apart.

In order to put the results of the present study in context, we illustrate these concepts with the simple model shown in Figure 4.

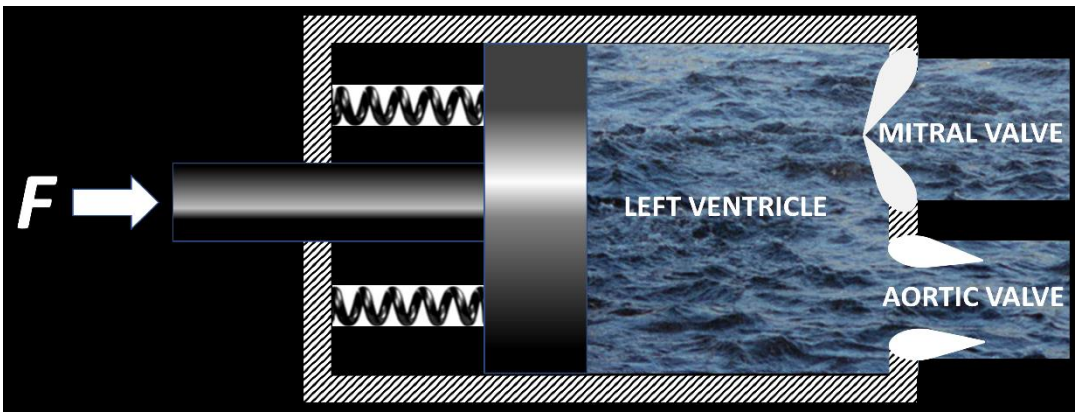

Figure 4: Simplified left heart model to illustrate the concepts of this paper. *The Left ventricular-valvular interaction modeled as a spring-loaded piston with a myocardial force (represented by F) ejecting fluid through the inertially flow-driven aortic valve during systole and a reverse force resulting from energy stored in myocardial springs during systole enhancing inflow through the inertially flow-driven mitral valve during diastole. See discussion in text.*

The force balance in the left ventricle in conjunction with tissue structure motion has been described extensively by our group and others[24,26-29]. The left ventricle is represented as a fluid-filled chamber driven by a force (represented by F in Figure 4) applied to a spring-loaded piston. At the instant shown, mid-systole, the mitral valve is closed, and fluid is flowing out of the open aortic valve as the piston moves to the right. The force developed by the ventricular myocytes has risen to its maximum at this time, about 100 msec after the onset of the left ventricular pressure rise for this beat, with a similar rise-time as that measured by Holmes *et al.* in isolated rabbit ventricular papillary muscle at 37°C[30] and Askov *et al.* in the papillary muscles of beating porcine hearts[26]. The myocytes are not delivering their maximum isometric force at this instant, because the force they develop falls off

dramatically with their shortening velocity during ejection in accordance with their characteristic force-velocity relationship. The total force they are applying to the fluid at this instant can be estimated as 157 N by applying the fact that pressure is force per unit area, peak left ventricular pressure is 118 mmHg, and left ventricular internal area is about 100 cm^2.

Myocyte force wanes after this peak, finally falling to near-zero in the next 100 msec, at which time left ventricular pressure starts to fall. But, due to its inertia, fluid flow through the aortic valve does not cease for another 80 msec. At this instant, when left ventricular volume is barely changing and the very small left ventricular outflow is reversing to a very small inflow, the aortic valve shuts and, virtually at the same moment, the mitral valve starts to open. Aortic valve closure is thus a very gentle action at low flows, rather than an abrupt "water hammer" that would occur if it took place at large flows just as left ventricular pressure began its downward descent.

At the moment the aortic valve closes (and the mitral valve opens) the myocytes themselves are not developing much force, but the billions of elastic springs between the myocytes are maximally stretched and their pull creates a reverse force that finally overcomes the residual myocyte contractile force and applies a large negative force on the piston, pulling it leftward and thereby accelerating the flow of blood into the left ventricular chamber through the opening mitral valve. This is the well-known left ventricular suction that has been demonstrated during diastole in isolated hearts [31], intact hearts by using a mechanical device to abruptly shut the mitral valve[32], or a servomechanism to clamp left atrial pressure to zero[33,34]. This large negative force assists the relatively small left atrial driving pressure to create the characteristically rapid left ventricular inflow through the mitral valve during early diastole known as the E-wave. Left ventricular suction is vital to allow rapid left ventricular filling by sucking blood into the chamber rather than relying solely on left atrial pressure to force blood into the ventricle. If ventricular suction is lost, filling must be accomplished only by left atrial pressure, which rises to meet the demand, but this rise increases pressures across the delicate gas-exchange membranes of the lungs, causing them to leak fluid into the air spaces in the lungs, lose their gas-exchange ability, and initiate the drowning known as congestive heart failure.

Elastic restoring forces decline rapidly after this initial surge, as diastolic wall thinning accompanying ventricular filling reduces the inter-myocyte distance, thereby shortening the inter-myocyte springs, with a resulting diminution of left ventricular inflow as the piston is driven backwards less forcefully. Subsequent atrial contraction forces more blood into the chamber (the A-wave), without much assistance from the residual depleted energy stored in the collagen springs.

Left ventricular excitation then initiates myocyte force development, myocytes develop a force that begins to exert its action again on the piston, pushing it to the right, and left ventricular pressure starts its rapid rise (rapid because of blood's incompressibility). The instant of left ventricular pressure increase does not trigger immediate outward blood flow, because the inertia of the incoming blood continues to fill the chamber, although by an almost negligible amount at this point. As seen in 6 beats in this study, for a very brief interval, and due to inertial effects, blood may be flowing into and out of the ventricle at the same instant, with the mitral and aortic valves open at the same time. Finally, however, the rising left ventricular pressure reverses total left ventricular flow from slightly inward to slightly outward and at this moment, the mitral valve closes.

Although left ventricular pressure rises rapidly after its initial increase, once again, due to inertia, the resulting flow takes about 67 msec to begin to open the aortic valve which then requires an additional 50-67 msec for the increasing flow to open the valve to its widest position.

At this point we are back to where we started in discussing this model and the process repeats itself with each subsequent beat. Interestingly, both

diastolic and systolic flow patterns in the left ventricular chamber create a curving, momentum-preserving counterclockwise flow pattern from the mitral valve to the aortic valve, with very little mixing of the incoming and outgoing streams[35].

Conclusion

If, as taught in current courses and textbooks based on the Wiggers Diagram, pressure difference reversals controlled the valves, then valve closing would be quite abrupt. But these valves do not blast open or slam shut. Newton's Second Law describes the inertial mechanism coupling force and motion that produces a very gentle aortic and mitral valve opening and closing process during low-flow reversals. This low-stress behavior may be one reason that these left ventricular valves (as well, probably, as the tricuspid and pulmonary valves in the right heart) function so reliably for billions of uninterrupted cycles during a human lifetime. Wiggers' work was beautifully done with the technology available at the time. But now, at the 100-year anniversary of his publication, his concepts must be refined.

Conflicts of Interest Statement:

The authors have no conflicts of interest to declare.

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Author contributions:

N. Ingels, M. Karlsson, and M. Jensen, are the sole authors.

References:

1. Wiggers CJ. Studies on the consecutive phases of the cardiac cycle. I. The duration of the consecutive phases of the cardiac cycle and the criteria for their precise determination. *Am J Physiol*. 1921;56:415-438.

2. Dagum P, Green GR, Nistal FJ, et al. Deformational dynamics of the aortic root: modes and physiologic determinants. *Circulation*. Nov 9 1999;100(Suppl II):II54-II62.

3. Cheng A, Dagum P, Miller DC. Aortic root dynamics and surgery: from craft to science. *Phil Trans R Soc B*. 2007;362:1407-1419.

4. Bothe W, Kvitting JP, Swanson JC, Hartnett S, Ingels NB, Jr., Miller DC. Effects of different annuloplasty rings on anterior mitral leaflet dimensions. *J Thorac Cardiovasc Surg*. May 2010; 139(5):1114-22. doi:10.1016/j.jtcvs.2009.12.014

5. Bothe W, Rausch MK, Escobar Kvitting JP, et al. How do annuloplasty rings affect mitral annular strains in the normal beating ovine heart? 126/11_suppl_1/S231pii;10.1161/CIRCULATIONAHA.111.084046 doi. *Circulation*. 2012;126(11 Suppl 1): S231-S238.

6. Dagum P, Timek TA, Green GR, et al. Coordinate-free analysis of mitral valve dynamics in normal and ischemic hearts. *Circulation*. Nov 07 2000;102(19 Suppl 3):III62-9.

7. Glasson JR, Komeda M, Daughters GT, et al. Early systolic mitral leaflet "loitering" during acute ischemic mitral regurgitation. *J Thorac Cardiovasc Surg*. Aug 1998;116(2):193-205.

8. Goktepe S, Bothe W, Kvitting JP, et al. Anterior mitral leaflet curvature in the beating ovine heart: a case study using videofluoroscopic markers and subdivision surfaces. *BiomechModelMechanobiol*. 2009;

9. Itoh A, Krishnamurthy G, Swanson JC, et al. Active stiffening of mitral valve leaflets in the beating heart. *Am J Physiol Heart Circ Physiol*. Jun 2009; 296(6):H1766-73. doi:10.1152/ajpheart.00120.2009

10. Swanson JC, Krishnamurthy G, Itoh A, et al. Vagal nerve stimulation reduces anterior mitral valve leaflet stiffness in the beating ovine heart. S0021-9290(12)00227-8pii;10.1016/j.jbiomech.2012.04.009 doi. *J Biomech*. Jul 26 2012;45(11):2007-13. doi:10.1016/j.jbiomech.2012.04.009

11. Tibayan FA, Rodriguez F, Langer F, et al. Increases in mitral leaflet radii of curvature with chronic ischemic mitral regurgitation. *J Heart Valve Dis*. Sep 2004;13(5):772-8.

12. Timek T, Dagum P, Lai DT, et al. The role of atrial contraction in mitral valve closure. *J Heart Valve Dis*. May 2001;10(3):312-9.

13. Timek TA, Green GR, Tibayan FA, et al. Aorto-mitral annular dynamics. *Ann Thorac Surg*. Dec 2003;76(6):1944-50.

14. Timek TA, Liang D, Daughters GT, Ingels NB, Jr., Miller DC. Effect of semi-rigid or flexible mitral ring annuloplasty on anterior leaflet three-dimensional geometry. *J Heart Valve Dis*. Mar 2008;17(2):149-54.

15. Timek TA, Nielsen SL, Lai DT, et al. Mitral annular size predicts Alfieri stitch tension in mitral edge-to-edge repair. *J Heart Valve Dis*. Mar 2004; 13(2):165-73.

16. Ingels, Jr., Neil B, Karlsson M. *Mitral Valve Mechanics (https://www.diva-portal.org/smash/get/diva2:896340/FULLTEXT01.pdf)*. 2015.

17. Timek T, Glasson JR, Dagum P, et al. Ring annuloplasty prevents delayed leaflet coaptation and mitral regurgitation during acute left ventricular ischemia. *J Thorac Cardiovasc Surg*. 2000;119:774-783.

18. Niczyporuk MA, Miller DC. Automatic tracking and digitization of multiple radiopaque myocardial markers. *Computers and Biomedical Research*. 1991;24:129-142.

19. Moon MR, DeAnda A, Daughters GT, Ingels NB, Miller DC. Experimental evaluation of different chordal preservation methods during mitral valve replacement. *Ann Thorac Surg*. 1994;58:931-944.

20. Beyar R, Sideman S, eds. *Simulation and imaging of the cardiac system. Proceedings of the Henry Goldberg Workshop, held in Haifa, Israel, March 4-7, 1984*. Martinus Nijhoff Publ, The Hague; 1985.

Simulation and imaging of the cardiac system Proceedings of the Henry Goldberg Workshop, held in Haifa, Israel, March 4-7, 1984.

21. Pasipoularides A. *Heart's Vortex. Intracardiac Blood Flow Phenomena.* Peoples Medical Publishing House – USA; 2010.

22. Jensen MO, Lemmon JD, Gessaghi VC, Conrad CP, Levine RA, Yoganathan AP. Harvested porcine mitral xenograft fixation: impact on fluid dynamic performance. *J Heart Valve Dis.* Jan 2001;10(1): 111-24.

23. Jensen H, Jensen MO, Smerup MH, et al. Impact of papillary muscle relocation as adjunct procedure to mitral ring annuloplasty in functional ischemic mitral regurgitation. *Circulation.* Sep 15 2009;120(11 Suppl):S92-8. doi:10.1161/CIRCULATIONAHA.108.817833

24. Jensen MO, Hagege AA, Otsuji Y, Levine RA, Leducq Transatlantic MN. The unsaddled annulus: biomechanical culprit in mitral valve prolapse? *Circulation.* Feb 19 2013;127(7):766-8. doi:10.1161/CIRCULATIONAHA.112.000628

25. Jensen MO, Jensen H, Levine RA, et al. Saddle-shaped mitral valve annuloplasty rings improve leaflet coaptation geometry. *J Thorac Cardiovasc Surg.* Sep 2011;142(3):697-703. doi:10.1016/j.jtcvs.2011.01.022

26. Askov JB, Honge JL, Jensen MO, Nygaard H, Hasenkam JM, Nielsen SL. Significance of force transfer in mitral valve-left ventricular interaction: in vivo assessment. *J Thorac Cardiovasc Surg.* Jun 2013;145(6):1635-41.

27. Jensen MO, Jensen H, Smerup M, et al. Saddle-shaped mitral valve annuloplasty rings experience lower forces compared with flat rings. *Circulation.* Sep 30 2008;118(14 Suppl):S250-5. doi:10.1161/CIRCULATIONAHA.107.746776

28. Nielsen SL, Timek TA, Green GR, et al. Influence of anterior mitral leaflet second-order chordae tendineae on left ventricular systolic function. *Circulation.* Jul 29 2003;108(4):486-91. doi:10.1161/01.CIR.0000080504.70265.05

29. Jimenez JH, Soerensen DD, He Z, He S, Yoganathan AP. Effects of a saddle shaped annulus on mitral valve function and chordal force distribution: an in vitro study. *Annals of biomedical engineering.* Nov 2003;31(10):1171-81.

30. Holmes JW, Hunlich M, Hasenfuss G. Energetics of the Frank-Starling effect in rabbit myocardium: economy and efficiency depend on muscle length. *Am J Physiol Heart Circ Physiol.* Jul 2002;283(1):H324-30. doi:10.1152/ajpheart.00687.2001

31. Suga HY, Goto Y, Igarashi Y, Yamada O, Nozawa T, Yasumura Y. Ventricular suction under zero source pressure for filling. *Am J Physiol 251 (Heart Circ Physiol 20).* 1986:H47-H55.

32. Yellin EL, Nikolic SD, Frater RW. Left ventricular filling dynamics and diastolic function. *Prog Cardiovasc Dis.* 1990;32:247-271.

33. Ingels NB, Jr., Daughters GT, 2nd, Nikolic SD, et al. Left atrial pressure-clamp servomechanism demonstrates LV suction in canine hearts with normal mitral valves. *Am J Physiol.* Jul 1994;267(1 Pt 2):H354-62.

34. Ingels NB, Jr., Daughters GT, Nikolic SD, et al. Left ventricular diastolic suction with zero left atrial pressure in open-chest dogs. *Am J Physiol.* Apr 1996;270(4 Pt 2):H1217-24.

35. Bolger AF, Heiberg E, Karlsson M, et al. Transit of blood flow through the human left ventricle mapped by cardiovascular magnetic resonance. *Journal of Cardiovascular Magnetic Resonance.* 2007;9:741-747.

