The Relationship of the First Heart Sound to Mitral Valve Closure in Dogs

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SUMMARY The relationship between the first heart sound (S₁), mitral valve (MV) closure, and left atrial (LA) and left ventricular (LV) hemodynamics was investigated in dogs during right-heart bypass. High-speed cineradiography (~350 frames/sec) of lightweight clips attached to the free edge of the anterior and posterior MV leaflets permitted study of MV motion with high time resolution. LA and LV pressures were recorded, along with simultaneous phono- and echocardiograms, on a multichannel strip-chart recorder. S₁ occurred 25.5 ± 3 msec after LA-LV pressure crossover and coincided with MV closure measured either echocardiographically or cineradiographically. Atrial-ventricular (AS-VS) sequential pacing was performed to vary the interval between atrial and ventricular systole. At AS-VS intervals of 0–50 msec, S₁ and MV closure occurred simultaneously approximately 25 msec after the onset of LV systole as described above. At an AS-VS interval of 100 msec, S₁ and MV closure occurred simultaneously but closer to the onset of ventricular systole. At an AS-VS interval of 150 msec, MV closure occurred before S₁, just preceding the onset of LV systole, and S₁ closely followed the onset of LV systole. At longer AS-VS intervals (200–300 msec), MV closure occurred at progressively earlier points in diastole without a detectable heart sound. Later in diastole, the MV reopened and then closed a second time after the onset of LV systole; S₁ was recorded with this closure. The amplitude of S₁ varied with the degree of separation of the mitral valve leaflets at the onset of LV systole. The results show that the S₁ occurs with MV closure when it follows the onset of LV systole. The timing and amplitude of S₁ are related to the degree of separation of the MV leaflets at the onset of LV systole and to the relative timing of LA and LV systole.

DESPITE 150 years of experimental study, debate about the genesis of the first heart sound (S₁) continues.¹ The two conflicting theories most frequently proposed are based on either a ventricular or a mitral valvular origin of the sound. Laennec attributed S₁ to ventricular systole, specifically vibrations developing in the heart muscle with contraction.² Joseph Rouanet presented evidence for a valvular origin of S₁, based on experiments with a model of the working heart and with membranes similar to valvular tissue.³ ⁴ Dock, in studies beginning in the 1930s, using both intact heart models and strips of cardiac tissue, also argued for the valvular theory.⁵ ⁶ He found that a filled contracting ventricle tied off at the atroventricular ring produced no sound; strips of ventricular muscle pulled taut under water produced little sound, whereas strips of chordae and cardiac valves pulled taut could be made to produce loud sounds quite easily.

Luisada and co-workers⁷-⁸ found that the left atrial–left ventricular pressure crossover point — which they assumed represented mitral valve closure — consistently preceded S₁. They concluded that sudden tension development in the closed left ventricular cham-
ber caused by a rapid pressure increase at the onset of systole, rather than mitral valve closure per se, generates $S_1$. MacCannon et al.\textsuperscript{10} supported this view, reasoning from measurements of the mass of the mitral valve apparatus and its extent of motion that the mitral valve apparatus alone was physically incapable of producing enough energy to create $S_1$. Parisi\textsuperscript{11} reported that mitral valve closure measured by M-mode echocardiography preceded $S_1$ by 20 msec. These views have been challenged by other investigators who demonstrated that mitral valve closure, recorded echocardiographically and angiographically, occurs simultaneously with $S_1$. Laniado and co-workers\textsuperscript{12} showed that mitral valve closure, depicted by cineradiography of radiopaque threads on the mitral valve leaflets, occurred at the point of cessation of flow across the mitral valve as measured by electromagnetic flow probes, approximately 20 msec after the pressure crossover point, and that it coincided with $S_1$. In a similar study, Tsakiris et al.\textsuperscript{13} showed that mitral valve closure clearly followed left atrial–left ventricular pressure crossover and bore a relatively constant relationship to the onset of left ventricular systole, following it by an average of 25 msec. Shah et al.,\textsuperscript{14} Craigie et al.\textsuperscript{15} and others\textsuperscript{16-18} have shown in clinical and experimental studies that mitral valve closure, depicted echocardiographically, coincides with $S_1$. Factors that govern the timing and amplitude of $S_1$ continue to be the subject of clinical and experimental study. Atrial systole, left ventricular hemodynamics and valve motion itself have been reported to be important factors in the generation of $S_1$.\textsuperscript{19-27}

Some of these early studies were limited by the incorrect assumption that left atrial–left ventricular diastolic pressure crossover was a marker of mitral valve closure. In more recent studies, the precision of radiographic techniques has been limited by slow film speeds with limited time resolution. Finally, although recent studies have depended largely upon echocardiography to track mitral valve motion, the precise relationship between echocardiographic mitral valve leaflet coaptation and actual mitral valve closure has never been validated. In fact, previous work from our laboratory showed that the anterior leaflet echocardiogram lags behind mitral valve free edge motion as defined by cineradiography of radiopaque clips.\textsuperscript{28}

The factors that determine the relationship of $S_1$ to hemodynamic events and to mitral valve motion are still controversial. The echocardiographic studies of Parisi\textsuperscript{11} and of Craigie and others\textsuperscript{15-17} conflict. There are also conflicting data regarding the influence of the PR interval on the timing and amplitude of $S_1$. Sakamoto et al.\textsuperscript{21} found no relationship between PR interval and the amplitude of $S_1$ in an animal model. However, numerous clinical studies have shown a relationship between timing and amplitude of $S_1$ and the PR interval in patients with complete atrioventricular block.\textsuperscript{14, 16, 20, 27, 29} As early as 1930, Wolfert and Margolis\textsuperscript{19} proposed that the position of the mitral leaflets at the onset of left ventricular systole, which was related to the relative timing of atrial and ventricular systole, was important in modifying $S_1$.\textsuperscript{19}

The present study was designed to determine the role of hemodynamics, the timing of atrial systole and ventricular systole, and mitral valve motion as observed by both echocardiography and high-speed cine-radiography in altering the timing and amplitude of $S_1$ in an experimental model in which all variables were measured simultaneously.

**Methods**

**Preparation**

Fourteen dogs that weighed 25–30 kg were anesthetized with chloralose, 100 mg/kg, and urethane, 1 g/kg. The femoral arteries and veins and the external jugular vein were cannulated. The chest was opened through a median sternotomy and bilateral thoracotomy and the heart was suspended in a pericardial cradle. The superior and inferior venae cavae were isolated and the azygos vein was tied. The dog was placed on total heart bypass by occluding the venae cavae, draining venous blood and returning it to the femoral arteries. Coronary sinus blood was drained by cannula to the oxygenator. The heart was fibrillated electrically, and the left atrium was opened and tantalum surgical clips (approximate combined weight 42 mg) were applied to the midportion of the free edge of the anterior and posterior leaflets of the mitral valve. The atrium was closed and the heart defibrillated. The sinus node was crushed and the heart paced from the right atrium. Millar Mikro-tip catheters were placed in the left atrium through a pulmonary vein and into the left ventricle through the apex to record high-fidelity pressures and intracardiac heart sounds. Pressures from the micromanometer were zeroed and checked for accuracy by comparison with simultaneous pressures recorded from the fluid-filled catheter accompanying the Millar transducers. This procedure was repeated frequently during the study.

Right-heart bypass was instituted by cannulating the pulmonary artery and returning blood to the dog from the oxygenator through this cannula. The femoral cannulas were then used to control blood pressure. Aortic blood pressure was recorded through a catheter introduced into an internal mammary artery. A limb lead II ECG and ventricular and atrial point electrograms obtained from leads sutured to the right ventricle and atrium were recorded. Intracardiac phonocardiograms were obtained from the left atrial and left ventricular micromanometer-tipped catheter by 20–100 Hz filtering and were recorded simultaneously with the ECG and intracardiac pressures on an eight-channel Irex recorder at a paper speed of 200 mm/sec. The interval between the onset of electrical depolarization and the peak of the first high-frequency component of $S_1$ was measured ($Q_S$).

**Producing a Range of $Q_S$, Intervals**

Eleven dogs were used to determine the relative importance of the factors that might change the $Q_S$,
interval. In the first six dogs, cardiac output and heart rate were varied to produce a range of QS₁ intervals to determine the relationship between S₁ and mitral valve closure. These maneuvers produced only a narrow range of QS₁ intervals. Accordingly, in five dogs, perfusion temperature was varied from 32°C to 38°C to produce a wider range of QS₁ intervals.

**Time of S₁ Compared with Hemodynamic and Echocardiographic Markers of Mitral Valve Closure**

In five dogs subjected to variations in perfusion temperature, an echocardiogram of the two mitral valve leaflets was recorded using an SKI 20A echograph equipped with a 7.5-cm focused transducer. The transducer was placed directly on the anterior right ventricular epicardium. Echocardiograms of the mitral valve leaflets before and after placement of the tantalum clips were identical. The echocardiogram, intracardiac phonocardiogram, ventricular epicardial and limb lead II ECGs, and intracardiac pressures were recorded simultaneously on the multichannel recorder (fig. 1). The QS₁ interval was compared with the following intervals: (1) The onset of the electrocardiographic Q wave to coaptation of the mitral valve leaflets by echocardiogram (QCecho). (2) The Q-wave onset to the crossover point between left ventricular and left atrial diastolic pressure (QLV₅₃₋₃). When the crossover point was not well defined, the interval between the onset of the Q wave and the onset of left ventricular systole (QLV₅₃₋₃), as defined by the initial rapid rise of the left ventricular systolic pressure described by Weisfeldt et al.,³⁰ was used.

**Time of S₁ Compared with Cineradiographic Markers of Mitral Valve Closure**

Cineradiography of the mitral clips was performed on 16-mm film at a film speed of approximately 350 frames/sec (Siemens Corp.). The ventricular ECG and left atrial phonocardiogram were recorded on the same film by cine trace (fig. 2). Multichannel recordings of the ECG, intracardiac phonocardiogram, echocardiogram and left atrial, left ventricular and aortic pressures were obtained simultaneously (fig. 1). Events recorded on the cine trace were synchronized with those recorded on the multichannel recorder by creating a large-amplitude pacing artifact that was recorded on both systems at the beginning of each series of measurements. The events were timed from the cineradiogram by counting the number of frames between events and multiplying by the time per frame. The time per frame was determined precisely by counting the number of frames between sequential ventricular pac-
ing spikes recorded on the cine trace and dividing by the pacemaker RR interval. The QSi interval was compared with the interval between the Q-wave onset and cineradiographically determined coaptation of mitral valve clips (Qcine). These intervals were also compared with the corresponding QLVx and Qecho intervals measured from the multichannel recordings. Perfusion temperature was varied to produce a wide range of intervals. The Qcine, Qcine, and QLVx systole or QLVx, intervals from the five dogs were measured from three consecutive heart beats for each intervention and averaged.

Data points were acceptable only if the echocardiographic closure point, pressure tracings, cine trace and phonocardiogram were all simultaneously clearly recorded on three consecutive, nonectopic, nonpostectopic heart beats. Because of this requirement, not all points at each perfusion temperature for each dog are presented, which accounts for the variation in number of data points in figures 3–5.

Effects of Variations in the Interval Between Atrial and Ventricular Systole on Mitral Valve Motion and on Timing and Amplitude of S1

In three additional dogs, a suture was placed around the His bundle to induce complete atrioventricular block. Pacing electrode pairs were sutured to the right atrium and right ventricle and connected to a sequential atrioventricular pacemaker (Medtronic model 5837). The interval between atrial and ventricular systole was varied by sequentially increasing the interval between atrial pacing stimulus (AS) and ventricular pacing stimulus (VS). The effects of such alterations on the timing of atrial systole relative to ventricular systole and on the timing and amplitude of S1 relative to mitral valve closure assessed by cineradiography were studied at constant temperature and cardiac output. Separation of mitral valve leaflet clips was measured by projecting the cineradiograms from a fixed distance and measuring the distance between clips on sequential frames. To correct for variation in gain setting on the phonocardiogram, the amplitude of S1 was expressed as the ratio of S1 to S2.

Statistical Analysis

Linear regression analysis was used to determine the relationships between hemodynamic, echocardiographic and cineradiographic markers of valve closure and QSi. The p values presented are for a test of the significance of the r value. Comparison of QLVx and Qcine is expressed as mean difference ± sd.

Results

Variation in QS1 Interval

The range of QS1 intervals resulting from varying cardiac output and heart rate was limited. The QS1 was constant for cardiac outputs of 1000, 1200 and 2000 ml/min and decreased slightly (from 50 msec to 41 msec) for a cardiac output of 2500 ml/min. The QS1 was also constant (51–52 msec) at heart rates of 100, 120, 140 and 160 beats/min. However, varying perfusion temperature between 32°C and 38°C resulted in intervals of 59–80 msec.

Time of S1 Compared with Hemodynamic, Cineradiographic, and Echocardiographic Markers of Mitral Valve Closure

The relationship of QS1 to QLVx and Qcine is shown in figure 3. There was a significant correlation between QS1 and QLVx (QS1 = 0.72 [QLVx] + 36.7; r = 0.74, p < 0.01). However, QLVx, was significantly shorter than QS1 by 25.5 ± 3 msec (n = 17), indicating that LVx precedes QS1 by 25.5 ± 3 msec. QS1 and Qcine also correlated significantly (Qcine = 11.6 ± 0.84 [QS1]; r = 0.86, p < 0.01). QS1 and Qcine were not significantly different from each other, which suggests that S1 is simultaneous with coaptation of mitral valve leaflet clips.

The relationship between QS1 and Qecho is illustrated in figure 4. These two intervals also correlated (QS1 = 17.14 + 0.76 × Qecho ± 2.78; r = 0.96, p < 0.01). Over the physiologic range studied, Qcine and QSi were within 6.5 msec of each other, which implies that S1 and echocardiographic mitral valve leaflet coaptation are virtually simultaneous.

The significant relationship between Qcine and Qecho was confirmed by the data in figure 5, which show that mitral valve leaflet coaptation recorded echocardiographically was coincident with mitral valve leaflet coaptation depicted cineradiographically (Qecho = 0.8 [Qcine] + 13.0; r = 0.96, p < 0.01).

Effect of Relative Timing of Atrial and Ventricular Systole on the Amplitude and Timing of S1

Figure 6 shows intracardiac pressures, phonocardiogram and ECG at AS–VS intervals of 0, 50, 100, 150

![Figure 3](image-url)
and 200 msec in a representative study. At an AS–VS interval of 0, the a-wave of the left atrial tracing began simultaneous with the onset of left ventricular systole. At an AS–VS interval of 50 msec, the onset of atrial systole occurred just before the onset of left ventricular systole. As the interval lengthened, atrial systole occurred progressively earlier in diastole as evidenced by earlier diastolic appearance of the left atrial a-wave. At AS–VS intervals of 150 msec and above, atrial systole and relaxation were completed before the onset of left ventricular systole. The amplitude of S₁ changed substantially over the range of AS–VS intervals. S₁ was relatively loud at AS–VS intervals of 0 and 50 msec. It was substantially less intense at intervals of 100 and 150 msec and increased again at 200 msec.

Figures 7, 8 and 9 show the effect of changes in AS–VS interval on the timing and amplitude of the S₁ (QS₁), the onset of left ventricular systole (QLV_systole), and coaptation of the mitral valve leaflets as recorded by cineradiography of mitral valve clips (QC_cine). The interval between the Q-wave onset and the onset of left ventricular systole remained constant. This dog differed from the one whose data are presented in figure 6 in that the maximal range of AS–VS intervals achievable was greater (0–300 msec) because of a lower endogenous escape pacemaker, which enabled us to pace the ventricle more slowly. Figure 7 shows that at short AS–VS intervals (0 and 50 msec), mitral leaflet coaptation and S₁ were nearly coincident; both occurred approximately 25 msec after the onset of left ventricular systole. At an AS–VS interval of 100 msec,
coaptation and \( S_1 \) were again nearly coincident, but both occurred earlier, approximately 15 msec after the onset of left ventricular systole. At a longer AS–VS interval of 150 msec, mitral valve closure occurred before the onset of left ventricular systole and before the \( S_1 \), which closely followed the onset of left ventricular systole. At AS–VS intervals of 200–300 msec, the mitral valve closed progressively earlier in diastole (QC cine1), before the onset of left ventricular systole without any detectable sound. However, later in diastole, the mitral valve leaflets reopened and a second closure occurred at the onset of ventricular systole and was associated with \( S_1 \). Figure 8 illustrates the same plots shown in figure 7. In addition, mitral valve motion throughout a single diastole is plotted at four representative AS–VS intervals.

The distance between the anterior and posterior free edge clips was measured on successive cine frames and is schematically represented as the shaded area on the graph. At an AS–VS interval of 50 msec, the mitral valve clips first separated in early diastole (approximately 320 msec before the Q wave onset), drifted partially closed in middle diastole (approximately 170 msec before the Q wave onset), and were reopened by atrial contraction in late diastole so that they were widely separated at the onset of ventricular systole. This pattern resembles the usual echocardiographic pattern of normal mitral valve motion. At an AS–VS interval of 150 msec, atrial systole occurred earlier in diastole, resulting in earlier mitral valve leaflet separation and mitral valve closure before the onset of left ventricular systole. At an AS–VS interval of 250 msec, atrial systole began earlier in diastole (approximately 250 msec before the Q wave onset) so that the clips opened 220 msec before the Q wave onset and closed 70 msec before the Q wave onset. By late diastole, the

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**Figure 7.** Timing of the onset of left ventricular (LV) systole, the first heart sound and mitral valve leaflet coaptation measured cine-radiographically and relative to the Q-wave onset, which is represented as time zero by a Q on the horizontal axis. Negative values indicate the timing of events preceding the onset of the Q wave; positive values indicate the timing of events after the onset of the Q wave. AS–VS intervals starting from 0 msec and repeated at 50-msec increments are depicted along the vertical axis. These data are from a single dog (different from that in figure 6). Each data point is the average of values from three consecutive heart beats. At AS–VS intervals of 200–300 msec, when mitral valve closure occurred before the onset of LV systole, it reopened and then closed a second time after the onset of LV systole. The interval between the Q-wave onset and this secondary coaptation is indicated as QC cine2. AS–VS = interval between atrial and ventricular pacing stimuli.

**Figure 8.** Data from the same dog depicted in figure 7. The interval between the Q wave and the onset of left ventricular systole (Q–LV systole), the first heart sound (Q–S1), and mitral valve leaflet coaptation measured cine-radiographically (QC cine) at four AS–VS intervals are presented as in figure 7. The measured distance between mitral valve leaflet clips on successive cine frames is represented by the shaded areas. The timing of events relative to the Q-wave onset is expressed along the horizontal axis, as in figure 7, but the scale has been expanded to include events early in diastole (320 msec before the Q-wave onset). AS–VS = interval between atrial and ventricular pacing stimuli.
mitral valve had reopened so that the leaflet clips were again separated at the onset of left ventricular systole. The leaflets then rapidly closed with the onset of left ventricular systole and a heart sound occurred simultaneously with this second coaptation. Cineradiographic frames of mitral valve clips showing this sequence are illustrated in figure 2.

Figure 9 illustrates the amplitude of S1 expressed as the ratio of S1 to S2 over the range of AS–VS intervals. S1 was loudest at an AS–VS interval of 50 msec, when the mitral valve leaflets were widely separated just before the onset of left ventricular systole. At an AS–VS interval of 0 msec, atrial systole occurred coincident with left ventricular systole, the leaflets were not opened as widely and S1 was less intense. At AS–VS intervals of 150 and 200 msec, when early atrial relaxation had caused the leaflets to drift partially closed by the onset of left ventricular systole, S1 occurred earlier and was softer. At very long PR intervals, when the valve was reopened after early diastolic closure, S1 was again louder.

Discussion

Controversy about the origin of S1 has centered on the relative role of left atrial and left ventricular diastolic pressure crossover, coaptation of the mitral leaflets, and the so-called cardiohemic factors,31 i.e., the vibrations set up in the heart and great vessels at the onset of left ventricular systole. Studies of the relationship of mitral valve closure and hemodynamic events to the timing and amplitude of S1 have been technically limited by the lack of precise direct markers of mitral valve closure and by controversy over validation of indirect markers. The present study eliminated some of these problems by using high-speed cineradiography and by validating the echocardiographic approach. The placement of lightweight tantalum surgical clips on the midportion of the anterior and posterior mitral valve leaflet free edges filmed at the speed of 350 frames/sec allowed imaging of leaflet motion at approximately 3-msec intervals. Simultaneous phonocardiogram and hemodynamic data were obtained by intracardiac micromanometer-tipped catheters, precluding significant recording delays. Echocardiograms were obtained simultaneously by a transducer placed directly on the epicardial surface of the heart, and the point of coaptation of anterior and posterior mitral valve leaflets was recorded.

Relationship of Timing of S1 to Hemodynamic, Echocardiographic, and Cineradiographic Events

We have shown that coaptation of the mitral valve leaflets as demonstrated echocardiographically coincides with coaptation depicted by cineradiography of clips placed on the midportion of the free edge of each leaflet. Validation of echocardiography as an accurate marker of mitral valve closure was important because a prior study from this laboratory showed a lag between cineradiographic tracking of mitral leaflet clips and echocardiographic anterior leaflet motion.28 In that study, the end point of rapid posterior motion of the anterior mitral leaflet on the echocardiogram occurred 18 msec after the corresponding point of maximal posterior motion of the anterior leaflet clip on cine. The most likely explanation for the apparent lag between motion of the clip on the free edge of the anterior mitral valve leaflet by cineradiograph and anterior mitral leaflet motion by echocardiography relates to nonuniformity of mitral leaflet motion and failure of the ultrasound beam to intersect the mitral leaflet precisely at the midportion of the free edge where the clips were positioned. During mitral valve closure, clip motion may precede echocardiographically tracked motion of portions of the free edge closer to the commissures. Edler et al.32 demonstrated this nonuniformity of mitral valve leaflet motion by cineradiography. An additional point regarding the apparent discrepancy between mitral valve motion by cineradiography and echocardiography in the previous study is that because the posterior leaflet was not visualized, coaptation of the mitral valve leaflets on echo could not be recorded. In the present study we show that coaptation of the anterior and posterior mitral valve leaflets demonstrated echocardiographically by visualization of both leaflets coincides with coaptation of midposition mitral valve clips depicted on cineradiography. Thus, echocardiography performed in this manner is an accurate marker of mitral valve free edge coaptation.

As discussed by Laniado et al.12 and Tsakiris et al.,13 left ventricular–left atrial pressure crossover precedes
mitral valve closure by 25.5 ± 3 msec. The delay between pressure crossover and mitral valve closure appears to be related to the inertia of both the valve and the column of blood flowing from left atrium to left ventricle.33

In the present study, $S_1$ was simultaneous with coaptation of the mitral leaflets whenever mitral valve closure followed the onset of left ventricular systole, despite alterations in hemodynamics and temperature (figs. 3, 4). Variation of the AS–VS interval altered the relationship between $S_1$ and leaflet coaptation (fig. 7). At short AS–VS intervals of 0–50 msec, mitral valve closure followed the onset of left ventricular systole and coincided with $S_1$. At very long AS–VS intervals of 200–300 msec, the mitral valve closed twice. Initial closure occurred before the onset of left ventricular systole in association with atrial contraction and relaxation. This event was silent. Mills et al.17 recorded a very low amplitude high-frequency sound coincident with mitral valve closure preceding left ventricular systole in three patients with very long PR intervals. However, neither Shah et al.,14 nor Burggraf and Craigie,10 in studies of a total of 17 patients with complete atrioventricular block or atrial fibrillation. The highest-amplitude $S_1$ occurred when the AS–VS interval was 50 msec. At this interval, mitral valve closure occurred 25 msec after the onset of left ventricular systole, when atrial contraction had maximally separated the two mitral leaflets. Under these circumstances, the mitral valve leaflets, propelled by a relatively high left ventricular pressure (i.e., 25 msec into the development of left ventricular systole), close at a high velocity and come to an abrupt halt with rapid deceleration of the column of blood flowing from left atrium to left ventricle. At an AS–VS interval of 100 msec when the first heart sound was only one-third of the amplitude recorded at an AS–VS interval of 50 msec, atrial systole had occurred earlier, the mitral leaflets had already separated maximally and would have begun to close with atrial relaxation when left ventricular systole began. Under these circumstances, when the mitral aperture is smaller at the onset of left ventricular systole, mitral closure and $S_1$ occurred closer to the onset of left ventricular systole. At this time, left ventricular pressure is lower, less force is applied to the mitral valve area, and a lower-amplitude $S_1$ would result. At an AS–VS interval of 150 msec, the mitral leaflets were closed or nearly closed at the onset of left ventricular systole. Under these circumstances, a markedly attenuated sound occurred only 10 msec from the onset of left ventricular systole when the left ventricular pressure was low so that little force would be applied to the closed system. As the AS–VS interval was further increased, atrial contraction and relaxation would be completed during diastole. However, the mitral valve begins to reopen before the onset of left ventricular systole as blood continues to flow passively from left atrium to left ventricle. As the degree of reopening increases, mitral valve leaflet separation is greater at the onset of left ventricular systole and the mitral valve again closes later and at a higher developed left ventricular pressure, resulting in more force related to deceleration of blood within the closed system. Thus, $S_1$ occurs progressively later and with increasing amplitude.

Finally, at an AS–VS interval of 0 msec, $S_1$ was of lower amplitude than at an AS–VS interval of 50 msec. This phenomenon can be explained by the timing of the left atrial systole. At an AS–VS interval of 0 msec, atrial systole had begun at the same time as ventricular systole. Indeed, the high left atrial pressure generated (fig. 6) was consistent with the left atrium contracting against rising left ventricular pressure. This would prevent maximal opening of the mitral valve leaflets and under these circumstances, the distance which the mitral valve leaflets travel during closure is less than at an AS–VS interval of 50 msec. Diminished leaflet excursion and a persistent left atrial–left ventricular pressure gradient would have the effect of lowering the amplitude of $S_1$. In this case, the first heart sound did not occur earlier, as it did at AS–VS intervals of 100 and 150 msec when the leaflets were relatively close together. Zaky et al.25 showed that when the left atrium contracts against high left ventricular pressure, causing a marked rise in left atrial pressure with persistence.

**Relationship of the Amplitude of $S_1$ to AS–VS Interval and Leaflet Position at the Onset of Left Ventricular Systole**

The relationship between the amplitude of $S_1$ and the degree of separation of the mitral valve leaflets is similar to previous observations on the variation in amplitude of $S_1$ in patients with complete atrioventricular block or atrial fibrillation. The highest-amplitude $S_1$ occurred when the AS–VS interval was 50 msec. At this interval, mitral valve closure occurred 25 msec after the onset of left ventricular systole, when atrial contraction had maximally separated the two mitral leaflets. Under these circumstances, the mitral valve leaflets, propelled by a relatively high left ventricular pressure (i.e., 25 msec into the development of left ventricular systole), close at a high velocity and come to an abrupt halt with rapid deceleration of the column of blood flowing from left atrium to left ventricle. At an AS–VS interval of 100 msec when the first heart sound was only one-third of the amplitude recorded at an AS–VS interval of 50 msec, atrial systole had occurred earlier, the mitral leaflets had already separated maximally and would have begun to close with atrial relaxation when left ventricular systole began. Under these circumstances, when the mitral aperture is smaller at the onset of left ventricular systole, mitral closure and $S_1$ occurred closer to the onset of left ventricular systole. At this time, left ventricular pressure is lower, less force is applied to the mitral valve area, and a lower-amplitude $S_1$ would result. At an AS–VS interval of 150 msec, the mitral leaflets were closed or nearly closed at the onset of left ventricular systole. Under these circumstances, a markedly attenuated sound occurred only 10 msec from the onset of left ventricular systole when the left ventricular pressure was low so that little force would be applied to the closed system. As the AS–VS interval was further increased, atrial contraction and relaxation would be completed during diastole. However, the mitral valve begins to reopen before the onset of left ventricular systole as blood continues to flow passively from left atrium to left ventricle. As the degree of reopening increases, mitral valve leaflet separation is greater at the onset of left ventricular systole and the mitral valve again closes later and at a higher developed left ventricular pressure, resulting in more force related to deceleration of blood within the closed system. Thus, $S_1$ occurs progressively later and with increasing amplitude.

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of a positive left atrial–left ventricular pressure gradient, mitral valve closure is delayed. 26

Although secondary reopening of the mitral valve leaflets at very long AS–VS intervals was demonstrated cineradiographically, this phenomenon could not be demonstrated by echocardiography in our study. However, Burggraf and Craig16 demonstrated mitral valve reopening by echocardiography at very long PR intervals. Because different parts of the mitral valve leaflets may open to a greater or lesser extent, we probably failed to detect mitral valve reopening because of the single-beam view of the mitral valve leaflets we obtained.

In conclusion, the intensity and timing of S2 seem to be related to the amount of separation of the mitral valve leaflets at the onset of left ventricular systole, as well as the relative timing of atrial and ventricular systole. In this experimental preparation, as well as in most clinical studies, left ventricular systole is a prerequisite for S2 because closure resulting from atrial events alone does not produce recordable sound. This suggests that the walls of the left ventricle must be in the active process of generating a pressure before sound vibrations of the amplitude and frequency of S2 can be produced, either by the walls themselves or by vibrations of their hematic contents.

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