Effect of Altering P-R Interval on the Amplitude of the First Heart Sound in the Anesthetized Dog

By Michael E. Stept, Charles E. Heid, James A. Shaver, M.D., Donald F. Leon, M.D., and James J. Leonard, M.D.

ABSTRACT

To determine the effect of changing the P-R interval on the intensity of the mitral component of the first heart sound (M1 amplitude), fixed-rate sequential atrioventricular pacing was used to vary the P-R interval in a steady hemodynamic state in six anesthetized dogs. Left ventricular sound and pressure events were monitored with a catheter-tip micromanometer, and the rate of rise of left ventricular pressure (dP/dt) was recorded using an R/C differentiator. The P-R interval was varied from the longest interval at which continuous ventricular capture was achieved (indifferent P-R interval) to 0.00 msec in 10-msec increments. The mean increase in M1 amplitude at the short P-R intervals (30 to 50 msec) was 119% compared to the amplitude at the indifferent P-R interval; there was no significant change in maximum dP/dt. No significant changes in left ventricular ejection time and left ventricular peak pressure occurred over the range of P-R intervals. At the indifferent P-R interval, a norepinephrine infusion increased M1 amplitude 22% and maximum dP/dt 50%. At short P-R intervals in the new inotropic state, the M1 amplitude was further augmented.

These data indicate that both the timing of atrial and ventricular systoles and the force of left ventricular contraction are major, independent determinants of M1 amplitude. These findings are consistent with the concept that the abrupt deceleration of blood by the mitral valve shortly after the onset of ventricular systole sets the cardiohemic system into vibration producing the M1 sound. The intensity of the first heart sound is proportional to the force produced in this manner.

ADDITIONAL KEY WORDS  maximal rate of rise of left ventricular pressure  sequential atrioventricular pacing  left ventricular contractility

The development of new techniques for the recording of intracardiac sound and pressure events has generated considerable interest in the hemodynamic determinants of the first heart sound (1-5). Investigations by Sakamoto and Luisada (1) have shown that the maximum rate of rise of left ventricular pressure correlates with the intensity of the first heart sound, but no direct relation was observed between the amplitude of the first sound and heart rate, stroke volume, left ventricular end diastolic pressure, or peak systolic pressure. They concluded that left ventricular contractility as indicated by the peak rate of rise of left ventricular pressure is the primary determinant of the intensity of the first heart sound. In contrast to clinical observations in complete heart block where the first heart sound is increased at shorter P-R intervals (6), they observed no correlation of the intensity of the first heart sound with P-R interval. However, they did not observe the effects of P-R interval variations independent of changes in other hemodynamic variables.

The purpose of this investigation was to...
study the effect of changing the P-R interval on the intensity of the first heart sound in a steady hemodynamic state. With the advent of sequential atrioventricular pacing, it is now possible to vary the P-R interval without changing heart rate or the inotropic state of the heart. Utilizing this technique, the P-R interval could be shortened, and the effect of this upon the first heart sound intensity was studied in the range of clinically important P-R intervals.

**Materials and Methods**

Experiments were performed in six adult, male mongrel dogs weighing from 16 to 24 kg. The animals were premedicated with morphine sulfate, 1 mg/kg, and then lightly anesthetized with 0.2 ml/kg of a mixture of 1:1 Dial-urethane$^1$ and sodium pentobarbital (30 mg/ml).

Sequential atrioventricular (A-V) pacing was instituted using a Medtronic model 5837 pulse generator. Under fluoroscopic guidance a no. 5 bipolar pacing catheter was placed in the right atrial appendage through the right femoral vein and another no. 5 bipolar pacing catheter in the apex of the right ventricle from the right jugular vein. The position of the right atrial pacing catheter in the right atrial appendage was confirmed by opening the chest after one experiment to demonstrate the catheter position. The atrium was captured by right atrial appendage pacing at a rate of 10 beats/min above the control rate. The P-R interval was selected by setting the delay between the atrial and ventricular stimuli at various intervals less than the dogs' control P-R interval. The P-R interval could be reduced to 0.00 seconds by pacing both the atrium and ventricle from a single terminal of the Medtronic pulse generator.

Left ventricular pressure and sound were recorded from a Dallons-Telco catheter-tip micromanometer$^2$ placed in the ventricle by retrograde passage from the right carotid artery. The Dallons-Telco micromanometer is a variable inductance transducer from which low frequency vibrations (0.1 to 40 cps) are recorded as pressure and high-frequency vibrations (above 40 cps) are recorded as sound. This system has a linear amplitude response to frequencies up to 200 cps and gives pressure and sound traces free of distortion and with no time delay. The first derivative of the left ventricular pressure was continuously recorded using an R/C differentiator.$^3$ Central aortic pressure was monitored through a no. 8 Cournand catheter attached to a Statham P23G transducer. A simultaneous lead II electrocardiogram was recorded using subcutaneous needle electrodes.

In the experiments, left ventricular pressure and its first derivative, left ventricular sound, aortic root pressure, and a lead II electrocardiogram were recorded simultaneously on a polybeam photographic recorder$^4$ at a paper speed of 100 mm/sec and with 0.02-second time lines. Heart rate was held constant during each experiment, and the above data were recorded at P-R intervals from 0.00 seconds to the longest interval at which continuous ventricular capture was achieved. Observations were made at 10-msec increments over the range of P-R intervals.

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$^1$Dial with urethane solution; Ciba Pharmaceutical Company, Summit, New Jersey.

$^2$Dallon Laboratories Inc., 5066 Santa Monica Boulevard, Los Angeles, California.

$^3$Electronics for Medicine, White Plains, New York.

$^4$Electronics for Medicine, White Plains, New York.

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**FIGURE 1**

Comparison of the effects of atrial pacing and sequential atrioventricular pacing during the control state in dog A. Note that atrial and sequential A-V pacing produced no physiologically significant alteration in the hemodynamic variables of left ventricular ejection time, peak left ventricular pressure, and maximum rate of rise of left ventricular pressure (max dP/dt). The slight decrease in P-R interval produced by A-V pacing caused no alteration in the intensity of the first heart sound (M, amplitude). The arrows indicate the atrial and ventricular pacing artifacts. Heart rate was 120 in each instance. Paper speed 100 mm/sec; time markers 20 msec. Circulation Research, Vol. XXV, September 1969
At each P-R interval sufficient time (25 to 35 seconds) was allowed for a steady left ventricular peak pressure and peak rate of pressure rise to develop before data were recorded. During one experiment norepinephrine was infused at a constant rate of 8.6 µg/min. In another study the experimental protocol was performed after injecting 0.4 mg deslanoside5 intravenously.

In measuring the data, five consecutive steady state beats were randomly selected at each P-R interval and the following measurements were made: (1) P-R interval, (2) amplitude of the mitral component of the first heart sound (M1 amplitude), (3) heart rate, (4) peak left ventricular pressure, (5) maximum rate of rise of left ventricular pressure (maximum dP/dt), and (6) left ventricular ejection time. The values for five steady state beats were statistically analyzed using the paired Student t-test to compare the values at the indifferent P-R interval to those at the P-R interval at which amplitude of the mitral component was greatest. The indifferent P-R interval was the longest interval at which continuous ventricular capture was possible. The amplitude of the mitral component was measured as the vertical peak-to-peak value of the deflection on the internal phonocardiogram. The percent changes in the mitral component and the maximum first derivative of left ventricular pressure were calculated using the values at the indifferent interval in each study as 100%.

Results

In this study atrial pacing and sequential A-V pacing caused no statistically significant changes in left ventricular ejection time, left ventricular pressure, maximum dP/dt, and M1 amplitude when compared to the control state. Figure 1 illustrates the effects of atrial and sequential A-V pacing in one experiment (dog A) and shows that these procedures caused no physiological alterations in the hemodynamic variables measured.

Figure 2 depicts the effect of changing the P-R interval on the amplitude of the mitral component of the first heart sound and on the first derivative of left ventricular pressure in one experiment (dog C). As P-R interval was shortened from 130 msec to 100 msec, there was no change in M1 amplitude while maximum dP/dt increased 14% (P < 0.001). With further shortening of the P-R interval to 30 msec the M1 amplitude increased 151% (P < 0.001) while there was no further change in maximum dP/dt. As the P-R interval was

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5Cedilanid D; Sandoz Pharmaceuticals, Hanover, New Jersey.
TABLE 1

Effect of Changing P-R Interval on Left Ventricular Sound and Pressure Events

<table>
<thead>
<tr>
<th>Study</th>
<th>P-R interval (msec)</th>
<th>Max % change in M1 amplitude</th>
<th>Max % change in max dP/dt</th>
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<tr>
<td></td>
<td>0 10   20  30  40  50  60  70  80  90  100  110  120  130  140  150</td>
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<tr>
<td>Control</td>
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<tr>
<td>Dog A</td>
<td>M1 amplitude*</td>
<td>72 212 224 236† 215 155 158 112 127 130 100 136 100‡</td>
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<tr>
<td>HR = 120</td>
<td>Max dP/dt*</td>
<td>64 85 85 88 89 89 80 79 74 81 89 97 96 100</td>
<td></td>
</tr>
<tr>
<td></td>
<td>LVET (msec)</td>
<td>168 174 173 175 174 176 178 178 181 181 181 182 180</td>
<td></td>
</tr>
<tr>
<td></td>
<td>LVPP (mm Hg)</td>
<td>130 136 136 137 139 141 142 142 140 138 141 141</td>
<td></td>
</tr>
<tr>
<td>Dog B</td>
<td>M1 amplitude</td>
<td>46 57 103 158 153 190 213† 155 131 106 100‡</td>
<td></td>
</tr>
<tr>
<td>HR = 130</td>
<td>Max dP/dt</td>
<td>88 89 88 88 90 93 93 92 90 90 100</td>
<td></td>
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<tr>
<td></td>
<td>LVET (msec)</td>
<td>162 164 167 165 165 168 168 168 171 172 176</td>
<td></td>
</tr>
<tr>
<td></td>
<td>LVPP (mm Hg)</td>
<td>153 150 151 153 153 155 157 157 157 157 161</td>
<td></td>
</tr>
<tr>
<td>Dog C</td>
<td>M1 amplitude</td>
<td>115 122 190 251† 213 206 187 182 122 96 103 104 104 100‡</td>
<td></td>
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<tr>
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<td>Max dP/dt</td>
<td>90 98 98 101 100 100 100 100 96 97 96 95 96 100</td>
<td></td>
</tr>
<tr>
<td></td>
<td>LVET (msec)</td>
<td>160 161 161 160 162 160 163 168 168 159 160 159 161 158</td>
<td></td>
</tr>
<tr>
<td></td>
<td>LVPP (mm Hg)</td>
<td>152 153 153 155 155 153 154 152 157 157 156 157 155 158</td>
<td></td>
</tr>
<tr>
<td>Dog D</td>
<td>M1 amplitude</td>
<td>178 159 163 187† 170 167 157 137 131 109 104 100‡</td>
<td></td>
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<tr>
<td>HR = 111</td>
<td>Max dP/dt</td>
<td>96 98 100 101 100 100 100 100 96 97 96 95 100</td>
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<tr>
<td></td>
<td>LVET (msec)</td>
<td>180 180 180 181 181 182 183 181 184 181 177</td>
<td></td>
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<tr>
<td></td>
<td>LVPP (mm Hg)</td>
<td>139 136 136 141 139 139 137 141 138 136 140</td>
<td></td>
</tr>
<tr>
<td>Dog E</td>
<td>M1 amplitude</td>
<td>89 114 180 203 206† 184 172 150 142 130 84 86 84 91 78 100‡</td>
<td></td>
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<tr>
<td>HR = 130</td>
<td>Max dP/dt</td>
<td>92 102 125 127 135 132 130 117 92 100 100 100 100 100 100 100 100 100 100 100 100 100 100 100 100 100 100</td>
<td></td>
</tr>
<tr>
<td></td>
<td>LVET (msec)</td>
<td>156 156 154 156 159 159 160 160 160 159 164 162 165 167 160 100</td>
<td></td>
</tr>
<tr>
<td></td>
<td>LVPP (mm Hg)</td>
<td>135 133 135 144 144 144 144 144 144 144 144 144 144 144 144</td>
<td></td>
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Norepinephrine, 8.6 µg/min

<table>
<thead>
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<th>Study</th>
<th>P-R interval (msec)</th>
<th>Max % change in M1 amplitude</th>
<th>Max % change in max dP/dt</th>
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<tr>
<td></td>
<td>0 10   20  30  40  50  60  70  80  90  100  110  120  130  140  150</td>
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<tr>
<td>Dog E'</td>
<td>M1 amplitude</td>
<td>100 129 188 209 217 218* 217 212 218 209 167 118 76 78 94 100‡</td>
<td></td>
</tr>
<tr>
<td>HR = 130</td>
<td>Max dP/dt</td>
<td>89 83 89 102 107 111 107 101 101 101 96 99 99 100</td>
<td></td>
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<tr>
<td></td>
<td>LVET (msec)</td>
<td>162 166 167 170 168 172 176 165 168 165 170 172 167 176 172 173</td>
<td></td>
</tr>
<tr>
<td></td>
<td>LVPP (mm Hg)</td>
<td>138 138 138 144 144 148 150 163 168 170 173 177 185 187 187 191 189</td>
<td></td>
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Deslanoside, 0.4 mg

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<th>Max % change in M1 amplitude</th>
<th>Max % change in max dP/dt</th>
</tr>
</thead>
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<tr>
<td></td>
<td>0 10   20  30  40  50  60  70  80  90  100  110  120  130  140  150</td>
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<td></td>
</tr>
<tr>
<td>Dog F</td>
<td>M1 amplitude</td>
<td>128 175 304 337† 330 330 261 260 226 214 204 179 154 112 95 100‡</td>
<td></td>
</tr>
<tr>
<td>HR = 135</td>
<td>Max dP/dt</td>
<td>104 106 104 104 104 104 104 104 104 104 99 103 97 100</td>
<td></td>
</tr>
<tr>
<td></td>
<td>LVET (msec)</td>
<td>153 157 159 160 163 165 167 170 171 174 174 163 160 165 164</td>
<td></td>
</tr>
<tr>
<td></td>
<td>LVPP (mm Hg)</td>
<td>129 129 127 127 128 132 131 135 135 135 131 127 134 127 129</td>
<td></td>
</tr>
</tbody>
</table>

HR = heart rate; Max dP/dt = maximum rate of rise of left ventricular pressure; LVET = left ventricular ejection time; and LVPP = left ventricular peak pressure. * Percent of value of indifferent P-R interval. † P-R interval where maximum M1 amplitude occurred. ‡ Indifferent P-R interval.
shortened to 0 msec, there was a fall in the $M_1$ amplitude while maximum dP/dt rose slightly. The data for the five control experiments are presented in Table 1 and demonstrate a similar response of the $M_1$ amplitude to changing the P-R interval, while no consistent effect upon maximum dP/dt was observed.

When the maximum dP/dt of the indifferent P-R interval is compared with that recorded at the P-R interval at which the maximum change of $M_1$ amplitude occurred (Table 1), there was no change in the maximum dP/dt in study D, a statistically significant decrease in studies A, B, and C ($P < 0.005$), and a significant increase in study E ($P < 0.001$). Left ventricular ejection time and left ventricular peak pressure show no significant changes in studies C, D, and E and a decrease in studies A and B.

The mean change in $M_1$ amplitude for all studies was $119\%$ ($P < 0.005$). The mean change in maximum dP/dt was $0.6\%$, and this was not statistically significant. Comparison of the percent change of maximum dP/dt with the percent change in $M_1$ amplitude for each P-R interval in all studies demonstrated no correlation between maximum dP/dt and $M_1$ amplitude ($r = 0.17$) under the conditions of this experiment as shown in Figure 3.

Figure 4 shows the hemodynamic response to the alteration of P-R interval in dog A. The contour of the first derivative of the left ventricular pressure exhibits a notch similar to that observed by Piemme and Dexter (7), which is coincident with the mitral component...
Effect of changing P-R interval and inotropic state (norepinephrine) on left ventricular sound and pressure events. In the control state (top), the M₁ amplitude is markedly increased at the shorter P-R interval. At the indifferent P-R interval (left), the administration of norepinephrine increased both the M₁ amplitude and maximum dP/dt as compared to the control state. Again, at the new inotropic state (bottom), the M₁ amplitude was markedly increased at the short P-R interval. Paper speed 100 mm/sec; time markers 20 msec.

TABLE 1

of the first heart sound and with the abrupt change in the slope of the rising left ventricular pressure. As the P-R interval is decreased to 40 msec and the M₁ amplitude increases to its maximum, this notch becomes more prominent and appears later during left ventricular contraction, while the rate of rise of the left ventricular pressure tends to level off immediately before this notch. These alterations in the dP/dt contour disappear as the P-R interval is shortened to 10 msec and M₁ amplitude decreases. Similar alterations in the dP/dt contour were observed in all studies.

Table 1 also presents the data of two experiments in which alterations of the hemodynamic state of dogs were produced by positive inotropic agents. Dog F developed evidence of myocardial failure, and 0.4 mg of deslanoside was given intravenously over 2 minutes. The experimental protocol was performed after the dog had stabilized at a lower left ventricular end diastolic pressure. This procedure did not alter the relationship of the M₁ amplitude to variations in the P-R interval.

In study E' norepinephrine was given to dog E as a constant intravenous infusion of 8.6 μg/min after completion of the control study. The experimental protocol was then repeated during norepinephrine administration after the animal had stabilized. As illustrated in Figure 5, at the P-R interval of 150 msec the norepinephrine increased maximum dP/dt 50% (P < 0.005) when compared to the control study E. This was accompanied by an increase in M₁ amplitude of 22% (P < 0.01). Shortening of the P-R interval from 150 msec to 40 msec during norepinephrine infusion caused a further augmentation of the M₁ amplitude. Changing the P-R interval produced similar alterations in the height and the contour of the dP/dt in both the control and the norepinephrine studies. As the P-R interval was shortened during norepinephrine infusion, there was a marked decrease in the left ventricular peak pressure and a concomitant decrease in left ventricular ejection time.

**Discussion**

Using sequential A-V pacing, the P-R interval was varied while heart rate was held constant. With this experimental design it was possible to alter the sequence of atrial and ventricular contraction without altering the...
physiological condition of the animals. Under these experimental conditions left ventricular ejection time and left ventricular peak pressure remained constant or changed only minimally in contrast to the findings of others (8, 9) where P-R interval was varied from beat to beat. Thus, the effect of altering the P-R interval upon the M₁ amplitude could be studied during a hemodynamically steady state (10). The present study was designed to investigate the relationship between M₁ amplitude and maximum dP/dt within the range of P-R interval between 0 and 120 msec. Chough et al. (8) and McKusick (11) have demonstrated that alterations within this range of P-R interval have the greatest effect upon the intensity of the first heart sound in dogs with surgically produced heart block.

Our results demonstrate that significant increments in the M₁ amplitude occurred at short P-R intervals; while maximum dP/dt did not change significantly when compared to those at longer P-R intervals. At a steady hemodynamic state there was no correlation between M₁ amplitude and maximum dP/dt. Thus, the P-R interval independent of other variables is a major determinant of the mitral component of the first heart sound.

This is in marked contrast to the work of Sakamoto and Luisada (1), who demonstrated a direct correlation between M₁ amplitude and maximum dP/dt, but none between M₁ amplitude and P-R interval. They concluded that the contractility of the left ventricle was the sole determinant of M₁ amplitude. However, the changes of P-R interval in their experiments were not independent of the hemodynamic state of the animal, but were secondary to the effects of the procedures they used. Their observations on P-R interval and M₁ amplitude were made at different inotropic states where the P-R interval was a dependent variable.

In our preparation, a constant intravenous infusion of norepinephrine produced a marked increase of M₁ amplitude and maximum dP/dt at the same P-R interval. When the P-R interval was decreased at this new inotropic state, a further augmentation of M₁ amplitude was seen. Thus, it is evident that the force of left ventricular contraction and the sequential timing of the atrial and ventricular systoles are both major determinants of the amplitude of the first heart sound.

Studies by Piemme and Dexter (7) are consistent with the concept that the transient cardiovascular sounds are the result of the sudden accelerations and decelerations of blood which set the system of heart walls, valves, and blood into vibration (12, 13). When the mitral valve leaflets are stretched to their elastic limits during early ventricular contraction, flow is suddenly decelerated. This abrupt change in the momentum of flow provides the force which sets the cardiohemic system into vibratory motion and produces the mitral component of the first heart sound. The M₁ amplitude will vary directly with the momentum of the blood decelerated by the mitral valve leaflets. This momentum is determined by the force of left ventricular contraction accelerating the blood towards the mitral valve, the mass of blood, and the time during which the blood is accelerated.

Dean (14), Little (15), and Reinhold and Rudhe (16) have shown that at normal P-R intervals the mitral valve is closed by the inertial forces of left atrial contraction. The ensuing ventricular contraction tenses the valve leaflets to their elastic limits. At shorter P-R intervals left ventricular systole alone is responsible for mitral valve closure. When atrial and ventricular systole coincide, ventricular contraction closes the valve against the opposing force of atrial contraction. This concept of the mechanism of mitral valve closure has been supported by the recent studies of Brockman (17) and Zaky (18). The variations of M₁ amplitude with P-R interval seen in the present study can be interpreted in the light of this mechanism of mitral valve closure.

At the indifferent P-R interval the valve leaflets are apposed by atrial systole, and ventricular contraction accelerates blood towards the mitral valve only over the distance necessary to stretch the valve to its elastic limits. The blood is accelerated only during
the time it takes to traverse this short distance. However, at a short P-R interval atrial force has not yet approximated the valve leaflets. When ventricular systole begins, the valve leaflets are open and are farther from their final position. When the blood is finally checked by the valve, it has attained a greater velocity than at the indifferent P-R interval. Assuming that the mitral valve acts to check the blood over the same amount of time as at the longer P-R interval, the force generated from the deceleration of blood will be greater at the short P-R interval. Consequently, the sound produced will be of greater amplitude.

At the P-R intervals of 10 msec to 0 msec the atrial and ventricular contractions are almost simultaneous and the force of atrial contraction directly opposes the initial force of left ventricular contraction so that the velocity attained by the blood is diminished. Moreover, the mitral valve leaflets are partially closed after early rapid ventricular filling (18), and this also decreases the final velocity of the blood. This explains the reduction in $M_1$ amplitude seen at the P-R intervals of 10 msec and 0 msec.

Recent work by Shah et al. (3) supports this concept. Using an ultrasound technique to study the influence of atrial systole on mitral valve closure and the first heart sound in patients with complete heart block, they demonstrated that the intensity of the first heart sound is correlated with the distance over which the mitral leaflets are moved and the velocity of valve closure. They concluded that the intensity of the first heart sound is directly related to both the mechanics of mitral valve closure and the energy produced by left ventricular contraction.

The variations in the contour of the first derivative of the left ventricular pressure with P-R interval observed in our study are consistent with the theory presented here. As the P-R interval is shortened, the notch coincident with the $M_1$ occurs later in the course of ventricular systole. The plateau which develops prior to this notch at shorter P-R intervals indicates that left ventricular contraction is not yet truly isovolumetric and that the tension developed by the left ventricle is being utilized to accelerate blood towards the mitral valve until its elastic limits are met. At this point the left ventricle begins true isovolumetric contraction.

Acknowledgments

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References

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