Effects of Graded Reductions in Coronary Perfusion Pressure on the Diastolic Pressure-Segment Length Relation and the Rate of Isovolumic Relaxation in the Resting Conscious Dog

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To assess the relations between coronary perfusion pressure, blood flow, and the diastolic pressure–segment length relation in the conscious animal, circumflex pressure was incrementally decreased in 10 resting, chronically instrumented dogs by a hydraulic occluding cuff while monitoring left ventricular pressure and regional segment length (with piezoelectric crystals) in the circumflex and left anterior descending territories. In five dogs, regional blood flow was measured by microsphere injections at selected circumflex pressures. The diastolic portion of the pressure–segment length curve was unchanged when decrements in circumflex pressure were within the autoregulatory range, that is, unassociated with changes in blood flow or systolic function. Further decrements in circumflex pressure, which decreased blood flow and regional segment shortening (both p < 0.05), caused a progressive downward and rightward shift of the pressure–segment length curve (p < 0.05). The rate of relaxation, as measured by $\tau$ (the time constant of pressure decay during isovolumic relaxation, which is calculated assuming either a fixed or a variable asymptote) and peak negative $dP/dt$, decreased slightly during reductions in circumflex pressure within the autoregulatory range and greatly at lower pressures (all p < 0.05). Thus, in the conscious animal, reductions in coronary perfusion pressure within the autoregulatory range do not affect the diastolic pressure–segment length curve but cause modest decreases in the rate of isovolumic relaxation. Further reductions in coronary perfusion pressure, below the limits of blood flow autoregulation, cause an increased extent of relaxation with a marked downward shift of the diastolic pressure–segment length curve as well as a large decrease in the rate of relaxation. (Circulation 1989;80:1458–1468)

Despite recent interest in the physiologic, pathologic, and clinical effects of diastolic dysfunction, controversies persist as to the precise effects of ischemia on the rate and extent of ventricular relaxation. Ischemia prolongs the rate of relaxation, but the degree of ischemia required and the mechanisms involved have yet to be elucidated.1–10 Similarly, there is general agreement that ischemia affects the extent of relaxation, but the details of this association are also obscure; in different experimental preparations, ischemia has had opposite effects on the diastolic pressure-volume or pressure–segment length relation.5,6,11–23 These discrepancies could be at least partially due to the different definitions of ischemia used in the various experimental models, ranging from a total cessation of coronary blood flow in the isolated heart to tachycardia-induced angina in patients with coronary artery disease. Thus, both the nature and the extent of the ischemic insult differ among the various preparations. Also, it is difficult to determine quantitative relations between degrees of ischemia and changes in diastolic function from these experiments because none of these experiments has been able to examine the relations between ischemia and diastolic function throughout an entire range of perfusion pressures rather than at two (or
at the most three) perfusion pressures. Finally, the vast majority of experiments have been performed in anesthetized animals or in isolated, perfused heart preparations. Although results obtained in these models are usually qualitatively similar to those seen in the conscious animal, they often differ significantly from those obtained under more physiologic conditions.

We therefore decided to use a conscious chronically instrumented dog model to examine the effects of progressive reductions in steady-state coronary perfusion pressure on diastolic properties by focusing on two issues: 1) the quantitative relations between coronary perfusion pressure and the rate and extent of ventricular relaxation, and 2) the interactions of associated physiologic phenomena, such as coronary blood flow autoregulation and systolic function, on the relations between coronary perfusion pressure and left ventricular diastolic properties. We examined the effects of ischemia on both the rate and the extent of diastolic relaxation because these two characteristics of diastolic relaxation can vary independently. The rate of relaxation was evaluated by measurements of the rate of pressure fall during isovolumic relaxation, and the extent of relaxation was assessed by position of the diastolic pressure–segment length curve. Using these data, we developed an integrated model of diastolic function in the conscious animal for a wide range of coronary perfusion pressures and blood flows.

Methods

Animal Preparation

The results described in this study were obtained from 10 dogs in a retrospective analysis of data obtained in experiments originally designed to examine the effect of changes in coronary artery pressure on transmural myocardial perfusion and systolic function in the conscious dog. An earlier study describes the experimental preparation as well as some systolic data obtained from five of these 10 dogs.24 Briefly, in a sterile procedure through a left thoracotomy, catheters were placed into the left atrium, descending thoracic aorta, and circumflex artery, and a micromanometer (Model P6.5 Konigsberg, Pasadena, California) was placed in the left ventricle through a stab wound. A fluid-filled inflatable hydraulic occluder cuff was placed around the proximal circumflex artery. Two pairs of 3-mm piezoelectric crystals were placed subendocardially in the distal circumflex and left anterior descending (LAD) regions to measure segment length. These crystals were oriented parallel to the estimated endocardial fiber orientation at an angle of approximately 30° to the circumferential plane. The crystals were located in the innermost 10% of the myocardium (90±10% of the distance across the wall), which was established at the time of necropsy. Catheters and crystal wires were then tunneled subcutaneously and exteriorized, the chest was closed, and the animals were given routine postoperative care for at least 2 weeks before any experiments. Catheters were flushed with sterile saline and filled with heparin at 1–3-day intervals.

Experimental Procedure

Studies were conducted during light sedation with 1–3 ml innovar-vet i.m. (0.4 mg/ml fentanyl and 20 mg/ml droperidol); the animals were conscious and easily excited but hemodynamics were stable for periods of 2–3 hours in the absence of extraneous noise or stimulation. The micromanometer was calibrated at the beginning of each study by matching the systolic pressure to that measured simultaneously in the ascending aorta and by matching left ventricular end-diastolic pressure to the peak atrial wave pressure measured simultaneously in the left atrium. After at least 30 minutes were allowed for hemodynamics to stabilize, control measurements of hemodynamics and regional function were obtained. Subsequently, progressive stepwise reductions in distal circumflex pressures were produced by inflating the hydraulic occluder cuff. After each adjustment in coronary pressure (initially 2–5 mm Hg, then 1–2 mm Hg once regional function began to decrease) at least 2 minutes were allowed for the achievement of steady state before data were obtained; the cuff was released once systolic function was absent. By these means, 10–54 steady-state periods of measurement were obtained in each animal. During each sampling period, regional function measurements (circumflex and LAD segment shortening) and hemodynamic measurements (heart rate, aortic pressure, distal circumflex pressure, left ventricular pressure, and dP/dt, which is the first derivative of left ventricular pressure and was differentiated with a cutoff filter of 100 Hz) were obtained during at least 20 cardiac cycles during approximately 15 seconds. In five dogs, regional myocardial perfusion at selected levels of coronary perfusion pressure was measured with microspheres using the reference withdrawal technique24,25; between two and four measurements of flow were made (at different perfusion pressures) in each of these dogs.

For the controls, data were obtained during 30 minutes and during an hour in two dogs without pressure reductions. There were no significant changes in any of the measured variables.

Data Analysis

Experimental data were recorded on an eight-channel 2800 W recorder (Gould, Cleveland, Ohio) at a paper speed of 100 mm/sec. Hemodynamic and sonomicrometer signals were digitized at a sampling rate of 200 Hz using a Data Translation DT 2801-A analog-to-digital-converter interfaced with an IBM PC AT computer.

For each beat, end diastole was defined as the onset of positive dP/dt, and end systole was defined as occurring 20 msec before peak negative dP/dt.
End-systolic and end-diastolic segment length (ESSSL and EDSL, respectively) dimensions were then established, permitting determination of systolic segment shortening \([% SS = 100(ESDL−ESSSL)/ESDL]\) for each beat during that experimental period.

The *time constant of isovolumic relaxation*, \(\tau\). For each beat, isovolumic relaxation was defined as the time period from 5 msec after peak negative dP/dt to the time at which left ventricular pressure had decayed to 5 mm Hg above the left ventricular end-diastolic pressure of the preceding beat. \(\tau\) was calculated by two techniques. The first assumes that left ventricular pressure falls monoexponentially toward zero during isovolumic relaxation \({}^{26}\) so that

\[
P(t) = P_0 e^{-\tau t}
\]

and

\[
\ln(P) = -(1/\tau) t + \ln(P_0)
\]

where \(P\) is left ventricular pressure (and \(P_0\) is left ventricular pressure at time zero), \(t\) is time, and \(\tau\) is the time constant of isovolumic relaxation. With this technique, \(\ln(P)\) was plotted against time during isovolumic relaxation for each beat, a line was fit to the relation by a least squares fit, and \(\tau\) was calculated as the negative reciprocal of the slope of this line. The values of \(\tau\) obtained for each beat were then averaged to produce a mean value for that experimental period.

A second value of \(\tau\) was calculated assuming that the asymptote to which left ventricular pressure declines during isovolumic relaxation is not necessarily zero. \({}^{27}\) Thus

\[
P(t) = (P_0−P_b)e^{-\tau t} + P_b
\]

where, in addition to the symbols described previously, \(P_b\) is the pressure axis intercept, that is, the pressure to which left ventricular pressure would decay given infinite time. With this model, dP/dt is a linear function of ventricular pressure \({}^{27}\):

\[
dP/dt = -(1/\tau)(P−P_b)
\]

With this method, dP/dt was plotted against ventricular pressure during isovolumic relaxation for each beat, and \(\tau\) was calculated as the negative reciprocal of the slope of a line fit to this relation by a least squares fit. The values of \(\tau\) for each beat were then averaged to obtain a mean value for that experimental period.

*Pressure-segment length relations.* By plotting the left ventricular pressure against the segment length, we were able to obtain the pressure-length relations for the entire cardiac cycle. Our method of analysis (using beat averaging of all beats within the experimental period) is shown graphically in Figure 1. Each beat in every experimental period was examined to select all points occurring more than 3.5 \(\tau\) after peak negative dP/dt and before the onset of positive dP/dt (Figure 1A). These limits were chosen to exclude any effects of tension generated during systolic contraction on the pressure-segment length relation. Because systolic left ventricular pressure decays with a time constant \(\tau\), the effect of pressure from the preceding systole should be negligible 3.5 time constants after end systole \({}^{28}\) whereas pressure generation from the next contraction will not begin until after the onset of positive dP/dt. Figure 1A shows the diastolic pressure-segment length curves from one experimental period (solid lines), with points excluded from analysis shown as dots. Maximum and minimum segment lengths were determined, and the intervening distance was divided into 25 equal segments (vertical lines in Figure 1A). For each experimental period, all measurements of left ventricular pressure corresponding to a segment length within one of the 25 segments were averaged to obtain a composite diastolic pressure-segment length relation for that experimental period (Figure 1B). Segment length ranges with fewer than five left ventricular pressure measurements were arbitrarily rejected and are not included in the data analysis. For comparing the slopes of these composite diastolic pressure-segment length relations, the relations were plotted as log pressure versus segment length and the slope determined by least squares regression.

In all dogs, the diastolic pressure-segment length curve shifted downward and to the right during progressive coronary artery constriction; this shift began at a circumflex pressure of approximately 40 mm Hg. To quantify the extent of this shift without making any mathematical assumptions about the nature of the pressure–segment length relation, we developed the technique shown in Figure 1C–E. First, a control diastolic pressure-segment length curve was established for each dog by averaging the composite diastolic pressure-segment length curves from all experimental periods with a perfusion pressure above 50 mm Hg. The technique used is similar to the one described above. All of the individual composite segment length curves were plotted together, and the distance between the minimum and maximum segment lengths was divided into 25 segments (Figure 1C). All values of left ventricular pressure corresponding to circumflex segment lengths within each of the 25 segment length ranges were averaged to yield a control diastolic pressure-segment length curve (Figure 1D). Next, we quantified the shift of the individual pressure–segment length curves by comparing the shift to this control curve (Figure 1E); the extent of the shift was defined as the average vertical distance between the two curves. Because the pressure–segment length curves shifted to the right at lower perfusion pressures, the overlap between the control and experimental curves decreased as the perfusion pressure decreased (i.e., the five rightmost points in Figure 1E are not included in this calculation). We arbitrarily decided not to compare pressure–segment length curves when this overlap consisted of fewer than six ranges of segment length.
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As an internal control, diastolic pressure–segment length curves for the LAD region were calculated in the same manner. Unlike the circumflex territory, there was no consistent shift of the LAD pressure–segment length curves. The changes that did occur could reflect baseline drift of the micromanometer or the minimal changes in pleural pressures seen after beat averaging of more than 20
beats. (Hess et al. reported changes in pleural pressure ranging from -0.3 to -1.1 mm Hg when averaging 11–18 beats; we averaged 20–30 beats.) Although these changes are minimal, we nevertheless corrected the amount of shift of the circumflex curves by subtracting the shift of the LAD territory during the same experimental period, which ranged from 1.4 to -2.9 mm Hg (mean, -0.21±0.69 mm Hg). Thus, the shift of circumflex diastolic pressure–segment length curves shown in the upper panels in Figure 4 has been corrected by the shift of the LAD pressure–segment length curves (shown in the lower panels). Because the LAD territory shift is negative at the lowest mean circumflex pressures, the extent of the shift in the circumflex territory at these pressures would have appeared more negative had the LAD shift not been subtracted.

For each dog, results from all experimental periods within every 5-mm Hg range of mean circumflex pressure were first averaged. Results from all dogs were then averaged at each range of mean circumflex pressure to produce summary graphs. Thus, each point in Figure 4 represents the mean±SD of different dogs at that circumflex pressure. Comparisons of the effects of changes in circumflex pressure on the position and the slope of the composite pressure–segment length curves were performed with analysis of variance. Least squares linear regression was performed with standard techniques.

**Results**

During the control periods, the 10 dogs had an average heart rate of 102±10.2 beats/min, a blood pressure of 89±7.4 mm Hg (105±7.0/74±8.2 mm Hg) and a left ventricular end-diastolic pressure of 6±3.2 mm Hg. At the end of the experiment, the mean circumflex pressure was 23±5.6 mm Hg, and neither the mean aortic pressure (88±8.8 mm Hg) nor heart rate (108±14.7 beats/min) had changed significantly.

Complete pressure–segment length loops for individual beats are shown in Figure 2 for both the LAD and circumflex territories during progressive reductions in circumflex pressure in one dog. Reducing perfusion pressure from 100 to 50 mm Hg does not affect the pressure–segment length curves significantly, whereas further reductions in circumflex pressure cause the pressure–segment length curve for that region to shift to the right. At the lower pressures, the circumflex territory lengthens during isovolumic contraction and shortens during isovolu-
mic relaxation, whereas the reverse is seen in the LAD territory. Thus, the nonischemic region stretches the ischemic region during isovolumic contraction and is stretched by it during isovolumic relaxation.

The lower panels in Figure 2 show the effect of progressive ischemia on the diastolic portion of the pressure–segment length loops. The diastolic circumflex pressure–segment length curve is not significantly affected by pressure reductions throughout the range of 100–50 mm Hg. Further reductions cause the curve to shift progressively to the right, indicating an increase in ventricular volume at any given pressure. No such changes are seen in the diastolic portion of the LAD pressure–segment length loop, and apart from an increase in segment length at the end of isovolumic relaxation (discussed above), the curves are unchanged.

Diastolic pressure–segment length curves averaged between 20 and 30 beats (Figure 3) show the same rightward and downward shift. When the extent of this shift is quantified, a graph of the downward shift plotted against circumflex pressure can be produced and is shown for the ischemic and control regions in Figure 4. Mild reductions in circumflex pressure (to pressures above approximately 50 mm Hg) had no effect on the position of the diastolic pressure–segment length curve, whereas further reductions in pressure were associated with marked and progressive movement of the curve downward and to the right. As shown in the lower panel of Figure 4, no such effect was seen on the LAD pressure–segment length relation. Lowering circumflex perfusion pressure had no significant effect on the slope of the diastolic pressure–segment length curve, calculated assuming an exponential relation (Figure 5, \( p > 0.25 \) by analysis of variance), although there did appear to be a trend toward an increase in slope at lower circumflex pressures.

In five dogs, we were able to measure coronary blood flow using microspheres. The upper panel in Figure 6 shows the shift of the pressure–segment length curve plotted against endocardial blood flow.
Previous work from our laboratory has shown that systolic function and flow are closely linked in this experimental model. When the shift of the pressure–segment length curve is plotted against segment shortening, which is an index of systolic function (Figure 6, lower panel), it follows a linear pattern. Both of these relations showed a reasonably high degree of correlation ($r=0.81$ and 0.93, respectively).

The rate of relaxation was assessed by peak negative dP/dt and $\tau$, which is the time constant of pressure decay during isovolumic relaxation (calculated as a monoexponential value using both the fixed and variable asymptotic techniques as described above). The data fit both models for $\tau$ very well ($r=-0.997 \pm 0.003$ and $r=-0.975 \pm 0.039$ for the fixed and variable asymptotic techniques, respectively). The rate of relaxation decreased progressively as coronary perfusion pressure decreased. Results are shown for $\tau$ (calculated assuming a variable asymptote) in Figure 7 (upper panel); similar results (not shown) were obtained with the other indexes of relaxation. These changes are clearly most marked at the lower pressures, although decreasing pressure throughout the higher ranges also decreased the rate of relaxation significantly.

The slope of a line fit to the points at circumflex pressures greater than 50 mm Hg was significantly different from zero ($p<0.01$ and $p<0.05$ for the fixed and variable asymptotic techniques, respectively; $p<0.01$ for peak negative dP/dt).

The variable asymptotic technique for calculating $\tau$ also provides a measure of $P_b$, which is the pressure the ventricle would reach if isovolumic relaxation were infinitely prolonged. The effect of decreasing circumflex perfusion pressure on $P_b$ was similar to the effect on the pressure–segment length loop in that there was no effect of mild pressure reductions (to pressures above 50 mm Hg), whereas more severe pressure reductions caused a progressive fall in $P_b$ as shown in the lower panel of Figure 7.
Discussion

Extent of Diastolic Relaxation in the Ischemic Zone in the Conscious Animal

Figures 2–4 show the effect of progressive reductions in coronary perfusion pressure on the regional diastolic pressure–segment length curves. At coronary pressures above 40–50 mm Hg, reductions in circumflex pressure do not affect the position of the pressure–segment length curve, but further reductions in pressure cause a progressive rightward and downward shift of the pressure–segment length curve. The same effect of coronary perfusion pressure on global relaxation is evident in the effect of pressure reductions on \( P_b \), shown in Figure 7. \( P_b \), the intercept of the \( dP/dt \)-pressure relation during isovolumic relaxation, is the equilibrium pressure at that ventricular volume, that is, the pressure the ventricle would attain during an infinitely long isovolumic relaxation. Thus, at a constant end-systolic volume, changes in \( P_b \) reflect changes in the pressure-volume relation.\(^7,8,10\) We do not have any direct measurements of end-systolic volume, but we may reasonably infer that it does not decrease during ischemia. Thus, the equilibrium pressure is less when volume is either unchanged or increased, indicating a downward shift of the pressure-volume curve, a global effect consistent with the regional changes shown by the rightward shift of the pressure–segment length curves.

Although it is known that the position of the diastolic pressure segment–length curve is affected by myocardial ischemia, there have been no quantitative investigations into the interactions between coronary perfusion pressure, flow, systolic function, and the diastolic pressure–segment length curve. Indeed, even the qualitative aspects of these relations have been unclear; in different models, ischemia appears to have opposite effects on the diastolic pressure–segment length curve. The effect shown in our experiments, a downward shift of the pressure–segment length curve during decreased coronary perfusion pressure, was first reported by Salisbury et al\(^9,29,30\) and has been seen in two different experimental models. In the isolated, perfused heart\(^6,13–16\) and the anesthetized dog,\(^17–22\) coronary artery occlusion markedly shifts the diastolic pressure-volume loop downward and to the right. In the conscious animal, as well, coronary occlusion has been shown to increase diastolic dimensions at zero transmural pressure, the “creep” phenomenon.\(^9,21,22\) Only three previous studies have examined the relation between diastolic pressure and volume (or segment length) at pressures other than normal flow or complete occlusion. In the conscious animal, Hess et al\(^9\) found that complete, but not partial, coronary occlusion increased diastolic dimensions at zero transmural pressure, which is consistent with our results. The other two studies used an isolated heart model of cardiopulmonary bypass during potassium-induced asystole; in this preparation, the diastolic pressure-dimension relation changed when perfusion pressure was reduced from 150 to 80 mm Hg\(^13\) or from 120 to 80 and 40 mm Hg.\(^14\) Thus, they did not find the plateau seen in the range of 40–100 mm Hg of Figures 4 (upper panel) and 7 (lower panel). The differences between their experiments and those performed in the conscious animal may be related to the relatively less physiologic experimental conditions or to changes in the capacity for flow autoregulation, which could be affected by anesthesia\(^24\) as well as by the high levels of potassium. In addition, a certain amount of myocardial ischemia and damage is unavoidable in acute preparations on cardiopulmonary bypass, and the relation between coronary perfusion and the position of the diastolic pressure–segment length curve is markedly accentuated in the injured heart.\(^15,16,31\)

The perfusion pressure at which the diastolic pressure–segment length curve began to shift downward was indistinguishable from the lower limits of flow autoregulation, and the upper panel of Figure 6 shows a reasonably high degree of correlation between the shift of the pressure–segment length curve plotted and the endocardial blood flow measured using microspheres. The number of data points is small, however, and the nature of the relation cannot be adequately assessed from this graph alone. Work from our laboratory has indicated that flow is tightly coupled to systolic function in the conscious animal\(^24\) and the relation between systolic function and the shift of the pressure–segment length curve appears linear (Figure 6, lower panel), supporting the hypothesis that endocardial blood flow, systolic function, and the extent of diastolic relaxation are linearly related. In contrast, Hess et al\(^9\) reported that partial coronary occlusion (defined as the stenosis required to reduce wall thickening by 60%) was not associated with any changes in global diastolic function (as assessed by ventricular dimensions at zero transmural pressure). Possible reasons for this discrepancy include the different techniques used to evaluate diastolic function. Hess et al\(^9\) measured global ventricular diastolic function, whereas we measured changes in the ischemic region.

A number of possible mediators of the increase in diastolic relaxation seen during complete occlusion have been proposed. Cross et al\(^30\) suggested that “the coronary vessels become . . . more rigid, when the intracoronary pressure increases. The coronary tree apparently functions as a semirigid, resilient skeleton embedded in the myocardium, imparting its mechanical properties to the ventricular wall.” Other investigators have suggested that the link between intravascular pressure and diastolic function is more indirect, mediated by changes in ventricular wall thickness,\(^32,33\) systolic stretch of the ischemic segment,\(^18,21,22\) pericardial constraint, or various metabolic parameters, including decreases in high-energy phosphate levels and pH, which may
be related to changes in diastolic fiber tension. Our studies do not support the original mechanism proposed by Salisbury and colleagues because intravascular pressure (at least within the autoregulatory range) was not directly related to the shift of the diastolic pressure–segment length curve in these experiments. As the pericardium was left open in our preparation, pericardial constraint probably did not play a significant role in our experiments; in any case, the pericardium would tend to shift the diastolic pressure–segment length curve upward rather than downward.

Contrary to our results, a number of other investigators have reported that the diastolic pressure–segment length curve shifts upward during, or immediately after, ischemia. Again, these changes have been reported in different models, in patients during or immediately after anginal episodes, in dogs with stenoses on both coronary arteries immediately after pacing tachycardia, and in the isolated, perfused heart. To reconcile these observations, some investigators have proposed a model distinguishing “supply” ischemia (a primary decrease in coronary blood flow that is associated with a secondary decrease in myocardial systolic work and oxygen demand) from “demand” ischemia (a primary increase in myocardial systolic work and oxygen demand in the setting of limited coronary blood flow). They postulate that supply ischemia is associated with a downward shift and that demand ischemia is associated with an upward shift of the diastolic pressure–segment length curve (for review, see Apstein and Grossman). Within this framework, our experiments fit into the category of supply ischemia, and the downward shift seen in our preparation would, therefore, be consistent with this model. Nonetheless, differentiating between supply and demand ischemia can explain many but not all of the available data. For example, Wijns et al reported that the diastolic pressure–segment length curve shifts upward during coronary angioplasty, an intervention that should correspond to supply rather than to demand ischemia.

A number of other investigators have reported increases in the slope of the pressure–segment length or stress-strain relation during total coronary occlusion, but we did not see any significant changes in the slope of diastolic pressure–segment length relation when lowering mean circumflex pressure (Figure 5). This could be due to a less-precise method of analysis (because we do not have an unstrained length, we cannot calculate the stress-strain relation) or to the fact that we did not achieve total coronary occlusion. One study has reported no changes in the slope of the stress-strain relation during partial coronary occlusion. There does appear to be a trend toward an increase in slope at the lowest circumflex perfusion pressure included in this study. This is consistent with the idea that very severe reductions in circumflex perfusion pressure, close to total occlusions, might be needed to affect the slope of the pressure–segment length relation.

The Rate of Relaxation

Our data indicate that isovolumic relaxation slows progressively as coronary perfusion pressure decreases in the conscious dog. Previous investigations have reported that the rate of isovolumic relaxation, reflected by peak negative dP/dt or τ, decreases during ischemia, but these investigations have not provided any information on the quantitative aspects of this association. Figure 7 (upper panel) shows that there are two phases to this relation and that the sensitivity of the rate of isovolumic relaxation to reductions in coronary perfusion pressure depends on the pressure achieved. Below the limits of flow autoregulation, the rate of isovolumic relaxation is very sensitive to changes in coronary perfusion pressure. Within the autoregulatory range, however, the effects of decreasing circumflex arterial pressure, though significant, are much less pronounced. In retrospect, it is possible to fit a number of earlier results into this scheme. Many investigators have reported that the rate of isovolumic relaxation is perhaps the most sensitive index of ischemia, decreasing before (or in the absence of) global or regional changes in systolic function. These results may be analogous to pressure reductions within the autoregulatory range in the upper panel of Figure 7; such changes in circumflex pressure, though causing small changes in indexes of isovolumic relaxation, do not affect systolic function or endocardial flow in the conscious animal. On the other hand, coronary occlusion markedly decreases the rate of isovolumic relaxation in anesthetized and conscious animals. These changes would be equivalent to the pronounced decreases in the rate of isovolumic relaxation seen at the lowest circumflex pressures in Figure 7. Hess et al also measured indexes of the rate of isovolumic relaxation during reductions in coronary perfusion pressure short of total occlusion. They reported that peak negative dP/dt decreased at perfusion pressures that reduced systolic function to 40% of control; τ also increased in the ischemic zone, but these changes were not statistically significant. In our model, reduced systolic function occurs at pressures below 40 mm Hg, a range in which we too see decreases in indexes of the rate of isovolumic relaxation.

The large decrease in indexes of global relaxation seen at more severe levels of circumflex ischemia probably reflects the delayed contraction in the ischemic territory shown at the lower perfusion pressures in Figure 2. Tennant and Wiggers first showed that coronary artery occlusion is associated with contraction of the ischemic zone during isovolumic relaxation, and Gibson et al and Waters et al were the first to point out that this delayed contraction could decrease the rate of isometric relaxation, an idea that has since been confirmed by numerous other investigators.
cesses, such as direct effects of ischemia on the biochemical processes, especially calcium fluxes, involved in relaxation or changes in loading conditions due to uncoordinated patterns of ventricular contraction may also be involved (for review, see Brutsaert et al[37]). Because these mechanisms rely on the presence of ischemia or changes in systolic function, however, they cannot explain the decreased rate of relaxation we see at coronary perfusion pressures within the autoregulatory range when neither blood flow nor systolic function have decreased measurably. Although small changes in endocardial blood flow or function below the resolution of our measuring system might have occurred, a more plausible explanation for the increased rate of relaxation in the autoregulatory range could be the turgor or erectile effect. An increase in the pressure in the coronary bed could increase the rigidity of the "resilient skeleton embedded in the myocardium" postulated by Salisbury et al,[29,30] which in turn may stretch the sarcomeres in early diastole; thus, decreases in intracoronary pressure could decrease the rate of relaxation. Further investigations will be needed to elucidate the mechanisms involved in this phenomenon.

In summary, we have shown that reductions in coronary perfusion pressure in the conscious dog have different effects on the extent and the rate of diastolic relaxation (shown by changes in the pressure-segment length curves and in τ, respectively). Within the autoregulatory range, coronary perfusion pressure does not affect coronary blood flow, the diastolic pressure-segment length curve, or systolic function measurably, but it does decrease the rate of isovolumic relaxation slightly. Further reductions in coronary perfusion pressure, which reduce blood flow and systolic function, shift the diastolic pressure-segment length curve downward and decrease the rate of isovolumic relaxation markedly.

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