Regional Myocardial Function and Dimensions
Early and Late after Myocardial Infarction in the
Unanesthetized Dog

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SUMMARY Pairs of ultrasonic dimension gauges and a micro-
manometer implanted in the subendocardium of the left ven-
tricles of unanesthetized dogs were used to analyze serial
changes in hemodynamic status and segmental function for up to
4 weeks after permanent circumflex coronary artery occlusion.
Regional function was studied in control segments and in seg-
ments identified as marginal (hypokinetic) and ischemic. In three
dogs, after transient regional dysfunction, no myocardial infarc-
tion developed, whereas in five dogs regional dysfunction at 3
weeks after occlusion was followed by the development of per-
sistent dysfunction and infarction. Left ventricular end-diastolic
pressure increased progressively, but in marginal segments EDL
was 12% below control and in the ischemic segments 30% below
control by 4 weeks. Progressive increases in percent active
shortening occurred in control segments, but holosystolic bulging
was replaced by akinesia in ischemic segments, and persistent
reduction in shortening was present in marginal segments at 4
weeks. Correlations were found between percent scar and reduc-
tions in percent shortening, EDL, and the ratio of change in di-
astolic length to change in diastolic pressure. These methods
have detected hyperfunction in normal regions and variable seg-
mental loss of contractile function, together with reduction of
subendocardial dimensions and changes that may reflect de-
creased diastolic compliance in ischemic regions. We conclude
that this model for the conscious animals may be useful for study-
ing the influence of therapy on the extent of myocardial dam-
age after experimental coronary occlusion.

USING AN external dimension gauge, Tennant and Wigger's first documented the development of a systolic bulge in the ischemic region very early after coronary occlusion. Recent studies on regional myocardial function using pairs of miniature ultrasonic crystals implanted in the left ventricu-
lar subendocardium in both open-chest and chronically

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suitable for studying the possible influence of therapy designed to modify myocardial ischemic injury and infarct size. Therefore, we have studied the evolution of changes in dynamic function and dimensions in several myocardial segments of the left ventricle in unanesthetized dogs for up to 4 weeks after coronary occlusion.

**Methods**

The dogs were studied after recovery from an operation at which a high fidelity pressure manometer (Konigsberg, P-22) and a Silastic tube were inserted into the left ventricular chamber, and pairs of ultrasonic crystals were implanted in the subendocardium of the left ventricular wall. One pair was placed in a segment near to (but not in) the base of the posterior papillary muscle, one pair in a normal segment of the anterior wall, and the third pair in the wall well lateral to the posterior papillary muscle. The circumflex coronary artery was dissected free at its origin and a Doppler ultrasonic flowmeter probe was placed around the vessel; a hydraulic cuff was positioned distal to the probe. The pericardium was left open and all wires were exteriorized to the back of the dog.

Of 17 dogs operated on we were able to obtain serial studies successfully in eight dogs. In these there was satisfactory function of instrumentation, and a healthy condition was sustained for several weeks after the coronary occlusion. Studies were made at least 10 days after operation with the unanesthetized dog lying quietly on its left side. Recordings were made in the control state prior to coronary occlusion on two different days and averaged. Zero reference for pressure was at the midstest level. Morphine sulfate [5 mg, intravenously (iv), and 15 mg, subcutaneously (sc)] was administered about ½ hour prior to the coronary occlusion to obviate any delayed excitement or pain reaction, and the dogs remained awake, or lightly asleep but easily arousable. The coronary occlusion then was induced while monitoring coronary blood flow; the signal from the flowmeter was subsequently recorded during each study to ensure complete and sustained interruption of circumflex coronary blood flow. Recordings were made in the dogs for 3 hours after the coronary occlusion. Subsequently, studies in five of the dogs were made at 1 day, 2 days, and then at weekly intervals for 3 or 4 weeks; in two dogs the follow-up period was limited to 3 weeks because rapid severe heart failure developed in one and sudden death occurred in the other. The results in three of the eight dogs were analyzed separately, because early responses induced by the coronary occlusion were typical, but substantial recovery of segmental function then occurred during the first 3 hours of observation. Segments in the remaining five dogs were categorized by time trend analysis (see below) into three different groups: control segments, marginal segments, and ischemic segments. These groups exhibited normal function, reduced function, and dyskinesis (systolic expansion), respectively, at 3 hours after coronary occlusion. Five segments were included in each of these three groups, although not every dog had three different types of segments. All results reported were calculated in the resting state at the existing heart rate except on days 1 and 2, when procainamide (100-600 mg, iv) was given to obtain tracings in sinus rhythm; this procedure achieved sinus rhythm temporarily in all dogs and was necessary to avoid abnormal regional contraction patterns during the ectopic ventricular beats and bursts of ventricular tachycardia frequently observed during this period. After the 2nd day, however, no medications were given.

Ultrasonic measurements were made as previously described. An effort was made to determine the expected error produced by changing experimental conditions. The change in the velocity of sound with temperature in saline is on the order of 0.1% per degree at 37°C, and this source of error was neglected. To determine the maximum change in the velocity of sound in myocardium expected in this study, the velocity of sound was determined in freshly excised normal and fully scarred myocardium immersed in normal saline at 37°C. The velocity of sound in fully scarred tissue was 1.65 mm/μsec, or 3.1% greater than the velocity (1.60 mm/μsec) in normal myocardium. Thus, a very slight error in length due to a gradual small increase in the velocity of sound could have occurred in ischemic segments; if complete scar was present, this could have changed from 30% to as low as 27% of the average decrease in end-diastolic length noted in ischemic segments. In another evaluation in vitro, the transducers were attached to the opposing faces of a micrometer and immersed in normal saline at 37°C. The predicted absolute distance differed from the distance measured by the micrometer by less than the transducer thickness, i.e., <1.0 mm, and the change in separation of crystals could be predicted from transit time to within 0.02 mm, a capability that should be approximated in myocardium. A similar error in absolute distance (less than transducer thickness) was found when previously implanted crystals were exposed at autopsy of fresh myocardium and the separation of crystals, measured by calipers, was compared with the average separation computed from the measurement of transit time; studies at post mortem in fixed hearts also have indicated good agreement between in vivo and anatomical measurements. The stability of length measurements was examined over 10- to 20-day periods in five dogs in the resting state, in which coronary artery occlusion was not performed. In 13 segments the initial and final end-diastolic segment lengths did not differ significantly; the average increased by 0.62 ± 1.02% (SEM), as the average heart rate fell somewhat (15%) over this period.

The micromanometer was calibrated electronically from pressure recorded via the indwelling tube; occasionally, when the latter recording was not of adequate quality, a retrograde catheterization of the left ventricle was performed. All data and appropriate calibration signals were recorded on FM tape (Honeywell model 5600) and the analog signals of left ventricular pressure, dP/dt, and the pressure recorded via the indwelling tube; occasionally, when the latter recording was not of adequate quality, a retrograde catheterization of the left ventricle was performed. All data and appropriate calibration signals were recorded on FM tape (Honeywell model 5600) and the analog signals of left ventricular pressure, dP/dt, and the segments were digitized at 5-msec intervals using a hybrid computing system (EAI model 590). During this process, using the time of peak dP/dt as the reference signal, the average cardiac cycle length was obtained, beats outside a 100-msec range from the average were rejected, and 20 to 40 beats were averaged. Variables analyzed included...
left ventricular end-diastolic pressure, peak left ventricular pressure, peak positive dP/dt, end-diastolic segment length, and percent shortening calculated as the difference between the end-diastolic length and end-systolic length divided by end-diastolic length (× 100). As previously described, end-systolic length was taken as the nadir of the shortening tracing within 20 msec of peak negative dP/dt, and the data on end-diastolic length were normalized to a 10-mm segment length.

Digital x-y plots of left ventricular pressure vs. the segment lengths were obtained for several selected, averaged beats. The relationship between length (L) and pressure (P) during diastole was expressed by the equation, Ln P = slope L + intercept, using multiple simultaneous pressure and length points obtained from the onset of the slow filling phase (at pressures above 4 mm Hg) up to end-diastole. The reported slopes of the relationship between segment length and log-pressure were calculated from several averaged beats. In the control state, points at elevated diastolic pressures were obtained following an bolus injection of phenylephrine (0.05 to 0.1 mg), so that the higher range of pressures could be compared with the somewhat higher pressures often present after coronary occlusion.

At the end of each study the hearts were fixed with formaldehyde and sliced. The positions of the crystals then were assessed from drawings of each section; in the segments used in this study the crystals were inserted about 8 mm from the epicardium to within 0.5–3 mm of the endocardium and were not within the base of the papillary muscle. The segments between the crystals were carefully dissected en bloc to include the two crystals of each pair. These blocks then were subdivided to an appropriate size for histological examination and coded so that the observer interpreting the histology did not know the origin of the tissue. On histological examination, the amount of scar tissue in the block between the two crystals of each pair was estimated quantitatively. Nine blocks suitable for such analysis were obtained from marginal and ischemic segments.

In all statistical analyses a P value < 0.05 was considered significant. For the hemodynamic data, a single factor analysis of variance with repeated measures over time was used. For variables significantly different over time, a Dunnett's test was performed to determine those times at which the mean differed from its control value. The segment length data (end-diastolic length, percent shortening) were placed into three groups (control, marginal, ischemic) and a two-factor analysis of variance with one group factor (segment type) and one repeated measures factor (time) was employed. Standard procedures for testing time effects within each segment and segment differences at each point in time were employed. If significant, times within each segment were compared to the control by Dunnett's test. All possible comparisons among segment groups (control-marginal, marginal-ischemic, control-ischemic) at each time were made by Tukey's highest significant difference test. The analysis of variance program employed was BMD-PQV on an IBM 370/95 computer.

**Results**

**EARLY CHANGES FOLLOWING CORONARY OCCLUSION**

Two patterns of early response to coronary occlusion were observed. Although the acute responses to the coronary occlusion were similar in all dogs, segmental function recovered subsequently during the 3-hour occlusion in three dogs, whereas in the remaining five it did not. In the three dogs exhibiting early recovery, the coronary blood flow remained at zero throughout the study despite the return of segmental myocardial function. However, at 2 or 3 hours after coronary occlusion, increasing the heart rate by cardiac pacing in each of these three dogs resulted in prompt deterioration of segmental function with development of holosystolic expansion in the ischemic zone. This deleterious effect of increasing heart rate persisted in all three dogs during the first few days after coronary occlusion, but after 1 week the segmental responses during pacing became normal. During subsequent follow-up of these three dogs, hemodynamic measurements and the dimensions of the three segments remained close to the control values, and at post mortem examination no infarct, or an infarct of less than 1% of the left ventricular weight, was found.

**SERIAL CHANGES AFTER CORONARY OCCLUSION**

Data obtained in the five dogs that did not recover function during 3 hours of coronary occlusion, described below, are summarized in Table 1. During the acute phase of coronary occlusion, segment function in ischemic, marginal, and control segments was the same as that previously described.

**Serial Hemodynamic Changes**

Early after the coronary occlusion (5 minutes and 2 hours) heart rate was significantly increased and left ventricular end-diastolic pressure tended to rise, but this change was not significant; left ventricular systolic pressure did not vary significantly throughout the study. At 8–12 hours after the coronary occlusion, a phase of frequent ventricular premature contractions and ventricular tachycardia began which lasted from 2 to 6 days (average, 3 days) (Fig. 1), and the values on days 1 and 2 were calculated after procainamide had been administered to produce sinus rhythm. At that time, heart rate remained significantly faster than control. Peak positive dP/dt did not change significantly, except at 3 weeks, when it was increased. Because of considerable scatter, the left ventricular end-diastolic pressure changes were not significant throughout the study period.

**Serial Changes in End-Diastolic Segment Lengths**

The changes in the three types of segments are given in Table 1 and tracings from a single experiment are reproduced in Figure 1. The average percent changes are summarized in Figure 2 (upper panel).

There was a significant effect of time in all three segments. Control segments exhibited an increase in mean...
Serial Changes in Active Shortening

The changes in percent shortening of the three segments are given in Table 1. The tracings in Figure 1 show a representative experiment, and the average changes are summarized in Figure 2 (lower panel).

In the control segments, compared to the preocclusion value the percent shortening was significantly increased at 1, 2, and 3 weeks. There was no significant reduction in shortening at 1 time point because procainamide was used. In the marginal segments, compared to the preocclusion value the percent shortening was significantly reduced at all time periods from 3 minutes to 3 weeks. In addition, there was a significant increase from the reduced value at 1 day to the value at 3 weeks (Fig. 2, lower panel), suggesting some recovery of function. In the ischemic segments, compared to preocclusion values the percent shortening was reduced at all time periods from 5 minutes to 3 weeks.

There were no significant differences in percent shortening between the three groups of segments in the preocclusion period. The differences between percent shortening of the control, marginal, and ischemic segments were significant at all subsequent time periods from 5 minutes to 3 weeks (Table 1).

Serial Changes in Passive Length-Pressure Relations

Following coronary occlusion, different responses of the relationship between diastolic pressure and length were observed in the three segments. The length-pressure rela-
FIGURE 1 Tracings obtained from an unanesthetized dog in the control state (left panel) and following permanent coronary occlusion for 4 weeks. The calibrations for the right panels are the same as those shown on the left, the slow tracings are all taken at the same paper speed, and the paper speed during the initial and final tracings is the same. The heart rate (cardiotachometer) is shown in the lower tracings. Normal shortening of all three segments is evident in the left panel. Severe dysfunction is evident after 2 hours of coronary occlusion in the marginal and ischemic segments, whereas the control segment exhibits increased end-diastolic length and increased shortening. Severe arrhythmia is present at 1 day. Subsequently, the control segment exhibits an increasing end-diastolic length and improved shortening. The marginal segment exhibits an increase in dimension at 1 and 2 days, and then a progressive reduction in the segment dimension occurs, severe hypokinesis being evident in the tracing at 4 weeks (shown at rapid paper speed). The ischemic segment exhibits even more severe reduction in the dimension and there is akinesis at 4 weeks. LV = left ventricular.

Correlation of ischemic segment in a representative dog over time is illustrated in Figure 3, and the average slopes for all three segments are given in Table 1.

Although there was considerable scatter in the data, analysis of variance showed significant differences over time in the slopes of the pressure-length relations in the marginal and ischemic segments, but not in the control segments. In addition, in the ischemic segments the slope was significantly increased compared to preocclusion at all points in time from 5 minutes to 3 weeks; there also was a significant increase in slope between 1 and 2 days and 3 weeks. There was no significant difference between slopes prior to coronary occlusion in the three segments. The slope at 3 weeks was significantly higher in the ischemic segments than in the control and marginal segments (Table 1).

CORRELATIONS BETWEEN SEGMENT FUNCTION, DIMENSION CHANGES, AND HISTOLOGICAL ALTERATIONS

Correlations were made between segment function and dimensions and the percentage of scar tissue found on histological examination in sections taken between the crystals 3 or 4 weeks after coronary occlusion. The percent scar was compared with the percentage dimension changes from preocclusion values in the marginal and ischemic segments during the last study prior to postmortem examination. A correlation was found between the percent decrease in end-diastolic length and the percent scar (Fig. 4, left panel); segment lengths were decreased in the subendocardial region by approximately 30% when scar formation was complete. A correlation also was seen between the percent decrease in active shortening and the percent scar (Fig. 4, middle panel), complete loss of shortening being associated with nearly 100% scar on histological examination; it further appeared that rather substantial loss of function occurred with scar formation of 25% or less, giving a nonlinear shape to the relationship. Finally, the percent decrease in the ratio of the change in diastolic length to the change in diastolic pressure (Fig. 4, right panel), which may reflect decreasing compliance of the subendocardial segment, showed a nearly linear correlation with a percentage of scar when plotted on a log scale.

Discussion

There have been several studies of the acute and chronic changes that occur in overall left ventricular performance in dogs following experimental coronary occlusion and...
myocardial infarction. However, studies on regional myocardial function have dealt mainly with the effects of acute coronary occlusion, and there have been few studies on regional myocardial function during the healing phase of experimental myocardial infarction. Data obtained with mercury-in-rubber segment length gauges in anesthetized, open-chest dogs indicate that stiffening of the infarcted zone occurs several days after coronary occlusion.

Khavan et al., using Walton-Brodie strain gauge arches sutured to normal and ischemic areas, studied segmental myocardial tension development in open-chest dogs 8-10 weeks after the insertion of an ameroid constrictor around a coronary artery; they showed increased passive tension and an insignificant reduction in systolic tension in ischemic regions. Differences in the experimental model and in the method for assessing active function make comparisons with our study difficult, but their findings suggest that there was less loss of active function, perhaps due to collateral development with use of the ameroid constrictor. Active force recorded with strain gauge arches of this type can be influenced by forces generated in adjacent myocardium.

The ultrasonic technique used in the present study, which in effect provides a forceless dimension gauge, allowed stable dynamic measurements of active shortening.
properties and diastolic events throughout the cardiac cycle. The miniature crystals used are not sutured to the myocardium but are contained within a thin rim (<1 mm) of fibrous tissue, being moved toward one another under normal conditions primarily by contraction of the myocardium subtended between the pair of crystals.2,4 Thus we believe the present study has provided for the first time direct measurements of regional myocardial dimensions and function during the early and healing phases of myocardial infarction in the unanesthetized animal.

Studies in the three dogs that exhibited early recovery of function within 3 hours after coronary occlusion bear comment. This recovery could have reflected return of oxygen supply via coronary collateral vessels sufficient to maintain cardiac metabolic needs in the basal state; however, deterioration of regional function could be induced when oxygen demands were increased by rapid pacing during the first few days after coronary occlusion. Such rapid development of coronary collaterals after partial coronary occlusion has been well documented.21 After several days of coronary occlusion the collateral circulation appeared to develop further, preventing ischemia from occurring even at a rapid heart rate.

In the five dogs that developed myocardial infarction, characterization of regional myocardial function was made without an attempt to match heart rate, preload, or afterload, since our goal was to assess the natural evolution of regional function. Differences in heart rate undoubtedly influenced hemodynamic measures and end-diastolic segment lengths at several stages of the study. In addition, the apparent depression of function in marginal segments on days 1 and 2 after coronary occlusion could have been contributed to by the use of procainamide, although little or no depression of function in the control segment was evident at that time.

In the control segments, the progressive increase in function appears to represent an important adaptive mechanism in surviving regions of the left ventricle to the loss of myocardium elsewhere. Use of the Frank-Starling mechanism immediately after the coronary occlusion has been indicated by increased resting fiber length and enhanced shortening in normal segments of myocardium in earlier studies.2,4 Others have found acutely increased end-diastolic segment lengths,19-22 and enhanced sympathetic activity also has been postulated.23 However, the progressive further increase over several weeks of the diastolic lengths and function in normal regions has not previously been documented. Thus, after the first week of coronary occlusion, when evidence for increased sympathetic activity is no longer found,23 we observed a continued increase both in end-diastolic segment lengths and in percent shortening. By that time, systolic paradoxical motion in the ischemic segment which may affect control segment shortening2-4 was less marked (Fig. 1). The longer end-diastolic lengths, together with enhanced function, resemble responses we previously have observed in dogs subjected to chronic volume overloading of the left ventricle;34,25 such changes suggest that eccentric hypertrophy was occurring in the uninvolved myocardium. Biochemical changes consistent with hypertrophy also have been observed in the normal myocardium 2-3 weeks following coronary occlusion.24

The ischemic segments showed immediate loss of active function after occlusion, and over time systolic expansion was replaced by akinesia. The marginal segments showed immediate hypokinesis, followed by further deterioration during the first few days. Several factors could have contributed to this deterioration, including the rapid heart rate, arrhythmias,27 and tissue edema.28 The mild improvement in marginal segments observed in the ensuing weeks, along with the adaptations in the normal regions discussed earlier, could be related to hypertrophy of residual areas of viable myocardium and may contribute to the recovery of overall cardiac function observed previously following experimental myocardial infarction.16-17 Subendocardial tissue loss was most marked in ischemic regions and occurred to a lesser degree in the marginal segments. Histological studies suggested that such marginal regions are not composed of homogeneous tissue, but consist of areas of scarring mixed with residual islands of viable myocardial fibers. It should be emphasized that scarring in the subendocardial segments need not indicate that transmural tissue loss (wall thinning) has occurred, since it is possible that, in the dog, hypertrophy of the epicardial layers prevents significant wall thinning.29

Previously, we have recorded a longer diastolic length and an increased slope of the diastolic pressure-length relation (suggesting decreased compliance) in ischemic segments immediately after coronary occlusion in open-chest dogs.2 It was further suggested that the true stress-strain relationship may not be altered at this early stage, since the ventricular wall is thinner.3 In the present study, because of the relatively small number of segments analyzed and scatter in the data, the increased slope in marginal and ischemic segments was statistically significant only at 3 weeks. The shift of the relation and increases in slope appeared to be related to tissue loss in the subendocardial region and scar formation, respectively. Other studies of the histological changes following myocardial infarctions in the dog indicate that by about 11 days necrotic cells decrease in number, and there is evidence of their replacement by connective tissue; by 18 days a well defined scar is present, with persisting inflammatory cells,30 and the process of scarring appears to be complete by 4-6 weeks.

It seems likely that in these studies we have detected evidence in vivo of progressive myocardial scarring accompanied by compensatory hypertrophy in normal regions. These changes, coupled with detection of graded reductions in active regional contraction, which also correlated with extent of scarring, indicate that this model may be useful for studying the influence of therapy on the extent of myocardial damage after experimental coronary occlusion.31

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