

Regional Myocardial Functional and Electrophysiological Alterations after Brief Coronary Artery Occlusion in Conscious Dogs

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ABSTRACT The time relationship for recovery of mechanical function, the intramyocardial electrogram and coronary flow after brief periods of regional myocardial ischemia, was studied in conscious dogs. Total left ventricular (LV) function was assessed with measurements of LV systolic and diastolic pressures, rate of change of LV pressure (dP/dt), and dP/dt/P. Regional LV function was assessed with measurements of regional segment length and velocity of shortening. An implanted hydraulic occluder on either the left anterior descending or circumflex coronary artery was inflated for 5- and 15-min periods on separate days. A 5-min occlusion depressed overall LV function transiently, but just before release of occlusion overall function had nearly returned to control. At this time regional function in the ischemic zone was still depressed to the point of absent shortening or paradoxical motion during systole and was associated with marked ST segment elevation ($+10 \pm 2.2$ mV) at the sites where function was measured. With release of occlusion and reperfusion the intramyocardial electrogram returned to normal within 1 min, and reactive hyperemia subsided by 5–10 min. In contrast to the rapid return to preocclusion levels for coronary flow and the electrogram, regional mechanical function remained depressed for over 3 h. A 15-min coronary occlusion resulted in an even more prolonged (> 6 h) derangement of function in the ischemic zone. Thus, brief periods of coronary occlusion result in pro-

longed impairment of regional myocardial function which could not have been predicted from the rapid return of the electrogram and coronary flow. These observations indicate that brief interruptions of coronary flow result either in a prolonged period of local ischemia or that alterations of mechanical function induced by ischemia far outlast the repayment of the oxygen debt.

INTRODUCTION

It is currently held that coronary artery occlusions of 5–20-min duration do not result in permanent myocardial damage (1, 2), and, in fact, that any derangement in function due to the ischemia is repaired quickly (3, 4). This concept of rapid recovery is based primarily on studies in anesthetized animals with an open chest (3, 4) or on pathological studies demonstrating no histologic evidence of cellular injury after occlusions of less than 18 min (2). Furthermore, it is clear that electrocardiographic evidence of ischemia is abolished rapidly after brief periods of coronary occlusion in anesthetized (1, 5, 6) and conscious animals (7), but that these indices of ischemia do not provide information on the time-course of recovery for mechanical function of the myocardium.

The goals of this study were: (a) to analyze the effects of brief periods of coronary occlusion on overall as well as regional function in the normal and ischemic zones; and (b) to correlate the effects of reperfusion after brief coronary occlusions on regional mechanical and electrophysiological function. It was considered important to conduct this study in the conscious animal in which the myocardial depressant effects of a general anesthetic and recent operation were not present (8, 9).

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Received for publication 12 March 1975 and in revised form 30 May 1975.

METHODS

15 mongrel dogs, weighing between 25 and 35 kg, were anesthetized with i.v. pentobarbital Na, 30 mg/kg. Through a thoracotomy in the fifth left intercostal space, a miniature pressure gauge¹ was implanted within the left ventricle through a stab wound in the apex, a Doppler ultrasonic flow transducer and hydraulic occluder were placed around the left circumflex coronary artery or the left anterior descending coronary artery 2–3 cm from the bifurcation of these vessels, and heparin filled catheters were chronically implanted in the thoracic aorta and the left atrium. Pairs of miniature ultrasonic segment length transducers were implanted intramyocardially (2–10 mm in depth) parallel to the muscle fibers in normal and ischemic zones of the left ventricular (LV)² free wall. The zones were determined at the time of operation by brief interruption of flow distal to the occluder and inspection of the area of cyanosis. The miniature ultrasonic transducers are constructed from 3-MHz piezoelectric crystal and are approximately 2 mm in diameter with a thickness of 1 mm. The transducer leads constructed of lightweight, flexible stainless steel wire 0.15 mm in diameter³ are soldered to the crystal.

The miniature pressure gauges were calibrated statically *in vitro* and also dynamically *in vivo*. The catheter in the left atrium was used to calibrate the diastolic measurement of LV pressure. At autopsy the position of the ventricular gauges within the ventricular cavity was confirmed. Arterial pressure was sampled with the previously implanted heparin filled Tygon catheter⁴ and measured with a Statham P23 Db strain gauge manometer.⁵ Left circumflex or left anterior descending coronary blood flow was measured with an ultrasonic Doppler flowmeter, which has been described in detail previously (10, 11).

An improved ultrasonic transit time dimension gauge was used to measure myocardial segment length (12–14). It measures the transit time of acoustic impulses travelling at the sonic velocity of approximately 1.5×10^6 mm/s between pairs of implanted 3-MHz piezoelectric crystals. The position of the crystals were confirmed at necropsy. The crystals were surrounded by a fibrous scar averaging 1 mm in thickness. Calibration of the dimension gauge was performed by substituting signals of known time duration from a calibrated pulse generator. A voltage proportional to transit time was recorded and calibrated in terms of crystal separation. Simultaneous measurement of two different segment lengths was possible (Fig. 1). At a constant temperature, the drift of the instrument is minimal, i.e., less than 0.01 mm in 6 h, and its frequency response is flat to 60 Hz. Moreover, drift can be eliminated completely by repeated calibration reference throughout each experiment, which was done.

Regional electrograms were recorded from the intramyocardial transducers which also measured segment length and as mentioned above were implanted 2–10 mm in depth. The elevation of the ST segment was measured at the "J" point and expressed as mV change from base line.

¹ Konigsberg P22, Konigsberg Instruments, Inc., Pasadena, Calif.

² Abbreviations used in this paper: CPK, creatine phosphokinase; dP/dt, rate of change of LV pressure; dSL/dt, rate of change of segment length; LV, left ventricular.

³ Cooner Sales Co., Chatsworth, Calif.

⁴ Norton Company, Plastics and Synthetics Division, Akron, Ohio.

⁵ Statham Instruments, Inc., Oxnard, Calif.

Experiments were conducted 2–4 wk after operation while the conscious, unsedated dogs rested quietly. Control records of the segment length and LV pressure (P), rate of change of segment length (dSL/dt), i.e., velocity of myocardial segment length shortening, the rate of change of LVP (dP/dt), left circumflex or anterior descending coronary blood flow, and heart rate were obtained. These variables were continuously recorded during the experiments (Fig. 1).

Protocol. Either the left circumflex (seven dogs) or left anterior descending coronary artery (eight dogs) was occluded by inflating the cuff occluder for periods of either 5 or 15 min. Occlusion was confirmed by coronary flow measurement. A minimum of 2 days recovery was allowed between successive short occlusions. The same parameters were recorded after release of the occlusion for up to 24 h. Over the same period blood samples were obtained at 60–120-min intervals for serum creatine phosphokinase (CPK) determination. CPK activity in serum was assayed at 30°C by the method of Rosalki (15). Results are expressed as international units per milliliter of plasma.

Data were recorded on a multichannel tape recorder and played back on a direct writing oscillograph at a paper speed of 100 mm/s. A cardiometer, triggered by the pressure pulse signal, provided an instantaneous and continuous record of heart rate. An electronic resistor-capacitor (RC) filter with a 2-s time constant was used to derive mean coronary blood flow from the pulsatile flow signal. Continuous records of dP/dt and dSL/dt were derived from the LV pressure and segment length signals by differentiation using Philbrick operational amplifiers⁶ with frequency responses of 60 Hz. In addition, the effects on the quotient of dP/dt and developed pressure (isovolumic minus end diastolic pressure), i.e., dP/dt/P, were examined.

A triangular wave signal with known slope (rate of change) was substituted for pressure and segment length signals to calibrate dP/dt and dSL/dt channels. Control and response values were compared in the same animals by using the paired *t* test (16).

RESULTS

Overall LV function was assessed by measurement of LV systolic and end diastolic pressures, dP/dt, and dP/dt/P. Regional mechanical function was assessed by measurement of end diastolic and end systolic segment lengths and velocity of segment length shortening. Since the magnitude of change in segment length depends in part upon initial length, the changes expressed in absolute length (millimeters) could be variable to the extent that initial segment lengths varied. To determine if measurements of end diastolic and end systolic lengths expressed in millimeters were influenced significantly by initial length, the changes observed in this study were also calculated as percentage change of initial length. Conclusions based on the percentage change calculation were not significantly different from those expressed in millimeters; accordingly, the results will be expressed in terms of actual length changes in millimeters.

⁶ Teledyne Philbrick, Dedham, Mass.

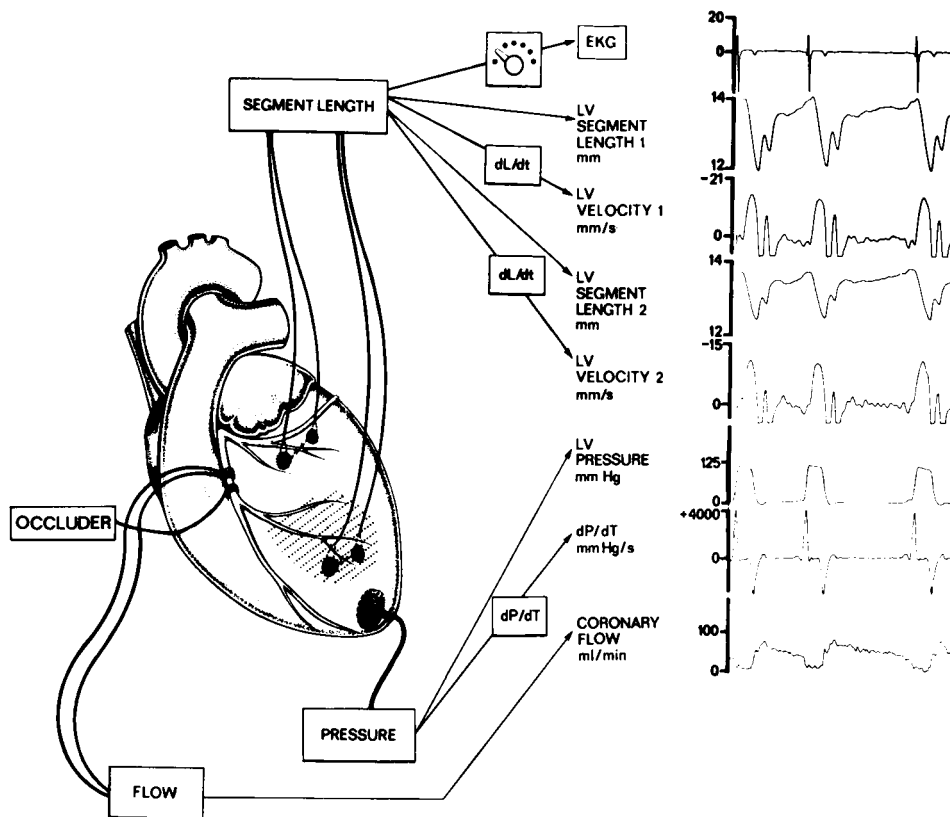


FIGURE 1 Technique for correlating overall and regional LV function with regional intramyocardial electrogram. In this example, overall LV function is assessed by the implanted LV pressure gauge for LV systolic and diastolic pressures and dP/dt . Pairs of ultrasonic transducers are implanted intramyocardially. Each pair of transducers measures LV segment length and velocity of myocardial fiber shortening in a specific region, i.e., normal or ischemic zone. In addition each transducer serves as an EKG electrode for simultaneous EKG mapping.

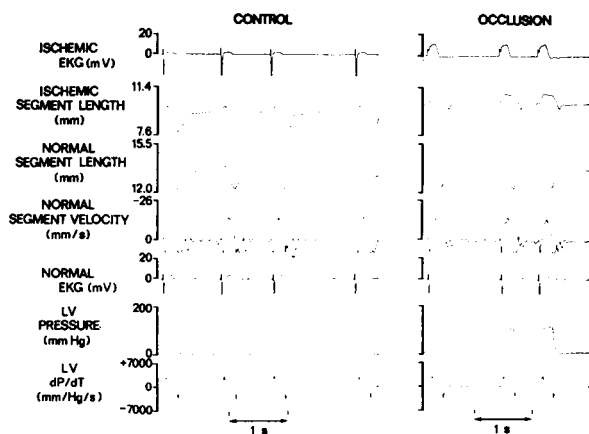


FIGURE 2 The effects of an occlusion of the left anterior descending coronary artery are shown on regional segment length and electrograms in the normal and ischemic zones along with LV pressure, dP/dt , and velocity of segment length shortening in the normal zone. During occlusion paradoxical bulging developed in the ischemic zone along with substantial ST segment elevation, while regional function in the normal zone remained essentially constant and no ST segment elevation was observed.

Effects of coronary occlusion on overall LV function

Coronary occlusion caused initial transient reductions in LV systolic pressure, dP/dt , and $dP/dt/P$, which returned to control while the occlusions were maintained. The responses to left anterior descending and circumflex coronary occlusions were not significantly different.

5-min occlusion. Just before release of occlusion LV systolic pressure, peak dP/dt , and $dP/dt/P$ were not different from the preocclusion controls, while LV end diastolic pressure and heart rate were significantly elevated (Table I). All these values returned to control by 15 min after release of occlusion.

15-min occlusion. Just before release of the 15-min occlusion changes in heart rate and LV end diastolic pressure were different from control by amounts similar to those described with a 5-min occlusion while LV systolic pressure, dP/dt , and $dP/dt/P$ were not significantly different from control (Table I). Upon reperfusion these values all returned to control by 30 min.

TABLE I
Effects of 5- and 15-min Occlusions

| | Control (n = 10) | 5 min* (n = 10) | Control (n = 9) | 15 min* (n = 9) |
|---|------------------|-----------------|-----------------|-----------------|
| Heart rate, <i>beats/min</i> | 80±5 | 115±8§ | 75±4 | 94±8§ |
| Mean coronary flow, ‡ <i>ml/min</i> | 37±3 | 0§ | 37±3 | 0§ |
| LV pressure, <i>mm Hg</i> | | | | |
| Systolic | 124±5 | 123±6 | 116±5 | 117±5 |
| End diastolic | 6±2 | 11±2§ | 6±3 | 11±2§ |
| Peak LV dP/dt, <i>mm Hg/s</i> | 3,670±500 | 3,580±680 | 3,320±220 | 2,850±290 |
| dP/dt/P, <i>s⁻¹</i> | 60±3 | 56±3 | 59±3 | 57±3 |
| Ischemic zone segment length, <i>mm</i> | | | | |
| End systolic | 11.25±0.12 | 13.08±0.29§ | 10.85±0.49 | 13.21±0.42§ |
| End diastolic | 12.24±0.18 | 12.77±0.23§ | 12.14±0.59 | 12.68±0.52§ |
| Ischemic zone velocity, <i>mm/s</i> | 14.6±2.3 | 0§ | 16.3±2.9 | 0§ |
| Ischemic zone ST segment, <i>mV</i> | 0.6±0.1 | 10.0±2.2§ | 0.9±0.3 | 11.3±2.6§ |

* Before release of occlusion.

‡ Left circumflex and left anterior descending coronary blood flows pooled.

§ Significantly different from preocclusion control, $P < 0.01$.

Effects of coronary occlusion on regional LV function

5-MIN OCCLUSION

Normal zone. During a 5-min occlusion of either the left anterior descending or left circumflex coronary artery, end diastolic segment length rose by 0.26 ± 0.04 mm from a control of 18.0 ± 3.3 mm, while end systolic segment length remained at 16.4 ± 2.7 mm, and stroke shortening rose by 0.26 ± 0.04 mm. Velocity of segment length shortening increased slightly ($P < 0.05$) by $13 \pm 4\%$ (control = 15.7 ± 4.5 mm/s) with occlusion of the left circumflex coronary artery. The velocity of segment length shortening in the nonischemic zone did not change significantly after occlusion of the left anterior descending coronary artery (Fig. 2). Upon reperfusion all measurements returned to control within 1 h.

Ischemic zones. In this study only those segments in areas of severe ischemia were considered, i.e., zones that showed either paradoxical (Fig. 2) or absent (Fig. 3) motion during occlusion of the coronary artery. With occlusion of either the left anterior descending or the left circumflex coronary artery, end diastolic segment length rose from 12.24 ± 0.48 to 12.77 ± 0.23 mm and end systolic rose from 11.25 ± 0.12 to 13.08 ± 0.29 mm, while by definition stroke shortening or velocity of segment length shortening was reduced to zero.

Upon reperfusion function gradually returned to control over the next 6 h (Fig. 4). End diastolic and end systolic segment lengths, segment stroke excursion, and

velocity were all still significantly different from control at 2 h and did not completely return to control until 6 hr after reperfusion.

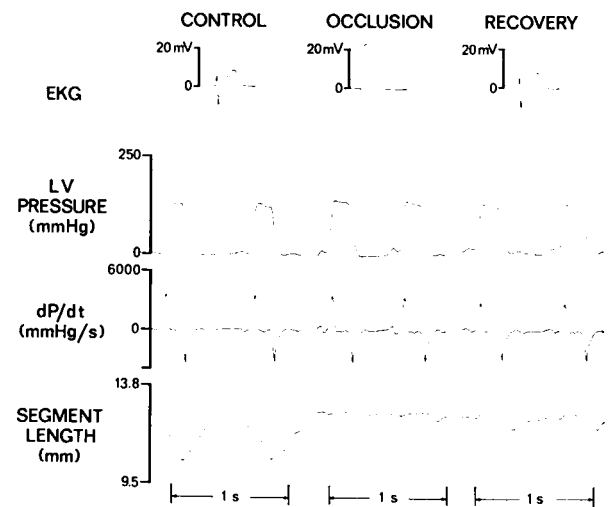


FIGURE 3 Effects of a 5-min left circumflex coronary occlusion on LV pressure, dP/dt, and segment length in the ischemic zone along with the electrogram from the ischemic zone (top). During coronary occlusion (middle panel) intense ischemia reflected by substantial ST segment elevation correlates well with impaired function in the ischemic zone. 5 min after release of occlusion, reperfusion and repayment of coronary flow debt (right panel), the electrogram is again completely normal, but regional function is still markedly deranged, i.e., the ischemic segment is expanding paradoxically during systole.

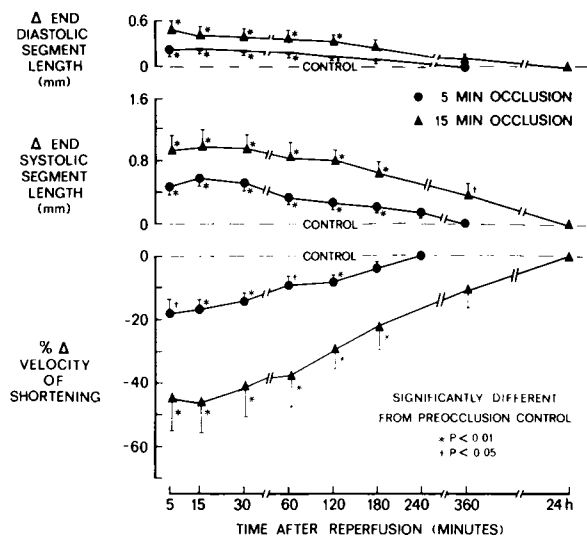


FIGURE 4 Comparison of recovery times for end diastolic and end systolic segment length and velocity of shortening after 5-min (circles) and 15-min (triangles) occlusions. Recovery times from 5 min to 24 h after reperfusion are shown. Values that were significantly different from control are shown by the asterisk ($P < 0.01$) and cross ($P < 0.05$).

15-MIN OCCLUSION

Normal zone. The changes in function were similar to those observed with a 5-min occlusion, i.e., function improved with left circumflex occlusions, but not with left anterior descending occlusion. With reperfusion all values returned to control in less than 1 h.

Ischemic zone. During occlusion of either left anterior descending or circumflex coronary arteries, end systolic and end diastolic segment lengths rose in each case. End systolic segment length increased from an average of 10.86 ± 0.49 to 13.21 ± 0.42 mm ($P < 0.01$), while end diastolic length rose from an average of 12.14 ± 0.59 to 12.68 ± 0.52 mm ($P < 0.01$). Thus paradoxical or absent motion occurred, as was observed during a 5-min occlusion (Fig. 2 and 3). Velocity was zero, as occurred with the 5-min occlusion.

Upon reperfusion all values returned gradually to control levels; velocity was depressed and end diastolic segment length was elevated significantly for 3 h, while end systolic segment length was still depressed significantly at 6 h. In four dogs all three measurements remained depressed at 6 h and function returned to control level at 24 h. The extent of segment shortening per stroke (control = 1.28 ± 0.14 mm) was also significantly depressed, reaching a minimum value of 0.56 ± 0.15 mm at 15 min after reperfusion.

The 15-min occlusions resulted in a greater depression of velocity and elevation in end systolic segment length, but no greater elevations in end diastolic segment length

(Fig. 4) than had occurred after 5-min occlusions. After 15-min occlusions the reductions in velocity were significantly greater ($P < 0.05$) up to 3 h after reperfusion, while the elevations in end systolic segment length were greater ($P < 0.05$) for 6 h after reperfusion.

Intramyocardial EKG

5-min occlusion. No ST segment elevation was observed in the normal zone during or after a 5 or 15-min occlusion. During a 5-min occlusion ST rose from an average of 0.6 ± 0.1 mV to an average of 10 ± 2.2 mV at each site where function was measured in the ischemic zone. After release of the 5-min occlusion the ST segment elevation returned to control within 1 min (Fig. 3).

15-min occlusion (ischemic zone). The maximal ST segment elevation for each site (11.3 ± 2.6 mV) was similar to that occurring with a 5-min occlusion. Upon reperfusion it returned to control in less than 1 min.

Coronary flow

Since the results from left anterior descending and circumflex coronary flows were not significantly different, pooled data will be presented. Marked reactive hyperemia was observed after release of coronary occlusions (Fig. 4); flow rose to 213 ± 19 ml/min and to 230 ± 22 ml/min after the release of 5- and 15-min occlusions, respectively, from similar control values (37 ± 3 ml/min). The reactive hyperemia subsided rapidly, coronary flow returning to control by 7 ± 2 and 10 ± 2 min, respectively, after release of the 5- and 15-min occlusion.

CPK

The 24 h serum CPK curve demonstrated a peak rise in CPK at 6 h; CPK rose from 18 ± 3 to 40 ± 6 IU/ml ($P < 0.05$) after a 5-min occlusion and from 18 ± 2 to 75 ± 16 IU/ml ($P < 0.05$) after a 15-min occlusion. The increase after a 15-min occlusion was not significantly greater than that after a 5-min occlusion.

DISCUSSION

Most previous methods used to describe regional myocardial function in response to coronary occlusion have been applied in anesthetized animals with an open chest (3-6, 14, 17, 18) where the myocardium is depressed (8, 9). Bugge-Asperheim et al. (19), Hawthorne (18), and Theroux et al. (14) have utilized techniques that are applicable to the study of regional myocardial function in the intact, conscious animal. A similar ultrasonic method as employed by Bugge-Asperheim et al. (19) and Theroux et al. (14) has been utilized in our laboratory to describe right ventricular function by measure-

ment of segment length and velocity of shortening (13). This technique was modified in the present study to provide simultaneous measurements of length and velocity of shortening of two segments along with the intramyocardial electrograms at the site of the implanted transducers. Thus, mechanical and electrophysiological function were assessed from the same sites allowing effects of regional myocardial ischemia to be examined by two simultaneous techniques. The most important feature of this technique is that instrument drift is negligible, and changes in function due to varying levels of anesthesia or deterioration in the preparation was excluded, since an intact, conscious animal was studied. This is of particular importance when examining changes that may take up to 24 h to return to control, as occurred in the present study.

The effects of coronary occlusion on the ischemic zone are well known since Tennant and Wiggers' classic description (17), but the effects on the normal myocardium are controversial. Theroux et al. (14) studying open chest anesthetized dogs showed that the contractility in the normal zones increases after coronary occlusion. They suggested that the mechanism of the improvement in function was due to operation of the Frank-Starling mechanism. On the other hand, a preliminary report by Wyatt et al. (20) noted a deterioration in function in the normal zone. Our data indicate that the behavior of the nonischemic zone varies depending upon whether the left anterior descending or left circumflex coronary artery is occluded. When the left circumflex coronary artery was occluded a significant increase of velocity of segment length shortening was observed. In contrast when the left anterior descending coronary artery was occluded only two out of seven dogs studied showed an increase in velocity, while three dogs showed a decrease in velocity of segment length shortening, and 2 dogs showed no change (Fig. 2). These results would explain the differences noted by Theroux et al. (14) and Wyatt et al. (20), since the former group occluded the left circumflex, while the latter group occluded the left anterior descending coronary artery.

Occlusion of the left anterior descending or left circumflex coronary artery always resulted in severe depression of function in the ischemic zone in all animals in this study, i.e., no shortening or paradoxical motion was observed. After release of a 5-min occlusion and reperfusion the ST segment elevation disappeared completely in less than 1 min. Coronary flow exhibited considerable reactive hyperemia which subsided by 5 to 10 min. In contrast, regional function, as reflected by measurements of end diastolic and end systolic segment lengths and velocity of segment length shortening, remained significantly depressed in the previously ischemic zones for up to 2 h. A 15-min occlusion resulted in derangement of function which was even greater and more prolonged

in duration. Studies by Banka et al. (4) and Puri (3) have reported that function returns rapidly after release of occlusions even up to 45 min. The two major differences between those studies (3, 4) and the present one are related to the preparation, i.e., conscious vs. anesthetized, and secondly, the techniques utilized for measurement of segment length. The difference is probably not due to effects of anesthesia inasmuch as a preliminary report by Weiner and coworkers (21) indicates prolonged impairment of function after release of brief coronary occlusions in anesthetized animals. Sayen et al. also noted prolonged recovery of mechanical function after brief coronary occlusion in open chest, anesthetized dogs (5), but in that study the time-course of recovery for mechanical function was on the order of 2-5 min in contrast to the extended recovery periods of several hours observed in the present study. The difference between our conclusions and those of Banka et al. (4) and of Puri (3) are probably related to the techniques utilized in the measurement of regional myocardial function. The instrument utilized in the present study can be calibrated precisely and exhibits minimal drift characteristics, thereby enabling accurate measurement of myocardial segment lengths over prolonged periods.

Several mechanisms may explain the protracted recovery of mechanical function observed in this study. It could be that the ischemic debt was not repaid completely by the marked reactive hyperemia and that flow to small zones of myocardium was subnormal and returned gradually to preocclusion levels over several hours. Local flow and oxygen delivery could be impeded by either cellular swelling, interstitial edema, or microthrombi in capillaries. This possibility cannot be eliminated since only total left anterior descending or left circumflex coronary blood flows were measured: although these measurements returned to control in 5-10 min, a small persistent reduction in coronary flow to the ischemic zone could not be discerned by these techniques. A recent study by Kerber et al. indicated that regional flow to the ischemic zone determined by microspheres was normal despite depressed function during recovery from a 45-min occlusion (22). On the other hand it is possible that the reactive hyperemia was sufficient to repay the ischemic debt, but that the effects of ischemia persisted. For instance, the derangement induced in contractile proteins, cellular ionic environment, or depletion of high energy phosphates induced by brief coronary occlusion could have taken several hours to recover completely. Thus, while ischemia was no longer present, its effects on some aspect of the myocardial contractile apparatus may have persisted for longer than could have been predicted by the rapid return of the electrogram or coronary flow.

Both the 5- and 15-min occlusions resulted in small but statistically significant elevations in serum CPK.

Using serum CPK disappearance curves, it was demonstrated that the amount of CPK released from the heart after a coronary artery occlusion of 24 h is proportional to the size of myocardial infarction as determined by myocardial CPK depletion (23). The results of the present study indicated that either CPK may be released by transient ischemia and thus is not always a marker of irreversible necrosis, or that the transient ischemia resulted in necrosis of a small quantity of myocardium sufficient enough to cause a detectable rise in CPK, but not great enough to result in permanent functional impairment. The latter explanation, however, conflicts with the currently held concept that necrosis does not occur with occlusion of less than 18 min (1, 2).

In conclusion, the major finding of the present investigation was that brief periods of coronary occlusion result in prolonged depression of myocardial function in the ischemic zone. While regional electrograms return to normal within seconds and the coronary flow debt is repaid rapidly, functional derangement lasts for several hours. These results are of clinical relevance for patients with brief episodes of myocardial ischemia and to surgical patients in whom the coronary vessels may be temporarily occluded. This finding might explain the ephemeral nature of abnormal auscultatory signs or cineangiographic results in patients with angina pectoris. In addition, the results of this study should be considered when conducting experiments involving repetitive coronary occlusions. It must be recognized that repetitive coronary occlusions less than 6 h apart involve the study of myocardium in which myocardial mechanical function has not returned to control levels.

ACKNOWLEDGMENTS

We acknowledge the technical assistance of T. Manders, R. Peters, and P. Quinn and the help in preparation of the manuscript from V. Fowler. We are also grateful for the encouragement and support from Dr. E. Braunwald.

This work was supported in part by U. S. Public Health Service Grants HL 17459, HL 15416, and HL 17665, National Institute of Health, and National Aeronautics Space Administration-Ames Grant 22 036 001.

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