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LOCAL VENTRICULAR BULGING FOLLOWING ACUTE CORONARY OCCLUSION

by

Constantine J. Tatooles

STRITCH SCHOOL
LOYOLA
UNIVERSITY
OF MEDICINE

A Thesis Submitted to the Faculty of the Graduate School of Loyola University in Partial Fulfillment of the Requirements for the Degree of Master of Science

June

1961

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BIOGRAPHY

Constantine J. Tatooles was born in Chicago, Illinois May 7, 1936. He was graduated from St. George High School in Evanston, Illinois in June, 1954. In September of the same year, he entered Albion College, Albion, Michigan. Here, he was on a combined pre-medical course and received a Bachelor of Arts degree in September, 1958 after the completion of his first year in Medical School.

He enrolled in the Stritch School of Medicine of Loyola University, Chicago in 1957 and during his sophomore year in Medical School he started work in the Graduate School of Loyola University.

At present time, he has received an appointment to a rotating internship at the University of Chicago Clinics.

INTRODUCTION

Experimental study of the influence of interruption of the coronary circulation on heart action began with J. E. Erichsen in 1842. In his paper "On the Influence of the Coronary Circulation on the Action of the Heart", published in the London Medical Gazette, Erichsen found that dogs died within twenty one minutes after the main coronary arteries had been tied. He observed this by pithing dogs and quickly putting ligatures around the coronary arteries and then noticing the response of the heart. Following death of the animal a slight tremulous motion of the ventricles persisted.

Since Erichsen's time extensive studies have been carried out to investigate the disturbances in rhythm and electrical activity in heart muscle associated with coronary occlusion, but relatively little is known about the immediate mechanical changes which follow the occlusion. This is particularly true regarding events which occur in the fractionate portions of myocardium which are directly influenced by varying degrees of ischemia.

In 1894 W. D. Porter (1,2) succeeded in ligating the anterior descending coronary artery while recording left intraventricular pressure. He found that a gradual and continuous decrease in ventricular pressure follows occlusion of the artery.

Orias in 1935 (3) described the summated influences of coronary occlusion on intraventricular and aortic pressures. Provided fibrillation did not occur promptly, major coronary artery occlusion resulted in a fall of both systolic and diastolic pressures, but this was "compensated" through more forceful contractions of unaffected muscle. From these findings Orias presumed that the ischemic area did not contract. With suitable instrumentation for more precise evaluation, Tennant and Wiggers (4) described myographic records made directly from ischemic muscle. This report presented incontestable evidence that following occlusion of a main coronary branch, the ischemic muscle no longer contracted normally and sometimes stretched during ventricular systole.

Gubner and Crawford (5) studied myocardial infarctions on humans with the multiple-slit moving film kymograph. They found a reversal of movement or an absence of pulsations in an infarcted area of the left ventricle. Later Prinzmetal et. al. (6) and Dack et. al. (7) observed that bulging or "ballooning" of an ischemic zone of myocardium may be observed clinically and recorded graphically on the electrokymogram or roentgenkymogram. At best, however, these clinical methods could only indicate whether ballooning in systole was present. Dack et. al. (7) cautioned that position changes produced by torsion, traction or pendulum movements of the heart as a whole may complicate the tracings. The Prinzmetal group (6), using a cinematographic

technique (48-100 frames/second), described the "ballooning" of the ischemic zone following large coronary artery occlusion, but significant differences from the observations of Tennant and Wiggers (4) raised important questions about the following: 1) time to onset of loss of contractility in the ischemic zone, 2) precise period during systole in which ballooning occurs, and 3) the question of whether the systolic out-thrust "waxes and wanes" during the period of occlusion.

In order to permit resolution of the above questions, a more accurate method of determining myocardial contractile force is required. Various types of myographic levers have been used to record contractile force of the ventricles (4, 8, 9), but these methods are not adequate to produce demonstrable, reproducible tracings. In the present study the force of ventricular contraction is qualitatively measured by the use of small electrical strain gage arches (10) sutured to the ventricles. These gages are superior to previous instruments used because: 1) they are easier to work with; 2) the contractile force may be recorded in multiple areas of the same ventricle; and 3) they are not effected by heart rate or position movements of the heart (11). Strain gage arches have been used to study directly ventricular contractile force in humans given various amines (12) and also during cardio-pulmonary bypass in patients with heart defects (13).

MATERIALS AND METHODS

Animals and Anesthesia:

Experiments were performed in twenty four mongrel dogs of both sexes, weighing between five and fifteen kilograms. The animals were all anesthetized with pentobarbital sodium (30 mg/Kg).

Recording Instruments and Techniques:

Strain gage arches were employed to measure the qualitative force of ventricular contraction of the dog's heart. The arch contains a strain wire resistor placed on a metal strip one centimeter long and one third centimeter wide. It has a foot plate at each end of the metal strip, each containing suture holes by which it may be sutured to the ventricle. The strain gage arch is the variable limb of bridge circuit, and any alteration in length of the wire alters its resistance, thus unbalancing the bridge and altering its output voltage.

The strain gage arch was wired to a 5PI Grass preamplifier coupled to a Grass model 5A driver amplifier. The latter was coupled to the Grass direct writing oscillograph.

The 5PI polygraph preamplifier is a chopper modulated and demodulated high gain, low noise, low frequency, DC preamplifier which has a frequency response to forty cycles per second. The input is designed to drive balance controls and excite the circuits of coupled recording instruments, such as the bridge of

the strain gage arch. The model 5A driver amplifier is a push pull, two stage direct coupled amplifier with a differential input. Its primary function is to amplify signals from the polygraph preamplifier sufficiently to drive the direct writing oscillograph. It also supplies voltages to operate the associated preamplifiers. The maximum sensitivity of the driver amplifier combined with the pen writer oscillograph is greater than one hundred millivolts per centimeter.

Records of blood pressure from a carotid artery were obtained by means of a Statham P23A transducer coupled to another channel of the polygraph. The P23A pressure transducer has a pressure range of zero to seventy five centimeters of mercury and an approximate natural frequency of thirty nine cycles per second at nineteen hundreths critical damping with a twenty gage needle five centimeters in length.

An integrating cardiotachometer (14) was added to the system. The input of the tachometer was taken from contact points in parellel with the pen writing galvanometer. The output of the tachometer was connected to another channel of the polygraph.

A standard limb lead of an electrocardiogram was also coupled to another channel through a P51 preamplifier and model 5A amplifier. In all experiments lead II was recorded.

The recording techniques used in this study are capable of reproducing simultaneous tracings from the various dynamic parameters under investigation.

Experimental Procedure:

Mongrel dogs were anesthetized with intraperitoneal injections of pentobarbital sodium. After an adequate plane of anesthesia had been established, an incision was made in the anterior mid-line of the neck so that both carotid arteries and both vagi could be dissected free. The common carotid artery was cannulated with a polyethylene catheter attached to the Statham pressure transducer calibrated so that two centimeters deflection equal 100 mm of Hg. A tracheotomy was performed and a positive pressure respirator connected to the tracheal catheter. A thorocotomy was then made through the fourth left interspace and a pericardial cradle made to expose and support the heart. The strain gage arches were sutured directly to the myocardium either parellel or at right angles to the main branches of the coronary arteries. Two to four arches were sutured to the ventricles (right or left) in the distribution area of the anterior descending or circumflex arteries, or at mid-points between these two arteries.

Needle ECG electrodes were positioned and lead II was recorded on the polygraph.

The proximal portion of the left coronary, anterior descending, or circumflex artery was dissected free and an umbilical ligature with a sliding glass rod placed about the isolated artery. Sliding the glass rod down the umbilical ligature effectively occluded the artery. After a suitable

control period the ligature was tightened around the artery and the occlusion maintained for periods varying from two seconds to twenty minutes. Repeated occlusions were carried out in the same animal with recovery intervals varying from five minutes to one hour.

In four of the experiments a bilateral vagotomy was performed before the initial occlusion.

Following termination of the experiments, the hearts were examined carefully to make certain that the ligatures were placed about the proximal portion of the artery under study.

RESULTS

Examination of tracings recorded from strain gage arches sutured to the left and right ventricles reveal that the sharp initial upstroke at the beginning of systole occurs at slightly different times in different muscle segments, and just prior to systolic upstroke in the carotid arterial pressure trace (Figure 1). Amplitudes of contraction remain reasonably constant during the control period. After tightening the ligature around the main left coronary artery, the amplitude of contraction in both ventricles began to decline within 2 seconds. The amplitude progressively declined until it reached a minimum which was 30% of preocclusive amplitudes on the left and 60% of control amplitude on the right ventricle after 15 seconds of occlusion. Carotid blood pressure actually increased during the initial portion (first 6 seconds) of the occlusion period, but then progressively declined and continued to fall even after the occlusion was released. Pulsus alternans developed briefly but was not sustained. Following release, the amplitude of myocardial contraction progressively and synchronously recovered in both ventricles, and the recovery was accompanied by return of blood pressure to normal. Heart rate decreased moderately throughout the experiment. Electrocardiographic changes rarely appeared or were minor unless the occlusion was prolonged, although ST segment depression

developed gradually as repeated occlusions gave rise to more pronounced ischemia.

In Figure 2, intermittent cycles of weak and strong contractions were recorded from muscle immediately adjacent to the ischemic zone of the left ventricle. Following an initial decline in contraction amplitude, cyclic alternations appeared superimposed on greater and greater amplitudes. Following release of occlusion, amplitudes were still further increased with return to normal after approximately 100 seconds. Blood pressure first increased slightly and then declined. ECG changes did not appear to be significant in lead II. Amplitude of contraction of normal myocardial segments in the left ventricle in the area of the circumflex artery did not change significantly.

In Figure 3, the anterior descending artery was permanently tied off and records continuously taken until fibrillation developed. The ischemic zone showed immediate depression of contractility but was marked by a slow phasic alteration in force of contraction. Pulsus alternans was detectable in the arterial pressure trace within a few seconds, considerably before it appeared in the ischemic muscle trace. It failed to develop in the non-ischemic zone of the same ventricle. As the alternation in arterial pressure pulses became more obvious a similar alternation appeared in the contractions of ischemic muscle. However, the more forceful contraction of the ischemic muscle was associated with the lesser of the two alternating arterial pressure waves.

ECG complexes of lead II remained consistently associated with myocardial contractions even though the alternating pressure waves disappeared from the arterial pressure trace. The ST segment became progressively more depressed as occlusion was prolonged, particularly during the heart cycle which resulted in the stronger arterial pulse.

With continued occlusion the amplitude of contraction of the ischemic muscle gradually increased, both components of the alternating contraction waves participating in this recovery. Intraventricular pressure was increased sufficiently to open the aortic valves and to restore arterial alternans. A ventricular tachycardial run then resulted in deterioration of the pressure and contractile phenomena, eventually ending in fibrillation. The full sequence of events from the time of arterial ligation to death was marked by an apparent "waxing and waning" in the amplitude of contraction of the ischemic zone. At no time was contraction of the ischemic zone entirely obliterated nor did systolic bulging develope. Pulsus alternans was continually observed in the contractile tracings from the ischemic zone until the experiment terminated in fibrillation. It is interesting that contraction waves continued regularly in the ischemic zone for some time after blood pressure began its terminal decline.

Tracings recorded from strain gage arches sutured to the left ventricle in the distribution area of the circumflex artery (top tracing) and the anterior descendens (2nd tracing) are shown

in Figure 4. Upon occlusion of the anterior descendens there was a slight increase in the force of contraction in the area of the circumflex. However, in the ischemic area of the anterior descendens the force of contraction, or contractility, rapidly decreased to zero and is replaced by expansion or bulging of the muscle tissue between the two limbs of the strain gage arch. This bulging represents stretching of the small mass of myocardium from which the gage was recording. The bulging progressively became more extensive until the release of the occlusion, which was followed by the gradual return of contracility. Note the progressive recovery in force of contraction, its significant increase to levels considerably in excess of control, and its eventual return to control levels after approximately two minutes. A transient increase in blood pressure was also noted during the occlusion. Heart rate and ECG remained essentially unchanged.

Figure 5 illustrates the changes in contractile force observed in three different locations on the left ventricle when the proximal region of the anterior descending branch of the left coronary artery was occluded. Only a very slight decrease in amplitude was recorded from the muscle supplied by the circumflex branch (top trace). A prompt and progressive decline in amplitude of contraction was recorded from an area between that predominantly supplied by the circumflex and the anterior descending branches (second trace). In the principal area of anterior descendens distribution, contractility rapidly declined to zero and was

replaced by expansion or inversion (third trace). The bulging became progressively more extensive, even after release of the occlusion, when in fact, it attained its maximum. During recovery there occurred a period in which the myocardium showed an initial weak contraction which was replaced (sometimes gradually and sometimes abruptly) by the normal pattern of systole.

A record of such bulging made at high speed is shown in Figure 6. Again, the initial change is a progressive decline in amplitude of the ischemic muscle contraction. A biphasic response then appeared in which the muscle showed an initial low intensity contraction lasting only a small portion of systole. This initial contraction was terminated and replaced by bulging as ventricular pressure attained maximum levels. The biphasic response was brief as the initial contraction became progressively weaker and gradually disappeared. Bulging then appeared immediately upon the initial development of intraventricular tension. Maximum bulging occurred late in the period of occlusion and was followed by progressive recovery. The latter was marked by a gradual decrease in amount of bulging during each successive cycle with the eventual reappearance of a small initial contraction. During this period there was neither significant contraction nor stretching of the muscle segment which had been ischemic. Contraction then progressively improved and all tendency to bulge disappeared.

Pulsus alternans developed in a significant number of experiments, either late in the period of occlusion or soon after

the ligature was released. In many instances the ischemic zone showed an alternans, either in or out of phase with the pressure pulses recorded in the carotid artery, while the non-ischemic zone did not. The alternans usually developed during the most severe period of myocardial depression and tended to disappear with recovery of normal contractility.

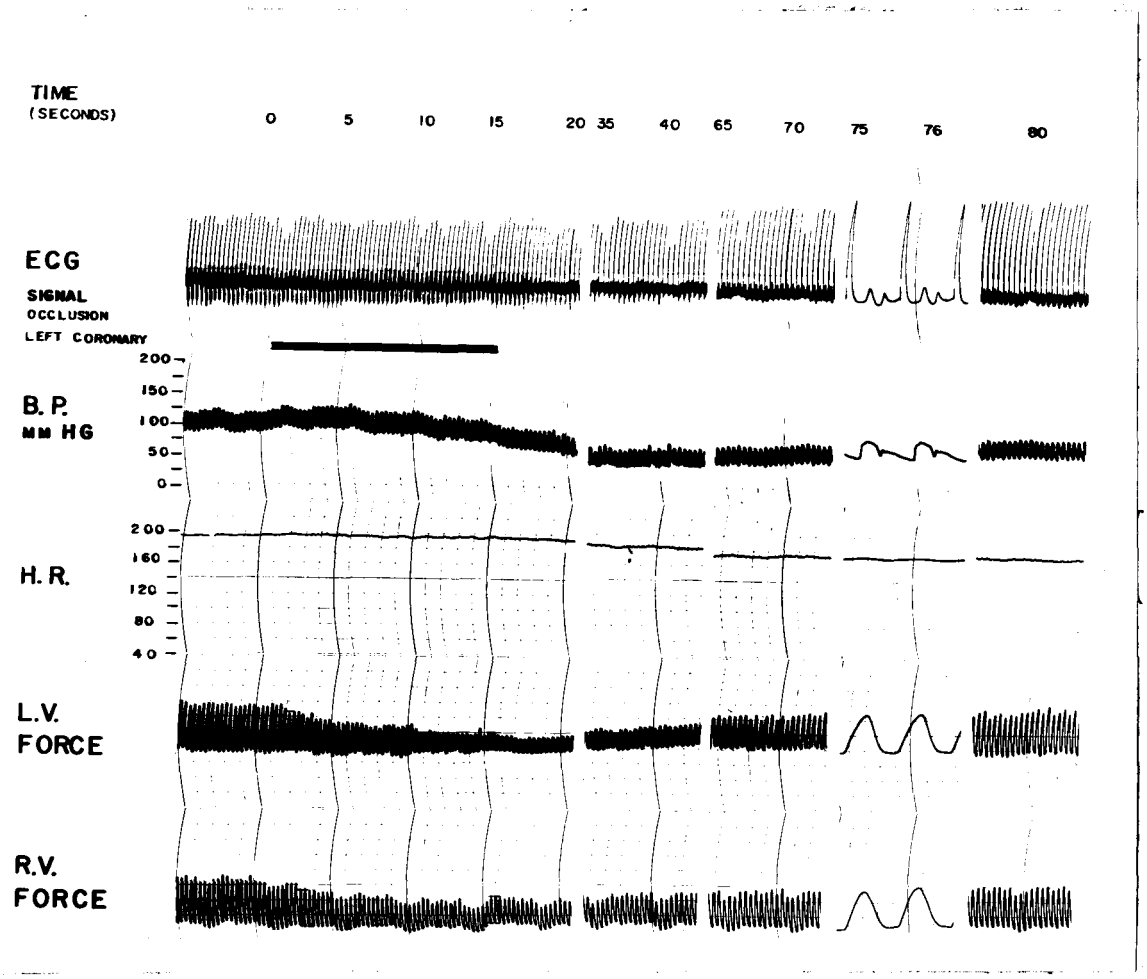

Figure 1

Simultaneous recordings of myocardial force of contraction of the right and left ventricles, together with other dynamic events, during occlusion of the main coronary artery.

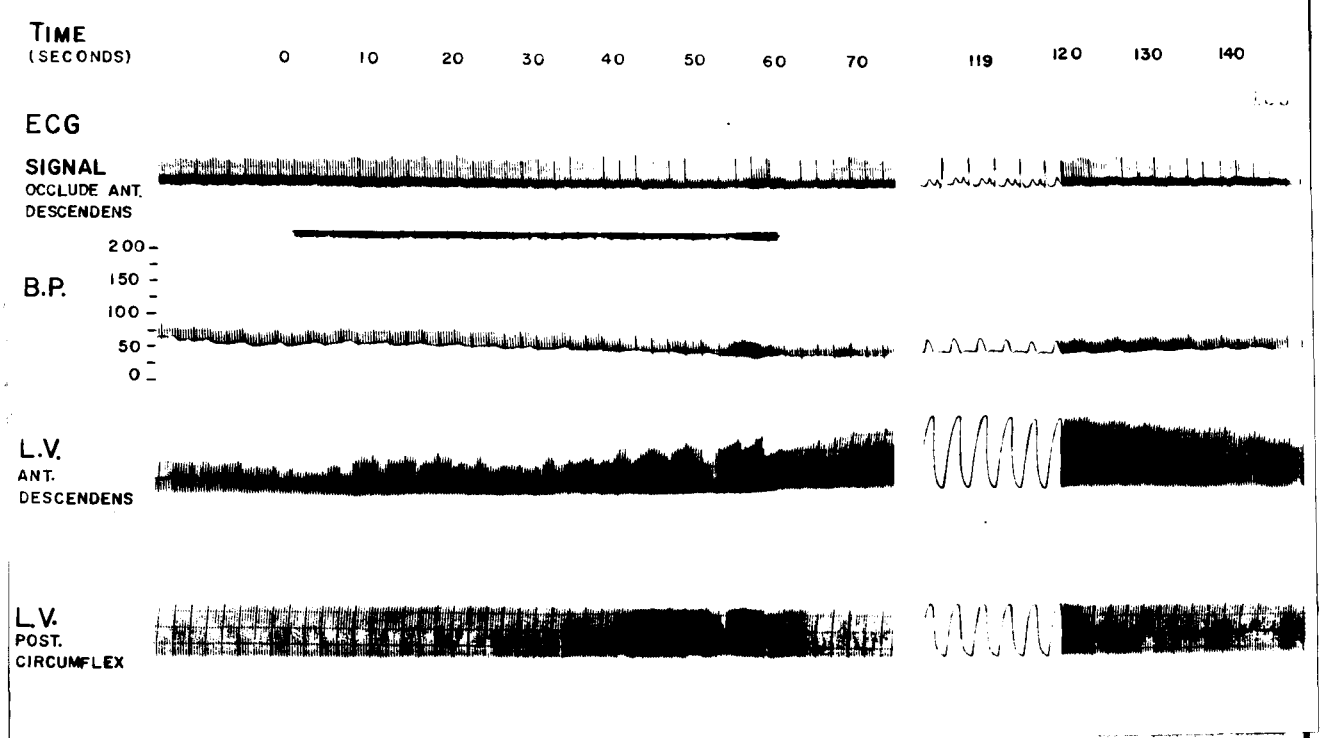

Figure 2

Records of myocardial contraction force in muscle supplied by the anterior descendens and circumflex arteries while the former was occluded. Note waxing and waning in contractile force in the "occluded" region and the exaggerated force following release.

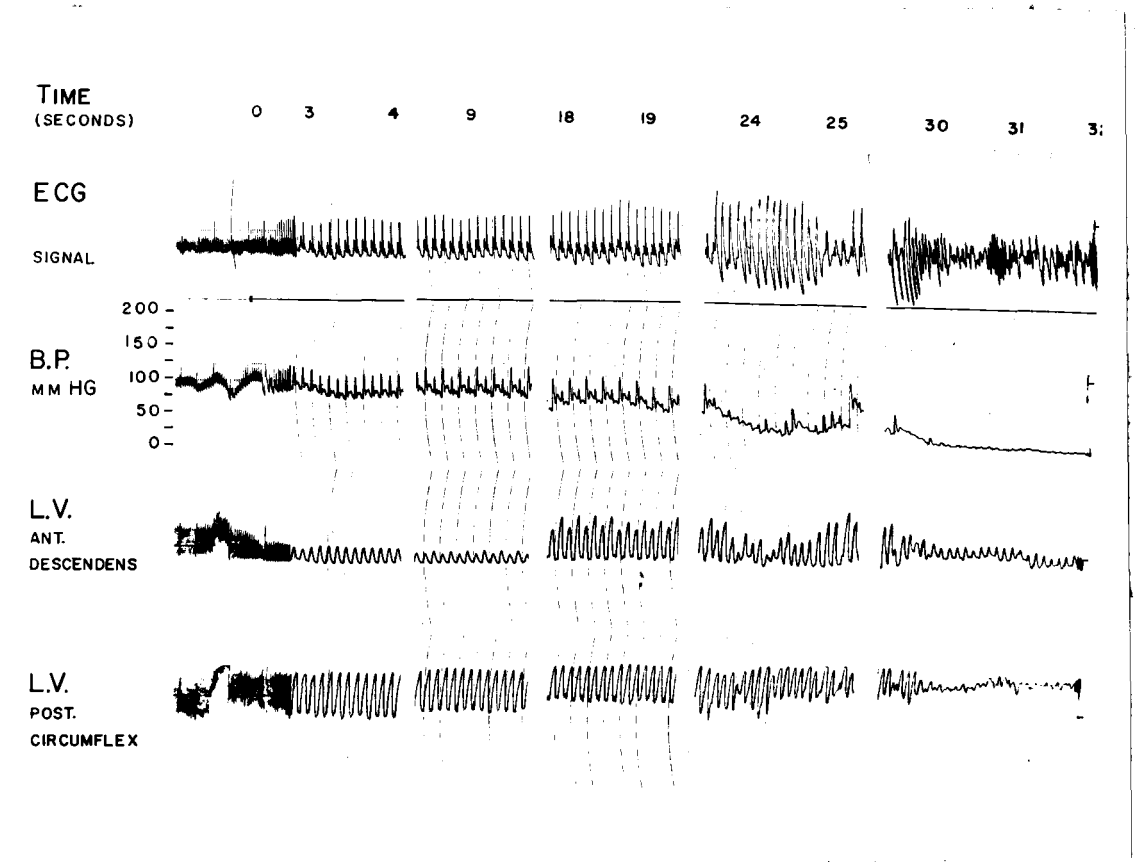

Figure 3

Contractile force following permanent occlusion of the anterior descendens artery (at signal). Note initial decline followed by phasic recovery in contractile force. Note also the pulsus alternans in the arterial pressure pulse and in the ischemic myocardial segment, but its absence in the ECG and in the non-occluded muscle.

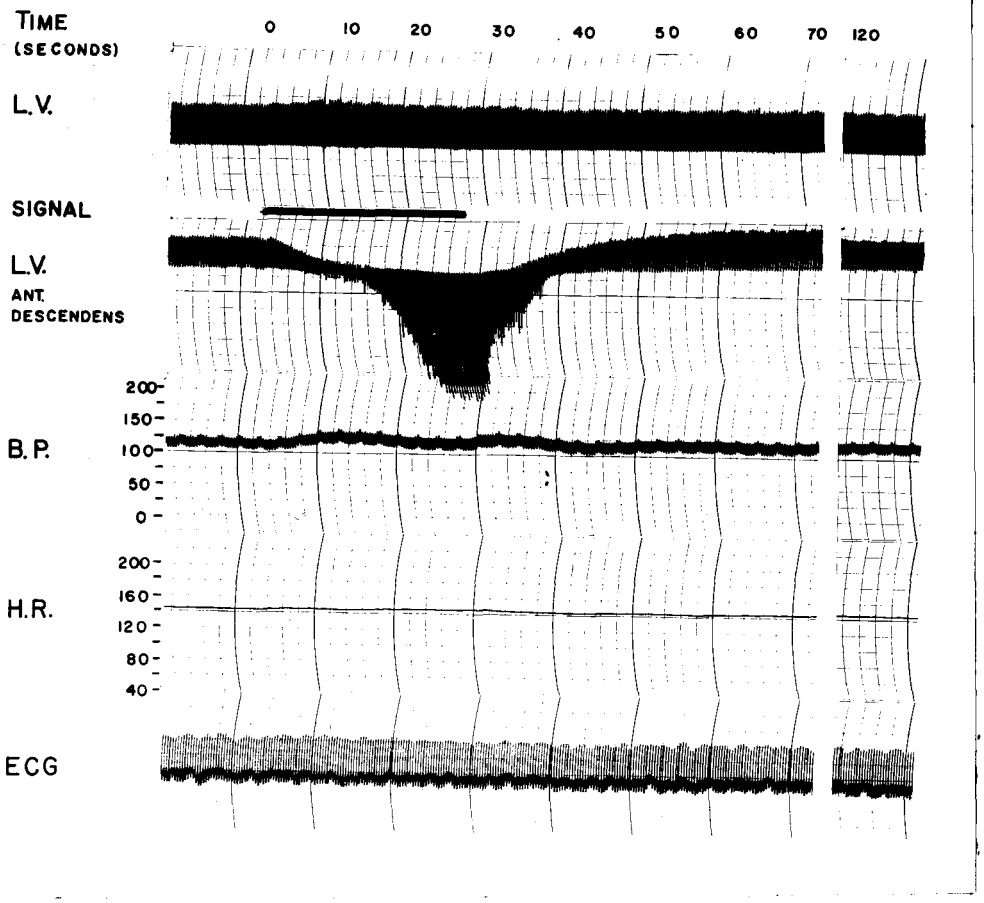

Figure 4

Simultaneous recordings of myocardial force of contraction of the left ventricle in the area of the circumflex artery, and anterior descendens, together with other dynamic events. The signal indicates the time when the proximal portion of the anterior descendens was occluded.

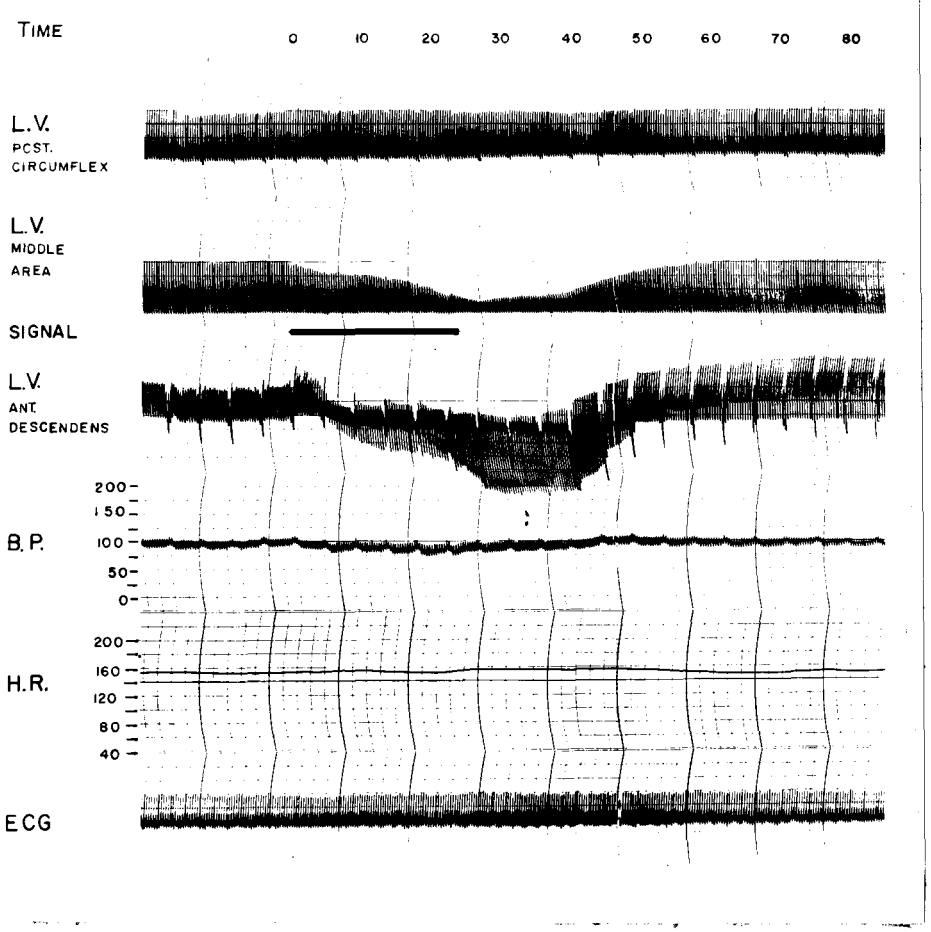

Figure 5

Changes in contractile force in three different segments of the left ventricle during occlusion of the anterior descendens artery. Note the reversal in the ischemic region representing bulging of this muscle segment during ventricular systole.

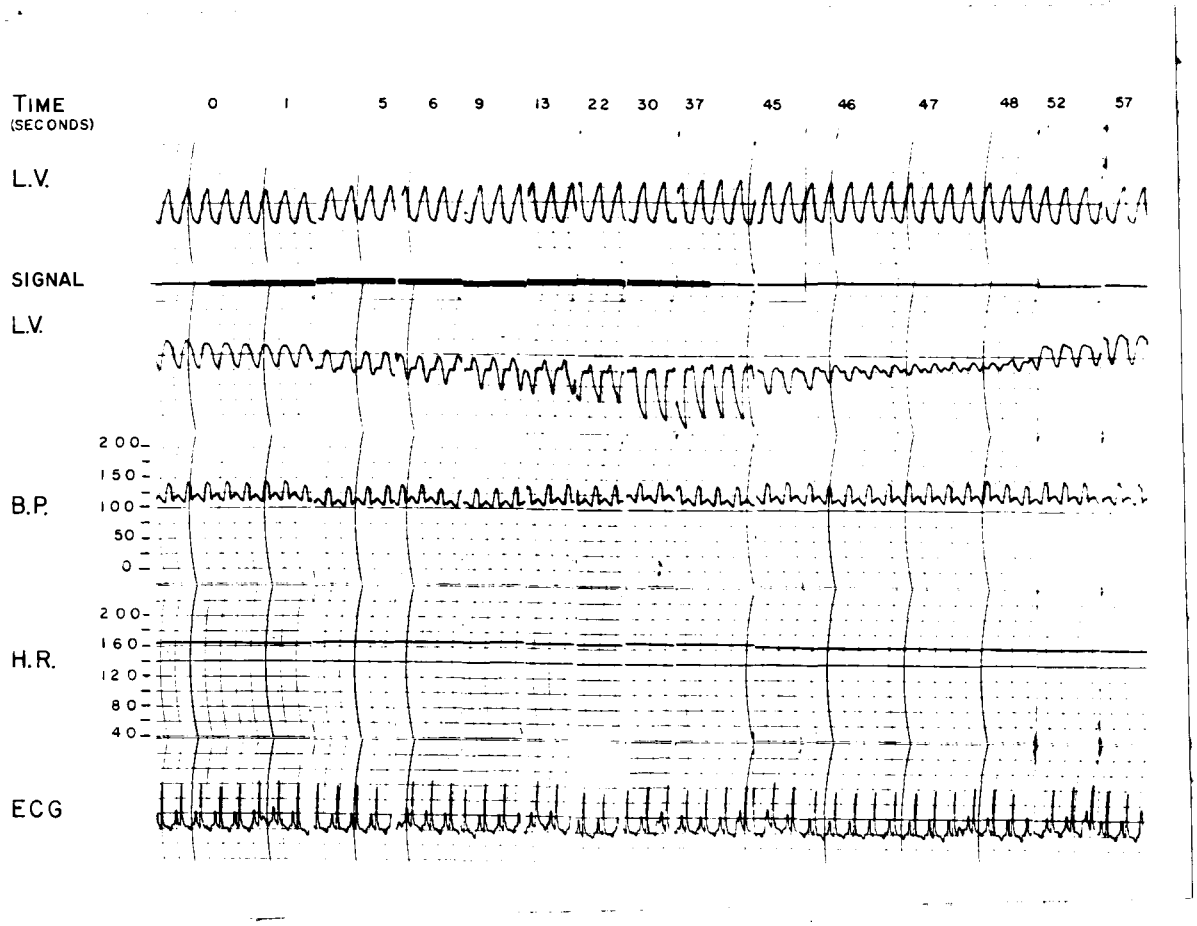

Figure 6

Effect of coronary artery occlusion recorded at high speed (25mm/sec.). Note the progressive decline in contractile force followed by the gradual development of bulging. The initial contraction gradually weakened until bulging was finally observed immediately after the beginning of systole. The reverse occurred during recovery.

DISCUSSION

The simultaneous decline in mechanical force of contraction of both ventricles during occlusion of the main left coronary artery presumably was related to the specific placement of the strain gages on areas supplied by the occluded artery. Considerable variation in coronary artery distribution patterns has been described (15, 16). However, when the gage was placed in an area supplied almost entirely by the occluded artery, amplitude of contraction promptly declined. We cannot agree with the Prinzmetal group (17) that "the ischemic myocardium ceases to contract within three to four seconds after the coronary artery is occluded" but the prompt depression of contraction was certainly an impressive feature of the experiments. In all fresh preparations, a transitory elevation in systemic blood pressure followed immediately after occlusion in spite of depressed contractility of the ischemic zone. This preliminary systemic pressure rise was generally abolished by bilateral vagotomy, and may be related to reflex vasoconstriction initiated by receptors within the ischemic myocardium.

In spite of the initial rise in systemic blood pressure immediately following ligation, blood pressure generally declined during the latter part of the occlusion period. Feil and his co-workers (18) recorded mean arterial pressures during the

ligation of the anterior descending artery, and observed instances in which pressure remained unchanged or rose than those in which it fell, regardless of whether the vagi were intact or sectioned. Only when smaller branches of the coronary arteries were occluded did blood pressure fail to decline in our experiments. However, even though the period of occlusion was prolonged, contractions of the epicardial muscle mass sometimes was not severely depressed and occasionally regained control amplitude. This circumstance reflects only partial ischemia in that particular mass of tissue. It was in this kind of situation that the "waxing and waning" shown in Figures 2 and 3 was occasionally observed. This phenomenon was never observed after contraction had been completely abolished or after the ischemic zone had started to bulge. Similar circumstances may account for the differing reports of Prinzmetal et. al. (6) who saw "waxing and waning" and Wiggers (19) and Gregg (20) who did not.

Following release from a short period of occlusion, contraction of myocardial segments within the involved zone often became much more forceful than in the control, pre-occlusion period. Such exaggerated contraction rose to a maximum and then gradually returned to control levels. Orias (3) also found that up to four minutes after ligation, aortic and ventricular pressures were not only restored to normal, but the heart action was dynamically better than normal. There is no explanation for such a response, but note that it corresponds in time to the

marked increase in coronary flow ascribed to reactive hyperemia (21) following similar occlusion procedures. By means of differential pressures and flow measurements Gregg and Green (22) found that following temporary ischemia of the coronary bed the inflow is increased greatly without significant alterations of the peripheral coronary pressure. The duration of the increased force of contraction seems also to be roughly proportional to the duration of occlusion, again in parallel with the duration of reactive hyperemia (23). Conceivably both responses could be associated with the local accumulation of metabolites and the catecholamines during the occlusion period, but as shown by Coffman and Gregg (23), the factors responsible did not appear to be washed out immediately with the elevated levels of flow, for the duration of hyperemia increased with the length of occlusion.

Figures 4, 5, and 6 illustrate the fact that a severely ischemic region soon loses its ability to shorten during systole. Both Wiggers et. al. (24) and Gregg (20) felt the ischemic muscle "attempted to shorten" but its force of contraction was too weak to withstand intraventricular pressures. Direct measurements of contractility by the strain gages failed to reveal any attempt to shorten once ischemic became profound, but until then confirmed the hypothesis that the muscle does continue to contract rhythmically.

These strain gage records clarify another point of difference between the Prinzmetal group which report that the

ischemic area "contracts early in systole and balloons late in systole" and Wiggers who observed that the bulging begins during the isometric contraction period and is sustained throughout. Figure 6 clearly reveals that both views are correct, depending upon the precise period of observation. During the initial period of ischemia, contraction appeared early in systole, followed by bulging, but with continued ischemic the tissue bulged at the onset of systole.

Manning et. al. (25) and Leroy and Snider (26) postulated the presence of a coronary vasoconstrictor reflex following coronary artery occlusion. The hypothesis was presented that sudden death in patients resulted from reflex coronary vasoconstriction whose stimulus was the infarct, whose afferent pathway is the cardiosensory innervation and whose efferent pathway is the vagus. The presumed result of such reflex vasoconstriction in a susceptible person is fatal ventricular fibrillation (26). Manning et. al. (25) noticed that the mortality of unanesthetized dogs was higher than in anesthetized dogs following coronary artery occlusion. They believed the reflex was inhibited by the depressant effect of the anesthetic agents. Opdyke and Selkurt (27) investigated this area by measuring flow rates from various coronary branches after an adjacent branch had been occluded. They found an increased flow in the non-occluded artery. If an intercoronary vasoconstrictor reflex were present, it would be logical to assume that a decrease in force of contraction would

result in a non-occluded area of the ventricle. However, the records of the amplitude of contraction recorded by the strain gage arches show a slight increase in the non-occluded areas. This favors the view and supports the findings of Opdyke and Selkurt.

The ability of the myocardium to withstand severe ischemia with full recovery is a matter of great practical interest. Our experiments were not designed to test this ability, but the following observations are apropos. The first occlusion in any given experiment was generally followed by considerably less dynamic change (in arterial pressure, E.C.G., or in force of muscle contraction) than in identical occlusions which followed. If the recovery period between occlusions were short, dynamic changes were correspondingly greater. Therefore, an initial occlusion frequently required 10 to 15 seconds before marked depression of contractions occurred. On successive occlusions of the same large artery, depression of the same zone of ischemic muscle appeared earlier and became more severe. Whereas bulging of the ischemic section did not appear during an initial short occlusion, it did appear after repeated occlusions. Also, prolonged occlusion frequently induced bulging when short occlusions did not. In all of our procedures contractions were restored provided release of the coronary ligatures was instituted within one minute. Wiggers (19) reported contractility was not restored when a coronary clamp was left in place longer than 20 to 60

minutes. Yabuki et. al. (28) presented pathologic evidence which demonstrated that a complete occlusion of a major branch of the coronary artery is associated with death of the cardiac muscle if the occlusion is maintained for forty five minutes or more.

The presence of pulsus alternans without electrical alternans is unexplained. It is clear from the ECG that the excitation wave arises rhythmically and spreads over the myocardium even though some fractions do not give a full mechanical response. H. C. Wiggers (29) demonstrated that action potentials can still be recorded from the ischemic area for at least 20 minutes after coronary occlusion, and indeed, Tennant and Wiggers (4) showed that the heart may be artificially driven for considerable periods by electrical stimulation within the ischemic zone.

SUMMARY

I. In anesthetized, open chest dogs under positive pressure respiration, strain gage arches were sutured to the myocardium, and the qualitative force of ventricular contraction was recorded from areas in and outside the distribution of a given occluded coronary artery.

II. A simultaneous decline in the force of contraction of both ventricles is illustrated when the left main coronary artery is occluded.

III. During occlusion of a large coronary artery the force of contraction of the affected myocardium decreased, and with continued occlusion the ischemic area no longer contracted but bulged during ventricular systole. Lead II of the ECG remained relatively unchanged during ventricular bulging.

IV. After several successive occlusions, ventricular bulging became more pronounced and occured more promptly after occlusion.

V. Restoration of contraction in the ischemic segment was observed in all instances of occlusion of one minute or less.

VI. Upon release of the occlusion, the force of contraction in the ischemic segment progressively became markedly greater than control with apparently complete recovery during the following one to three minutes.

VII. Pulsus alternans was frequently noticed without electrical alternans.

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APPROVAL SHEET

The thesis submitted by Constantine J. Tatooles has been read and approved by three members of the faculty of the Stritch School of Medicine, Loyola University.

The final copies have been examined by the director of the thesis and the signature which appears below verifies the fact that any necessary changes have been incorporated, and that the thesis is now given final approval with reference to content, form and mechanical accuracy.

The thesis is therefore accepted in partial fulfillment of the requirements for the Degree of Master of Science.

May 29, 1961
Date

Walter C. Randall
Signature of Adviser