A POSSIBLE METHOD OF LOCALIZATION AND ASSESSMENT

OF MYOCARDIAL DAMAGE USING THE

LIMB LEAD ELECTROCARDIOGRAM

By

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CHAPTER I

INTRODUCTION

Diseases of the cardiovascular system represent the most serious
health problem of our society, claiming over 1.1 million lives in the
United States annually (Corday and Swan, 1973a). More than half of
these deaths result from ischemic heart disease and its consequences,
i.e. myocardial infarction, ventricular arrhythmias, and cardiogenic
shock (Braunwald, 1976). Considering the scope of the problem, it is
not surprising that an enormous research effort has been devoted to the
assessment of these syndromes and their subsequent elimination. It is
with the former of these two objectives that this investigation is
concerned.

The primary function of the heart is to supply adequate amounts of
oxygenated blood so that the metabolic requirements of the tissues are
met. When a sufficient quantity is not delivered to any tissue, the
tissue is said to be ischemic. Unless relieved, this ischemia will
lead to progressive impairment of function with the ischemic cells
becoming irreversibly injured. Thus, evaluation of the heart's ability
to perform under these adverse conditions is of importance to both the
clinician, who is required to assess cardiac function in his patient,
and the research scientist, who must measure the effects of various
interventions on cardiac performance.

The collection of data necessary to assess cardiac function in the past has required the invasion of the circulatory system, but recently, non-invasive methods of assessment have become popular and are being used clinically. Existing non-invasive methods include echocardiography (Feigenbaum et al., 1968; Parisi et al., 1977), apexcardiography (Benchimol et al., 1963; Vetter et al., 1972; Denef et al., 1975), radionuclide imaging (Prinzmetal et al., 1949; Parisi et al., 1977), systolic-time intervals (Weissler, 1977) and exercise electrocardiography (Hartley, 1975). Although each of these techniques may provide valuable information, all have their limitations, and some have the distinct disadvantage of being too complex to apply routinely (Corday and Swan, 1973b). Therefore, the search for new methods of assessing cardiac function continues.

The purpose of this investigation was to determine whether the rate of voltage change (dV/dt) in the ascending limb of the R-spike in the limb lead electrocardiogram (ECG) provides any information regarding the contractile state of the heart. The first objective was to determine which portion of the myocardium produces changes in the ascending limb of the R-spike of the ECG as the activation wave front moves across the heart. The limb lead ECG represents the sum of a complex series of electrical events occurring in the heart (Estes, 1974). Each discrete segment of the ECG corresponds to the summated electrical activity of certain portions of the myocardium. More localized recordings directly from the surface of the heart, electrograms (EG), are better able to discriminate those areas whose summated discharge is reflected in the limb lead ECG. Thus, a relationship between dV/dt of the R-spike upstroke as recorded by an electrogram and its correlate in the limb

lead ECG may be demonstrated. A positive correlation between dV/dt in the ECG and in the electrogram in normal and ischemic hearts would give a predictive quality to the limb lead ECG with respect to the localization of ischemic myocardium. The maximum rate of rise of intraventricular pressure (dP/dt) was used to assess contractility. The relationship between the ECG dV/dt and left ventricular dP/dt was observed under normal conditions and after the production of experimental myocardial infarction. If a significant relationship could be shown to exist, then perhaps the standard ECG could be used to detect directional changes in contractility during the recovery phase of infarction.

In summary, it was anticipated that the rate of voltage change in the limb lead ECG may be realistically related to a discrete area of the myocardium (pinpointing ischemia), and may be useful in evaluating the contractile effort of the entire myocardium.

CHAPTER II

LITERATURE REVIEW

Even though cardiovascular disease is said to be the disease of
modern man, the writings of Hippocrates, Galen, and Pliny the Elder
contain accounts of sudden death, of which the majority were almost cer-
tainly the result of cardiovascular disorders. Centuries later, angina
pectoris, a disease characterized by transient myocardial ischemic
episodes and associated pain, was described by Heberden in 1768, without
knowledge of its cause (as cited by White, 1974). Jenner and Parry in
1799 (as cited by Porter, 1894) associated angina pectoris with the
calcification of the coronary arteries, and this prediction was borne
out by a post-mortem examination of a patient who died suddenly during
an anginal attack. The significance of coronary artery obstruction was
studied by Cohnheim in 1881, who concluded that the sudden occlusion of
one of these vessels causes death within a few minutes (as cited by
Herrick, 1912). Various investigators described the general clinical
symptoms of coronary artery obstruction in isolated cases for a number
of years after this, but it was not until 1912 that a full description
of the ischemic heart disease syndrome was presented in a classical
paper by Herrick (1912).

The experimental study of the effects of coronary artery occlusion
began with Erichsen in 1842 (as cited by Porter, 1894), who ligated the

coronary arteries in a pithed dog and produced cardiac arrest within
minutes. Erichsen described the ventricles as having a "slight tremu-
lous motion," which is now referred to as fibrillation. Occlusion by
embolus was investigated by Panum (as cited by Porter, 1894) 20 years
after Erichsen's study. Panum injected a mixture of tallow, wax, oil,
and lamp-black into the coronary arteries, but when the ventricles con-
tinued to contract regularly, he concluded that a lack of oxygenated
blood does not necessarily bring the heart to an immediate standstill.
In 1881, Samuelson (as cited by Porter, 1894) ligated the coronary
arteries of curarized dogs and demonstrated a weakening of contractile
force. This important observation, along with the others previously
described, form the basis of the use of coronary artery ligations as an
experimental model of myocardial ischemia and infarction.

The pathological changes induced by ischemia are of importance in
this study in that they are determinants of the hemodynamic and elec-
trophysiologic alterations (Jennings, 1969). When ischemia occurs, the
reduction in available oxygen produces a shift from aerobic to anaero-
bic metabolism within the cell (Bing, 1965; Sheuer, 1967). Stored
energy in the form of adenosine triphosphate and creatine phosphate is
quickly consumed (Braasch et al., 1968), and tissue oxygen tension
decreases. Within 15 seconds the myocardium appears cyanotic, and the
tissue becomes increasingly acidotic. The decrease in intracellular
energy produces an immediate reduction in contractile power and a de-
pression of the membrane potential (Jennings and Reimer, 1973), which
is demonstrated by electrophysiological (Johnson, 1976) and hemodynamic
evidence (Ross, 1976). Several investigators (Harris et al., 1954;
Regan et al., 1967) have demonstrated an efflux of potassium and

magnesium from the ischemic cells by measuring coronary sinus blood which drains the affected area, presumably the result of an inability to maintain proper ionic distribution. Along with this ionic efflux, there is a concomitant influx of sodium and water, and the resulting cellular swelling may compress the microvasculature and produce a further decrease in existing blood flow (Powell et al., 1976).

The cellular alterations described thus far occur prior to any irreversible injury, and a distinction should be made between these changes and cellular death. Jennings et al. (1960) demonstrated in dogs that all functions return to normal even in the most severely ischemic cells provided arterial blood flow is restored within 15 to 19 minutes after an occlusion. In his study, he observed the first myocardial cell death to occur after about 20 minutes of arterial occlusion, and most of the cells in the affected region have become irreversibly injured within one to two hours. Necrosis of the dead cells begins between 12 and 24 hours after arterial occlusion. Repair of this tissue begins almost immediately and can be detected by light microscopy within 36 hours. The dead cells must be removed by phagocytosis and are replaced by scar tissue. This process is usually completed in four to six weeks (Jennings and Reimer, 1973).

The reduction in contractile force described earlier is of considerable significance if adequacy of the circulation is to be maintained. A diminution of contractility may compromise circulation in other organs and further embarrass coronary blood flow. The reduction in contractility is rapid after coronary arterial obstruction, with measurable changes detected within 10 seconds (Ross and Franklin, 1976). This appears before ischemic ST-segment elevation in an epicardial

electrogram, and thus is a sensitive indicator of myocardial ischemia.
Although these very early changes in contractility described by Ross and
Franklin (1976) were detected by strain gauges attached to the heart,
investigators observed a loss of contractile force of the entire ven-
tricle years ago. Samuelson's demonstration in 1881 was followed by a
paper in 1887 by Bettelheim (as cited by Porter, 1894) who also des-
cribed a reduction of contractile force after arterial occlusion. These
observations were again confirmed by Porter (1894).

Attempts to quantitate this loss of contractility were begun almost
as quickly as it was observed. One method which has received attention
over the years and is still being used (Benfey, 1967; Beierhold et al.,
1975; Mahler et al., 1975; Mason et al., 1971; Ross and Franklin, 1976;
Rushmer, 1962; Theroux et al., 1976; Vatner et al., 1974) is the rate
of change of intraventricular pressure dP/dt expressed in millimeters
of mercury pressure per second (mm Hg/sec). The first investigator to
become interested in the rate of pressure development in the ventricles
was Otto Frank in 1895 who included the rate of pressure change along
with the maximal pressure attained in his analysis of the frog ven-
tricle (Frank, translated in 1959). Wiggers observed the rate of
pressure change in mammalian ventricles and the influence of various
hemodynamic factors (1914) and pharmacologic agents (1927; Wiggers and
Stimson, 1927) upon it. Patterson et al. (1914) also emphasized the
importance of the rate of change in pressure as a fundamental property
of the myocardium. The sensitivity of the maximal rate of rise of
ventricular pressure to changes in the contractile state of the heart
has been demonstrated by many investigators (Reeves et al., 1960; Wal-
lace et al., 1963; Mason et al., 1971), but it is also known that other

factors influence this value.

The rate of isovolumic pressure generation in the heart is said to be regulated by three principal factors: (a) the preload, which is determined by the end-diastolic fiber length, (b) the afterload, which is related to arterial diastolic pressure, and (c) the inotropic or contractile state of the myocardium (Katz, 1955; Braunwald et al., 1967, 1969). Measurements, or at least accurate indexes, have been developed for the first two factors, but it is much more difficult to assess the contractile state. The use of dP/dt as an index of myocardial contractility is limited by the extent it is influenced by the first two variables (Mason, 1969).

The preload conditions influence the maximal dP/dt, and these effects have been studied for years. After Patterson et al. (1914) had described the effects of initial tension and fiber length on the response of isolated hearts, Wiggers and Stimson (1927) showed that the rate of intraventricular pressure rise is increased when end-diastolic volume and pressure are elevated. This effect was again demonstrated by Wallace et al. (1963), and other studies were initiated to try to develop an index which would account for changes in preload conditions and allow comparison of contractility from one individual to another. Many elaborate indexes were developed and are reviewed by Mason (1969). Each has its advantages and limitations according to the degree it is affected by changes in other variables.

Alterations in peak dP/dt occur as a result of changes in arterial diastolic pressure, a determinant of ventricular afterload (Mason, 1969; Milnor, 1975). The rate of rise of ventricular pressure increases until the opening of the semilunar valves. When the valves open, the energy

generated by the ventricles is dissipated as flow rather than an increase in tension. Thus, peak dP/dt usually occurs at the instant of the opening of the semilunar valves (Wildenthal et al., 1969). Delay in valvular opening, which may result from an increase in arterial diastolic pressure, leads to an increased peak dP/dt. In this manner, a change in peak dP/dt can occur due to changes in arterial pressure with no change in contractility (Braunwald et al., 1969). Indexes for correction of afterload conditions have been developed by dividing dP/dt by the pressure developed during various stages of systole (Mason, 1969). Some have proven useful for correction of differing afterload conditions but remain sensitive to changes in preload.

Several other factors are known to influence ventricular pressure rise and are pertinent to this study. First, peak dP/dt is related to heart rate (Gleason and Braunwald, 1962). Tachycardia causes an increase in the rate of pressure rise reflecting an enhanced level of contractility. Second, the manner of ventricular activation influences peak dP/dt as demonstrated by Wallace et al. (1963). When activation is initiated in an aberrant manner the peak dP/dt is decreased. Ectopic rhythms, depending on the focus, would be expected to be associated with a decreased peak dP/dt. Third, various pharmacologic agents raise and lower peak dP/dt depending on their actions. Catecholamines increase dP/dt (Rushmer, 1962; Vatner et al., 1974). This action is due to the positive inotropic effect of these agents. An increase in circulating catecholamines is known to follow myocardial infarction in humans and dogs (as cited by Khan et al., 1972). The resulting effect of these agents must be considered in evaluating contractility from changes in peak dP/dt.

The sensitivity of peak dP/dt to the factors just described make it a complex function and somewhat difficult to interpret. Another limitation is the wide range of normal values from one individual to another. This makes comparison between individuals almost impossible on the basis of peak dP/dt alone (Mason, 1969). Comparison of the effects of acute interventions on contractility in a specific individual is permissible as described by Mason (1969) and Braunwald (1977); however, certain other limitations are indicated. If an intervention that alters peak dP/dt also changes one of the previously described factors in a manner which would tend to have altered dP/dt in the same direction, it is very difficult to decide whether the intervention or the change in the other factor caused the lateration in peak dP/dt. As a result, discrimination between the effects of the intervention and the other influences cannot be made if they change peak dP/dt in the same direction. However, if the change occurs in a direction opposite to that which would have been anticipated, it is proper to attribute the negative or positive inotropic change to the intervention (Mason, 1969; Ross and Peterson, 1973).

In comparing the sensitivities of peak dP/dt and the other indexes derived from it, peak dP/dt is reported to be more sensitive to acute changes in the contractile state (Ross and Sobel, 1972). Within the limitations described, it has been a standard reference for assessing acute changes in the contractile state of the heart. The existing controversy as to which index provides the most information with the fewest limitations remains to be settled. Most investigators would concur with Kreulen et al. (1975) that no single index can always be

used for defining an acute contractility change in the intact myocardium. It is with this understanding that the present study was initiated.

The use of the standard electrocardiogram (ECG) in studying cardiovascular disorders has been extensively reviewed by others (Schaefer and Haas, 1962), and it is beyond the scope of this project to present a review here. Analysis of the ECG in the manner done in this study has not been reported in the literature. The maximal rate of voltage change (dV/dt) of action potentials in single cardiac muscle fibers has been measured by many investigators and is often used to assess the effects of certain drugs on membrane responsiveness (Bassett and Hoffman, 1971; Chen et al., 1975). No application of this measurement has been reported for the components of the QRS complex of the ECG.

Certain factors are known to alter the rate of voltage change of cardiac muscle fibers. Antiarrhythmic drugs, such as lidocaine, quinidine, procainamide, and propranolol, decrease dV/dt (Bassett and Hoffman, 1971; Moe and Abildskov, 1975). Catecholamines increase dV/dt (Trautwein, 1963; Kassebaum and Van Dyke, 1966). For each drug which alters the rate of voltage change of cardiac muscle fibers, there is an established change in contractility in the same direction (Moe and Abildskov, 1975). Drugs which decrease dV/dt also decrease contractile force, while agents which increase dV/dt elicit an increase in contractile force of the muscle fiber.

The establishment of dV/dt in the limb lead ECG as a rough predictor of localized myocardial electrical activity was one objective of this study. An acute study was designed to test the correlation between dV/dt in the ECG and in random left ventricular epicardial

electrograms. A positive correlation would demonstrate that changes in dV/dt of individual cardiac muscle fibers is reflected in the epicardial electrogram, in turn related to the dV/dt of the R-spike ascending limb of the ECG. The second objective was to test the relationship between the rate of voltage change in the limb lead ECG and the rate of pressure change in the left ventricle. A positive correlation between these rates would provide hemodynamic data without requiring the catheterization of blood vessels--a non-invasive method. A third objective was to observe this relationship during ischemic conditions and after the development of experimental myocardial infarction. Provided the correlation remained positive, a new method of detecting ischemic injury would be demonstrated.

CHAPTER III

MATERIALS AND METHODS

Two different protocols were designed to study the relationship
between the rate of voltage change (dV/dt) of the ascending limb of the
R-spike in the limb lead electrocardiogram (ECG) and the rate of pres-
sure change (dP/dt) in the left ventricle prior to and after the acute
ligation of the left anterior descending (LAD) coronary artery. The
acute protocol was designed to determine those portions of the myocar-
dium which show a correlative relationship between these variables.
The second protocol was designed to observe the relationship on a
chronic basis. Under these conditions, each animal was allowed to re-
cover following the ligation and the ECG and left ventricular pressure
(LVP) was recorded every 24 hours for a period of five days. At the
end of the fifth day's recording, the animals were sacrificed, and
their hearts were examined grossly. The point of ligation was inspected
to document that the artery was completely occluded.

Animal Acquisition and Care

Eleven mongrel dogs of either sex with a 10-30 kilogram range in
body weight were used during this investigation. These animals were
acquired by the physiology department. All of the animals were shel-
tered in a large holding pen indoors prior to their use in this study.

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No special care was given to any animal to prepare him for use. All dogs received the same diet consisting of dry dog food (Purina).

The animals used in the chronic study were allowed to recover in a portable cage in the laboratory where each remained for the five-day post-ligation period. In this manner, their food and water intake was monitored, and the stress of competition with other animals was eliminated. (It might be noted here that the mortality rate was substantially reduced by keeping the animals in the laboratory during the post-ligation period and monitoring their status more closely.)

Although the animals were observed to experience some discomfort and pain after the surgery, analgesic drugs were not administered because of known and suspected influence on cardiac function. All of the animals were encouraged to walk as early as possible. Most were walking with some stiffness by the second day.

Surgical Technique

All of the dogs were anesthetized with intravenous injections of sodium pentobarbital (32 mg/kg). Each was then intubated with respiration maintained mechanically at a rate of 12-15 cycles per minute. The chest and throat areas were clipped and scrubbed, and the animal was draped if it was to be used in the chronic study in keeping with aseptic technique.

With the animal in the supine position, a small incision, approximately two centimeters long, was made through the skin along the left marginal edge of the trachea. The left common carotid artery was bluntly dissected and isolated with silk ligatures. The cephalad ligature was permanently tied, and the vessel was occluded temporarily by

the proximal ligature. A small nick was made in the artery, and a polyethylene catheter (Intramedic PE 240) filled with heparinized saline was inserted into the lumen of the vessel. The catheter was then introduced into the left ventricle and its location confirmed by recording the left ventricular pressure pulse. (After repeated efforts, it was discovered that curving the catheter tip a slight degree facilitated the left ventricular catheterization.)

Needle electrodes were inserted in the appropriate limbs so that a recording of the Lead II ECG could be made. The recording instrument used in this investigation was the Narco Physiograph (Narco Bio-Systems, Inc.). The ECG was recorded on this instrument through a solid-state amplifier calibrated to one millivolt per centimeter. Left ventricular pressure was simultaneously recorded with a P-1000-A pressure transducer (Narco Bio-Systems, Inc.) calibrated to 40 millimeters of mercury pressure (mm Hg) per centimeter. A control recording was then made for the dogs in both groups.

A left thoracotomy was performed at the fifth intercostal space, with an electric cautery used to minimize bleeding. The ribs were retracted, and the left lung gently packed away anteriorly and dorsally with saline-soaked gauze. The pericardium was incised along the length of the heart and temporarily sutured to the chest wall to present the best possible exposure of the left anterior descending coronary artery. The heart was thus cradled in the pericardial sac to facilitate isolation of artery.

A few millimeters of the artery was dissected free at a distance of five to eight millimeters from the distal edge of the left atrial appendage. The epicardium was teased away, and the artery was freed up

from the ventricular wall by blunt dissection. There was a consider-
able amount of variation from animal to animal in the depth at which
the artery was embedded in the left ventricular wall, and this depth
determined to a large extent how much time was required in surgery.
After the artery was dissected free, three ligatures were placed around
the vessel and loosely knotted.

At this point the surgical protocol differed depending on whether
the animal was to be used in the chronic study or the acute study. The
dogs were divided into two groups with five to be studied acutely and
six to be used in the chronic study. The protocol used in the acute
study will be described first followed by a description of the protocol
for the chronic study.

Protocol for Acute Study

Another set of electrodes was connected so that a unipolar electro-
gram (EG) could be recorded from points on the ventricular surface. The
electrogram was also calibrated to one millivolt per centimeter as was
the ECG and was recorded with a solid-state amplifier on the physio-
graph. It was often necessary to attenuate this recording so that the
amplitude of the excursion did not exceed the maximum travel of the
stylus. The exploring electrode was connected to the negative lead so
that an upward deflection was produced by ventricular depolarization.
The positive and ground leads were inserted under the skin.

A rough sketch of the heart was drawn showing the left atrial
appendage, left anterior descending coronary artery and its major visi-
ble branches, and the point at which the ligation would be made.
Approximately 12-14 random points were chosen on the anterior wall of

the left ventricle extending from the atrio-ventricular groove to the
apex. These points were distributed distally and laterally from the
left anterior descending artery, and some reached the left marginal
edge of the left ventricle. A dark blue stain was prepared by mixing
methylene blue (Allied Chemical Corp.) and a concentrated glucose solu-
tion, and the points on the ventricular wall were stained permanently
with this solution. Discrete points were made by using a tuberculin
syringe and a 25 or 27 gauge needle as the dropper. The drops were
quickly blotted to avoid running or smearing of the dye on the ventri-
cular surface. Each point was labelled alphabetically and represented
on the rough sketch in the appropriate relation to other points and the
visible vascular anatomy. At the end of the experiments, the points
were permanently marked by a coded suture drawn through the epicardium.

A recording of the electrogram, which is the representation of
local electrical activity recorded from the epicardial surface, was then
made at each point in alphabetical order while simultaneously recording
the Lead II ECG and left ventricular pressure. The exploring electrode
was held directly on the stained point by hand. The sketch provided a
"map" which could be followed so that each point was recorded sequen-
tially without missing any points or recording from the same point
more than once. Recordings were taken from each point for at least 20
consecutive cardiac cycles to insure that enough data were collected
for an accurate analysis. When the pre-ligation or control recordings
were complete, the left anterior descending artery was ligated.

The method used for coronary artery ligation was a slight modifi-
cation of the method first used by Harris (1950). Ventricular
fibrillation will usually follow the acute ligation of a coronary

artery particularly if the artery is a major branch. To prevent death by fibrillation, Harris developed a method of progressive arterial occlusion which usually protects the animal from fibrillation. However, delayed ectopic arrhythmias along with massive myocardial necrosis are produced (Figure 1). It is for these reasons that we chose to use this method.

The ligation was done in three successive steps. A blunted 20 gauge needle was laid parallel to the artery, and one of the loosely knotted ligatures was then pulled into a tight knot around both the artery and the needle leaving the artery completely occluded. The needle was quickly slipped out of the knot allowing the artery to reopen to approximately the same outside diameter of the needle. Blood flow was thus greatly reduced through the vessel but not entirely arrested. A waiting period of 15 minutes was allowed during which time the ECG was closely observed for signs of ventricular arrhythmias. If no serious arrhythmia developed during this time, a smaller diameter needle (22 gauge) was tied to the artery in the same manner and slipped out leaving the effective lumen of the artery further reduced along with a reduction in blood flow. Another 15-minute period was allowed with continuous observation of the ECG. At this point, the final tie was made completely occluding the artery.

Another waiting period of 20 minutes was allowed after making the final tie. This amount of time would insure production of severe ischemia of the myocardial tissue subserved by the left anterior descending artery distal to the ligation. A recording of the electrogram was then taken from each point again giving a pre-ligation and post-ligation record for every point. The recording was done in the same
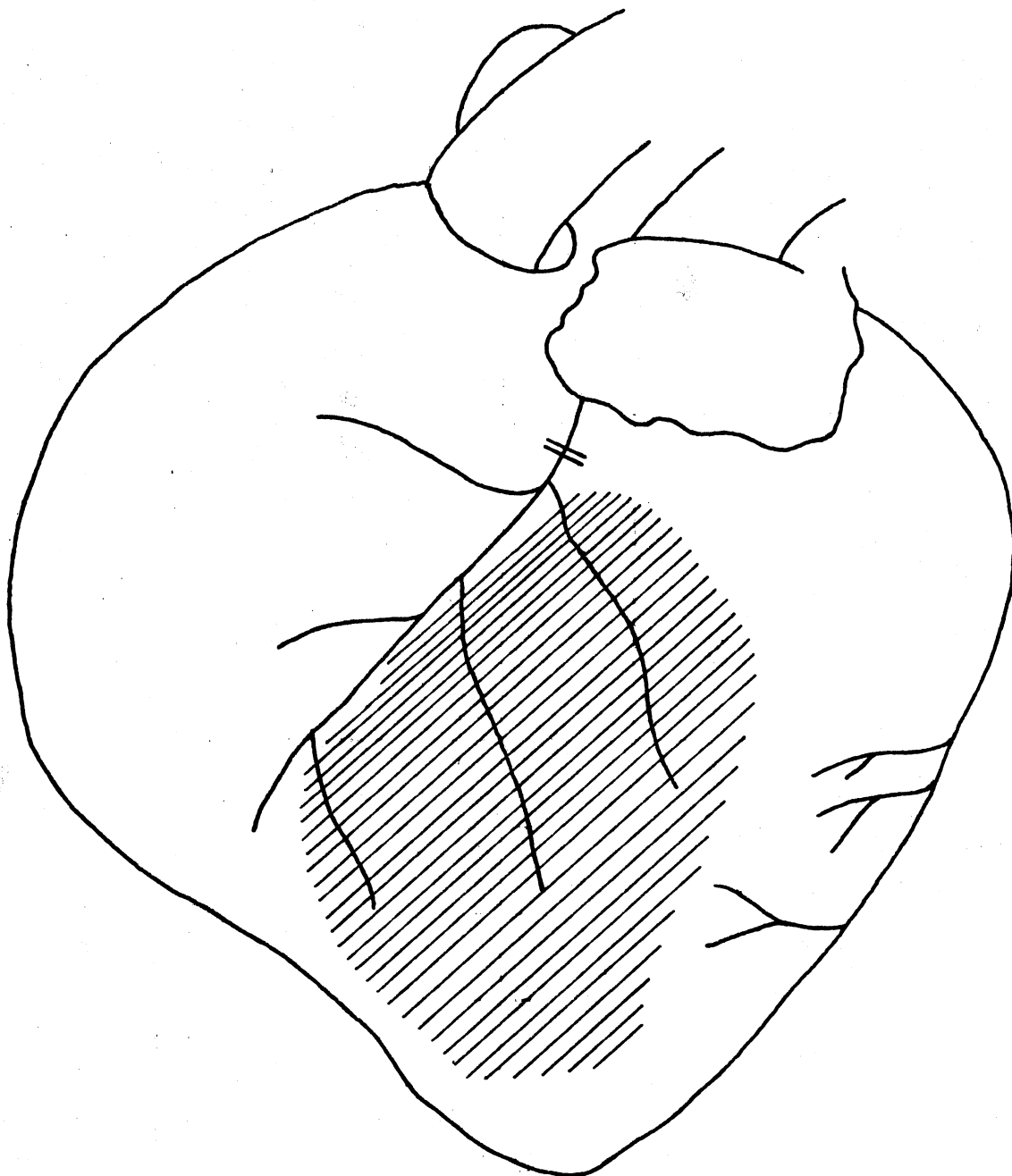
Figure 1. Illustration Depicting the Typical Ischemic Zone (shaded
     area) Produced by Ligation of the Left Anterior Des-
     cending (LAD) Coronary Artery Near Its Origin.

manner as before with continuous ECG and left ventricular pressure tracings. Data collection was completed for each animal used in the acute study in this manner. The animals were then sacrificed.

The heart of each of these dogs was removed, and a tiny knot was placed in the epicardium with silk suture to provide a permanent record of the points at which the electrograms were recorded. A transparency sheet was laid over the heart, and an accurate tracing of the artery and its point of ligation along with its major branches was drawn. Careful attention was made to see that the points were drawn in their positions relative to each other and labelled correctly. This transparency produced a permanent, accurate illustration of the anatomical arrangement of the vasculature and the electrogram points. The hearts were then placed in plastic containers in a formalin-acetic acid-alcohol (10-10-10) preservative and kept for any future reference.

Protocol for Chronic Study

The protocol for the chronic study differed in that no electrograms were recorded. Instead, the artery was ligated progressively using the technique described earlier. The ligation was made about five to eight millimeters from the distal edge of the left atrial appendage. If no signs of serious ventricular arrhythmias occurred within 10 minutes of the final tie, the ligature was observed to see that it remained secure and the vessel was completely occluded. Providing this condition was met, the animal's chest was closed.

The sutures used to suspend the pericardial sac were cut and removed. The pericardium was not sewn closed but was allowed to remain open to avoid the accumulation of fluid within the sac. The

saline-soaked gauzes were removed from the thoracic cavity and the left

lung hyperinflated to expand atelectic areas. The rib retractor was

removed, and the ribs were then approximated and tied together with

three or four heavy silk sutures doubled for added strength. The inter-

costal muscles were sewn together, and each successive layer was

approximated and closed.

Reduction of the pneumothorax was performed at periodic intervals

during the closure of the incision. The chest of the animal was com-

pressed while positive pressure from the respirator inflated the lungs.

The expanding lungs forced any trapped air out of the thoracic cavity

through the incision. The tissue layers being sutured effectively

closed the incision before any air could enter back into the cavity.

By repeating this technique several times, the pneumothorax was reduced,

and the negative intrathoracic pressure was restored. The animal was

usually then removed from the respirator and allowed to breathe spon-

taneously while the skin was closed.

The left ventricular catheter inserted earlier was maintained

throughout the five-day post-ligation recording period. A three-way

stopcock was attached to the catheter, and both were flushed with

heparinized saline. A polyethylene sleeve made from a larger diameter

tubing was wrapped around the catheter at the point where it entered

the neck of the animal. This sleeve helped to prevent kinking of the

catheter and was also sutured to the subcutaneous tissue for extra

security. It was important that the catheter remain in the ventricle

from day to day so that left ventricular pressure and not aortic pres-

sure was recorded. If at any time during the course of the

post-ligation period did the catheter pull out of the left ventricle,

it would have had to be replaced there. This would require anesthesia a second time and may have depressed cardiac function further. (On one occasion the catheter did pull out, but fortunately it was possible to replace it with local anesthesia.)

The neck incision was then closed with silk suture. Gauze was wrapped around the stopcock and laid over the incision. The entire neck was wrapped with Ace bandage and taped to prevent the animal from scratching at the catheter. Each animal was then placed in a portable cage in the laboratory to recover. Water was denied the animals until they had fully recovered from the anesthesia at which time they were encouraged to take both food and water.

Every 24 hours of the post-ligation period the animals were placed on a table, and the ECG was recorded. A five-minute period was allowed to let the animal adjust to the table and handling with noise held to a minimum. Records were then taken for approximately 50 cardiac cycles. After the recording was complete and the catheter was flushed with heparinized saline, the neck was retaped. All animals had the freedom to move about the laboratory during the day and were returned to their cage at night.

At the end of the fifth day's recording, the animals were sacrificed, and their hearts were removed. Inspection of the ligature revealed whether the artery remained occluded during the post-ligation period. Only those animals in which the ligation was secure were included in this investigation. Six animals met this criterion for inclusion in the chronic part of the study. The hearts were placed in preservative and kept for further possible use.

Procedure for Determining Effects of

Anesthesia and Catecholamines

Each of the control records of dV/dt and dP/dt was taken while the animal was anesthetized. The post-ligation records in the animals used in the chronic study were taken while the animal was conscious. A question was then raised in regard to the effects of barbiturate anesthesia on these parameters. An acute experiment was conducted to examine this possibility.

A mongrel dog (27 kilograms) was placed on a table in sternal recumbency, and the ECG was recorded after the animal had become adjusted to the surroundings. Fast tracings were also recorded by the procedure described earlier so that the rate of voltage change could be calculated. The animal was then anesthetized using the same dose of pentobarbital as previously described. Another set of fast records was taken while the animal was in the same position to allow comparison between the conscious and anesthetized records of the ECG.

The effects of catecholamines on the relationship between dV/dt and dP/dt were investigated in this same animal. The left ventricle was catheterized, and a set of fast tracings was taken with both the ECG and left ventricular pressure tracings being recorded simultaneously. With this record to serve as a control, the animal was then given an intravenous bolus of epinephrine (1 mcg/kg). Another set of fast tracings was taken during the peak effect of the epinephrine injection. When the tracings had returned to the control value, another bolus at the same dosage was administered, and the procedure was repeated a second time.

Analysis of Records

Several different functions were analyzed from each record. In the acute study, the rate of pressure generation (dP/dt) in the left ventricle and the rate of voltage change in the ascending limb of the R-spike of the ECG and the electrogram were measured for each of the points on the surface of the ventricle. These values were determined from 12 consecutive cardiac cycles with attention given to maintain their corresponding relationship (i.e. each value for the ECG was recorded with its corresponding electrogram and left ventricular pressure value.) Maintenance of this relationship was important in order to determine if a significant correlation existed between these values. The electrogram was not recorded in the animals used in the chronic study, but similar correlation analyses were made for the ECG and left ventricular pressure. Total heart rate with differentiation into normal and ectopic frequencies were determined.

Each record was analyzed entirely by hand methods. Heart rate and rhythm differentiation were determined over a five-minute period every 24 hours and then averaged for that day's recording. This five-minute period came after the time allowed for the animal to adjust to handling which was described earlier. Paper speed during this part of the recording was 2.5 centimeters per second. This speed allowed an accurate differentiation between normal and ectopic beats.

The determination of the rates of change of voltage and pressure was accomplished by triangulation (Figure 2). A straight-edge was laid along the slope of the ascending limb of the left ventricular pressure pulse or the R-spike of either the ECG or the electrogram. A line was
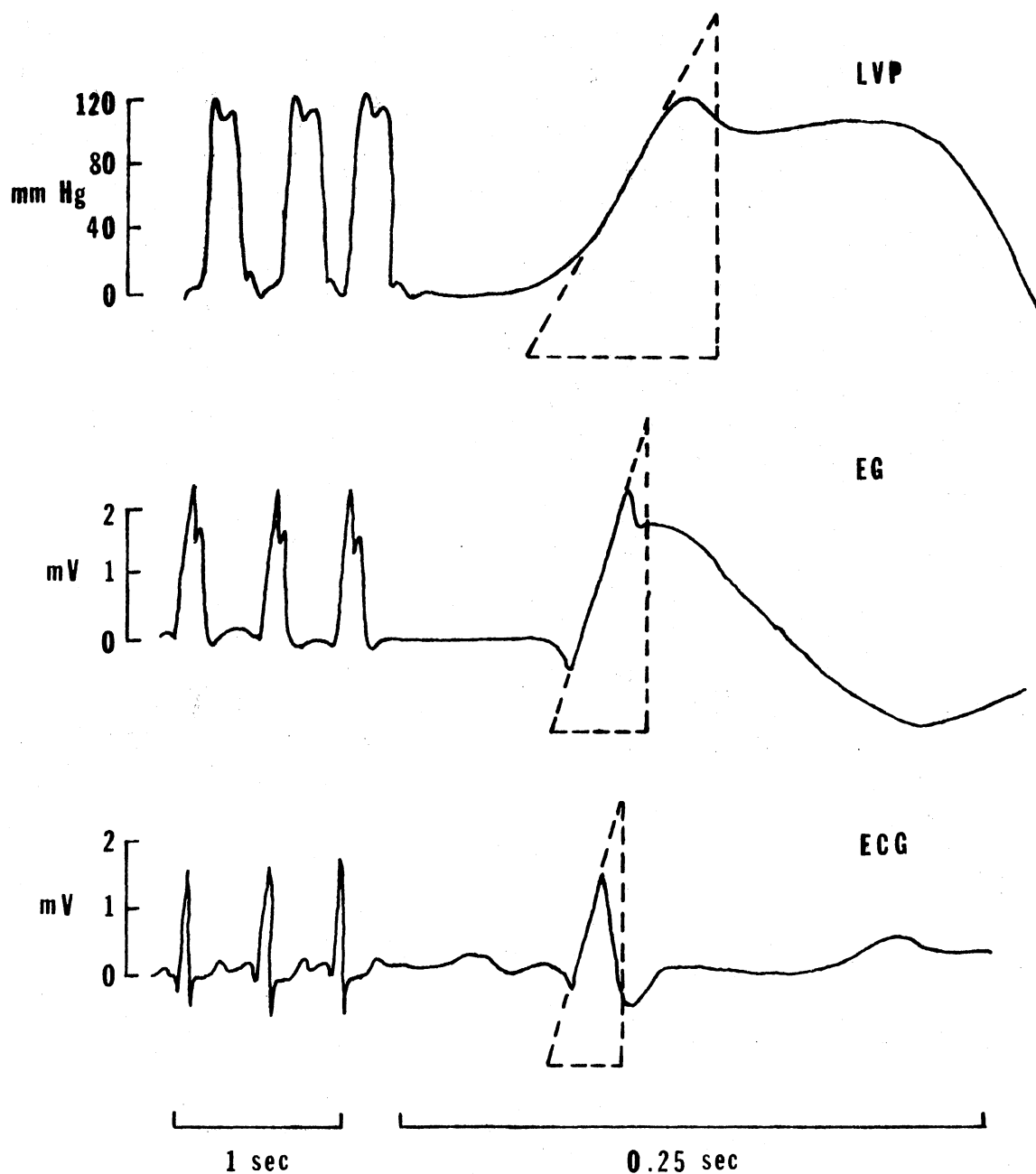
Figure 2. Method of Triangulation Used to Determine Rate of Rise of
Left Ventricular Pressure (LVP), and Rate of Voltage
Change in the R-spike Upstroke of the Electrogram (EG)
and Electrocardiogram (ECG).

drawn tangent to the slope and extended through it, thus assuming the exact slope of the record. The slope was then measured as the rise over the time elapsed during the rise. Since each centimeter of stylus excursion represented 40 mm Hg pressure in the left ventricular pressure recording, the measured pressure rise will be converted to its appropriate units by multiplying the rise (cm) times 40 mm Hg pressure. Each centimeter represented one millivolt in the ECG and electrogram recording and was converted to voltage change by multiplying the excursion by one millivolt. The resulting fraction of pressure or voltage over seconds was then divided out to produce a value expressed in mm Hg per second or mV per second. Millivolt values were expressed to the nearest tenth, and pressure values expressed to the nearest whole number.

Rapid paper speeds were necessary to spread out the wave forms so their slopes could be accurately measured. To compensate for the slow Narco recorder, the paper was pulled by hand. An effort was made to pull the paper at a constant rate, but the paper speed still varied between 30-70 centimeters per second. The variation in the paper speed induced by this method required that each cardiac cycle be timed by dividing its duration in centimeters by the time elapsed during the cycle. Although the paper speed varied considerably from second to second, it did not change greatly during the fraction of a second separating the electrical and mechanical events of any cardiac cycle. The assumption was thus made that the paper speed was constant during the time required for an upstroke of the stylus to be recorded in each channel. As long as the corresponding pressure and voltage curves were divided by the same number, their relationship to each would not be affected even though their absolute values may be somewhat in error.

The records were analyzed such that data were collected from 12 cardiac cycles from every point in the acute study. Approximately 26 cycles were measured in the chronic study each post-ligation day. These numbers were chosen to provide adequate sample sizes, and the data were then ready for statistical analysis.

Statistical Analysis of Data

The degree of correlation between dV/dt and dP/dt in acute and chronic studies was determined by linear regression analysis. Each dV/dt value was plotted with its corresponding dP/dt value and a correlation coefficient and t value was obtained for each series of measurements on an Olivetti P652 calculator. The t values were observed for significance in a one-tailed test at the 0.05 level. The significant values were then expressed as probability ranges.

In the acute study, dV/dt in the limb lead ECG was then correlated with dV/dt in the electrograms taken from the left ventricular surface points. The calculations were done in the manner described above. A correlation coefficient was obtained for each point, and the t values were again tested for significance at the 0.05 level. Points with significant correlations were then shaded on the map to depict the area in which the electrical activity recorded on the ventricular surface was positively correlated with the ascending limb of the R-spike in the limb lead ECG.

In the chronic study, the values of dV/dt and dP/dt were averaged for each day. Standard deviations and standard errors were calculated for each mean. Days in which all beats were ectopic in origin were

excluded from the dV/dt measurement, but dP/dt was measured on those days and recorded. Because of the considerable variation in pre-ligation dP/dt means from animal to animal, a transformation table was constructed to normalize the data and allow comparison between animals. The pre-ligation dP/dt mean was considered to be the control value, and any changes occurring during the post-ligation period were expressed as a percent of the control value. In the transformation table, the control value was expressed as unity with post-ligation values represented by decimal fractions. The recovery patterns for the animals in the chronic study could then be compared on a percent change basis.

CHAPTER IV

RESULTS

Two protocols have been described which were designed to investi-
gate the relationship between the rate of voltage change (dV/dt) in the
R-spike of the limb lead electrocardiogram (ECG) and/or the epicardial
electrogram (EG), and the maximal rate of pressure change (dP/dt) in
the left ventricle. The effects of various interventions on this rela-
tionship were also studied. The results of each experiment will be
presented individually.

Results of Acute Study

The purpose of the acute study was to determine that area of the
myocardium whose surface electrical activity as recorded in the EG was
reflected in the ascending limb of the R-spike of the limb lead ECG.
A linear regression analysis was performed relating dV/dt in the
R-spike of the ECG and epicardial electrograms, and a correlation co-
efficient (r value) was obtained. Those points in which the r values
were significant at the 0.05 level were then shaded on the map. A 10
millimeter radius was allowed around each point, and the area within
that circumference was considered to be homogeneous in its electrical
activity. This procedure was carried out under control conditions and
after the acute ligation of the left anterior descending (LAD) coronary

artery as described in the methods section. The results for each animal will be presented in tabular form and with figures.

Animal #370

An area of significant correlation between dV/dt in the ECG and the epicardial electrograms was shown to exist on the anterior wall of the left ventricle in the control condition (Figure 3). The area followed the interventricular septum in this animal, but was displaced slightly away from it near the base of the heart. The correlation tended to decrease as the electrograms were recorded laterally from the septum and approached the apex of the heart. The correlation coefficients and corresponding t values for each left ventricular point appear in Table I.

The correlations for many of the points were lost after the ligation (Figure 4). No points in the ischemic zone had significant correlations. Two points (A and C) did have significant correlations (post-ligation), but these areas were perfused by an arterial branch which was proximal to the occlusion, indicated by the double line in the figure.

Correlation coefficients were also calculated between dV/dt in the ECG and dP/dt in the left ventricle prior to ligation. The values appear in Table II.

Animal #360

The area of significant correlation was found to lie directly along the septum on the anterior wall (Figure 5). The correlation was

Figure 3. Areas of Significant Correlation Between dV/dt of the
R-spike Upstroke of the ECG and EG Prior to LAD
Ligation Are Shown by Stippling in Dog #370, 18.8 kg.

Figure 4. Areas of Significant Correlation Between dV/dt of
the R-spike Upstroke of the ECG and EG After LAD
Ligation Are Shown by Stippling in Dog #370, 18.8
kg.

Point of ligation indicated by double line.

TABLE I

CORRELATION BETWEEN dV/dt OF R–SPIKE UPSTROKE OF LEFT VENTRICULAR
ELECTROGRAMS AND LIMB LEAD ELECTROCARDIOGRAM FOR DOG #370

		Pre–Ligation			Post–Ligation	
Point	n	r Value	Probability	n	r Value	Probability
A	7	0.0767	ns	11	0.6535*	0.01 < p < 0.025
B	10	0.8701*	0.0005 < p < 0.005	11	0.2229	ns
C	10	0.8830*	0.0001 < p < 0.0005	11	0.6658*	0.01 < p < 0.025
D	8	0.6922*	0.025 < p < 0.05	11	0.3764	ns
E	7	0.6677*	0.025 < p < 0.05	11	0.3986	ns
F	9	0.7209*	0.01 < p < 0.025	11	0.2806	ns
G	10	0.7071*	0.01 < p < 0.025	11	0.2024	ns
H	9	0.6832*	0.01 < p < 0.025	11	0.4765	ns
I	8	0.8495*	0.005 < p < 0.01	10	0.4782	ns
J	––	––	––	––	––	––
K	8	0.3195	ns	11	0.4350	ns
L	10	0.8149*	0.0005 < p < 0.005	11	0.0658	ns

Points with asterisk were shaded on the appropriate pre–ligation or post–ligation map. Symbol n equals number of tracings analyzed for each respective point.

TABLE II

CORRELATION BETWEEN dV/dt OF R-SPIKE UPSTROKE OF
ELECTROCARDIOGRAM AND LEFT VENTRICULAR dP/dt
PRIOR TO AND AFTER LIGATION, #370

	Pre-Ligation		Post-Ligation	
	dV/dt	dP/dt	dV/dt	dP/dt
n	30	30	30	30
mean ± S.E	127.6 ± 3.7	4253 ± 191	99.9 ± 3.0	3847 ± 176
r	0.6495		0.5110	
	4.3556*		3.1461*	

Asterisk indicates significance at 0.05 level or better.

lost at points displaced laterally from the septum. An isolated point with significant correlation was observed along the lateral margin of the left ventricle. After ligation, the correlation was lost at points distal to the occlusion with the exception of two points which did not have significant correlations in the control condition (Figure 6). The correlation coefficients and t values for this animal are presented in Table III. The correlation between dV/dt and dP/dt in this animal was calculated, and the result is presented in Table IV.

Animal #342

Prior to ligation, an area of correlation was observed along the septum and extended antero-laterally from it in this animal (Figure 7). These points were relatively high on the anterior wall, and the correlation was lost after moving toward the apex. All points retained their correlation after the ligation. The continued significant correlation can most probably be explained by the fact that the ligation was made distal to the arterial branch perfusing these points (Figure 8). Two points (E and H) did not lose their correlation and yet were in the presumed ischemic zone. Table V presents the correlation coefficients and t values for this animal. The correlation between dV/dt and dP/dt in this animal is given in Table VI.

Animal #321

The area of correlation was adjacent to the septum and covered a large portion of the anterior wall (Figure 9). The correlation did not tend to decrease as records were taken from points lying lateral to the septum as in other dogs. A high degree of correlation was also
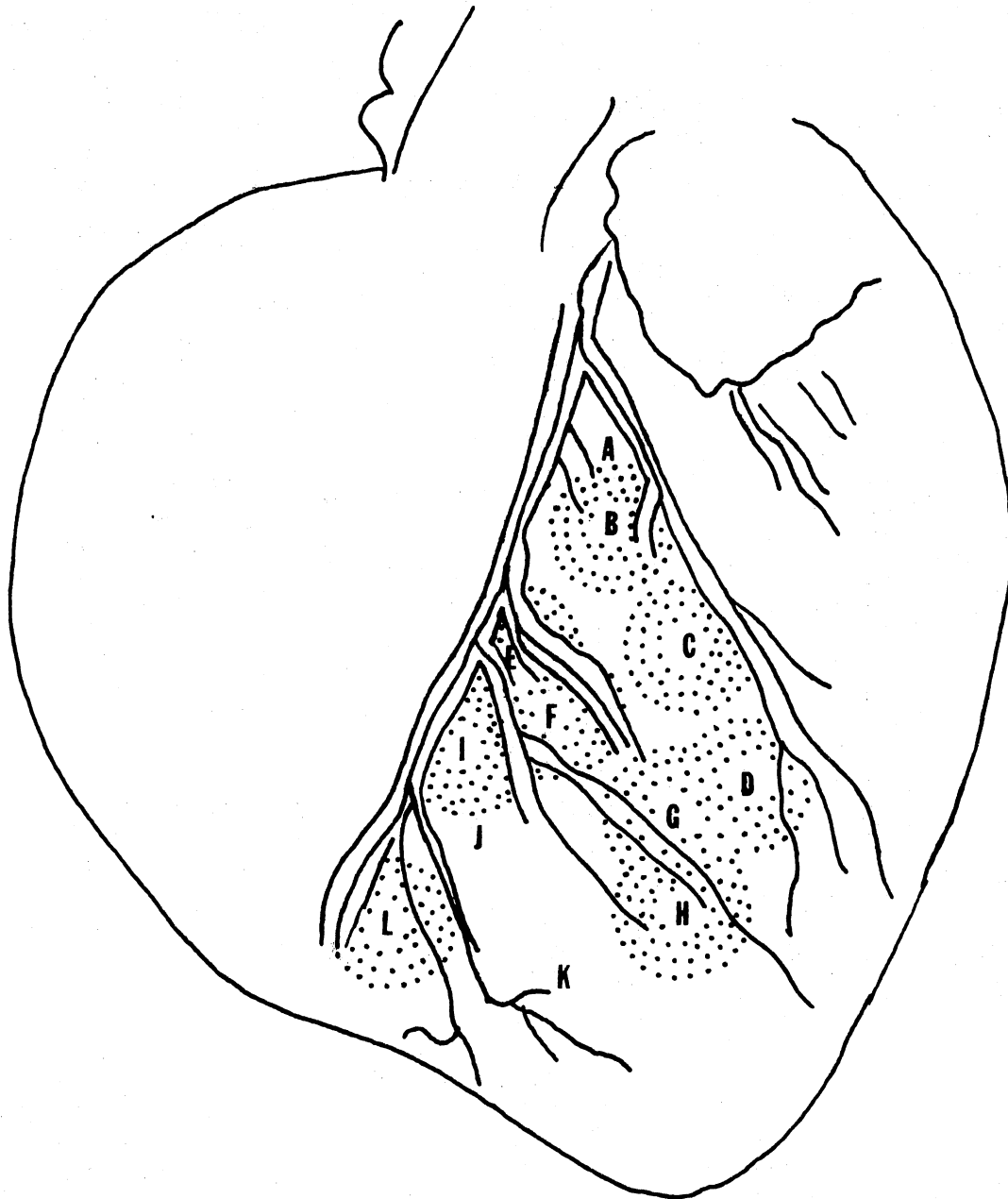
Figure 5. Areas of Significant Correlation Between dV/dt of the R-spike Upstroke of the ECG and EG Prior to LAD Ligation Are Shown by Stippling in Dog #360, 12.1 kg.
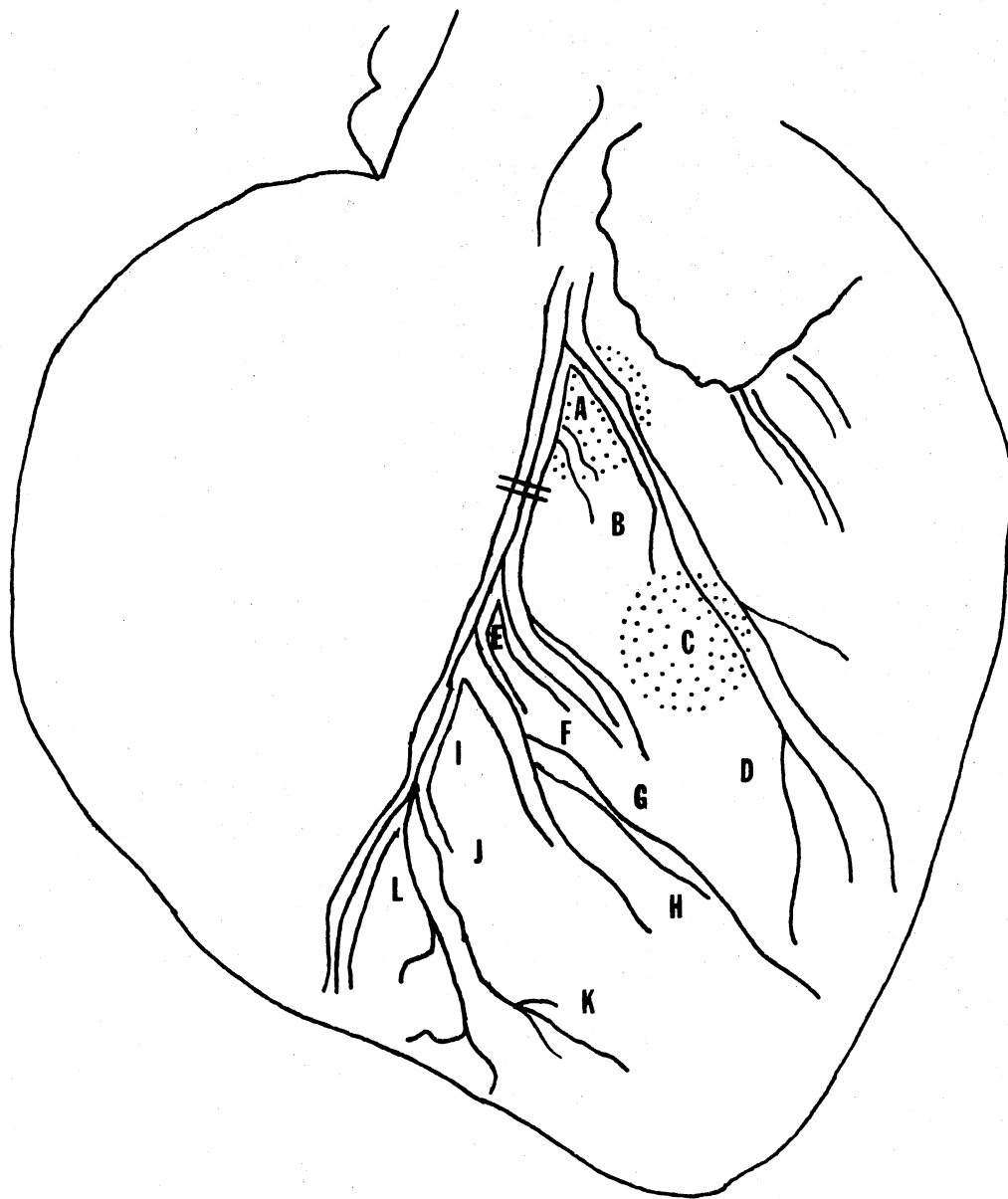
Figure 6. Areas of Significant Correlation Between dV/dt of the
R-spike Upstroke of the ECG and EG After LAD Liga-
tion Are Shown by Stippling in Dog #360, 12.1 kg.

Point of ligation indicated by double line.

TABLE III

CORRELATION BETWEEN dV/dt OF R-SPIKE UPSTROKE OF LEFT VENTRICULAR
ELECTROGRAMS AND LIMB LEAD ELECTROCARDIOGRAM FOR DOG #360

	Pre-Ligation			Post-Ligation		
Point	n	r Value	Probability	n	r Value	Probability
A	10	0.9431*	0.0001 < p < 0.0005	7	0.7632*	0.01 < p < 0.025
B	10	0.2946	ns	6	0.8756*	0.005 < p < 0.01
C	10	0.2492	ns	10	0.4784	ns
D	11	0.5138	ns	8	0.2361	ns
E	11	0.6769*	0.01 < p < 0.025	10	0.3181	ns
F	11	0.7968*	0.0005 < p < 0.005	9	0.5359	ns
G	11	0.0272	ns	10	0.6429*	0.025 < p < 0.05
H	7	0.9024*	0.0005 < p < 0.005	8	0.2765	ns
I	11	0.9210*	0.0001 < p < 0.0005	7	0.6393	ns
J	9	0.8600*	0.0005 < p < 0.005	7	0.4680	ns
K	10	0.2650	ns	7	0.8518*	0.005 < p < 0.01

Points with asterisk were shaded on the appropriate pre-ligation or post-ligation map. Symbol n equals number of tracings analyzed for each respective point.

TABLE IV

CORRELATION BETWEEN dV/dt OF R-SPIKE UPSTROKE OF
ELECTROCARDIOGRAM AND LEFT VENTRICULAR dP/dt
PRIOR TO AND AFTER LIGATION, #360

	Pre-Ligation		Post-Ligation	
	dV/dt	dP/dt	dV/dt	dP/dt
n	30	30	30	30
mean ± S.E	187.6 ± 5.0	4334 ± 182	210.9 ± 3.7	4469 ± 268
r		0.0267		0.4816
t		0.1415		2.9077*

Asterisk indicates significance at 0.05 level or better.
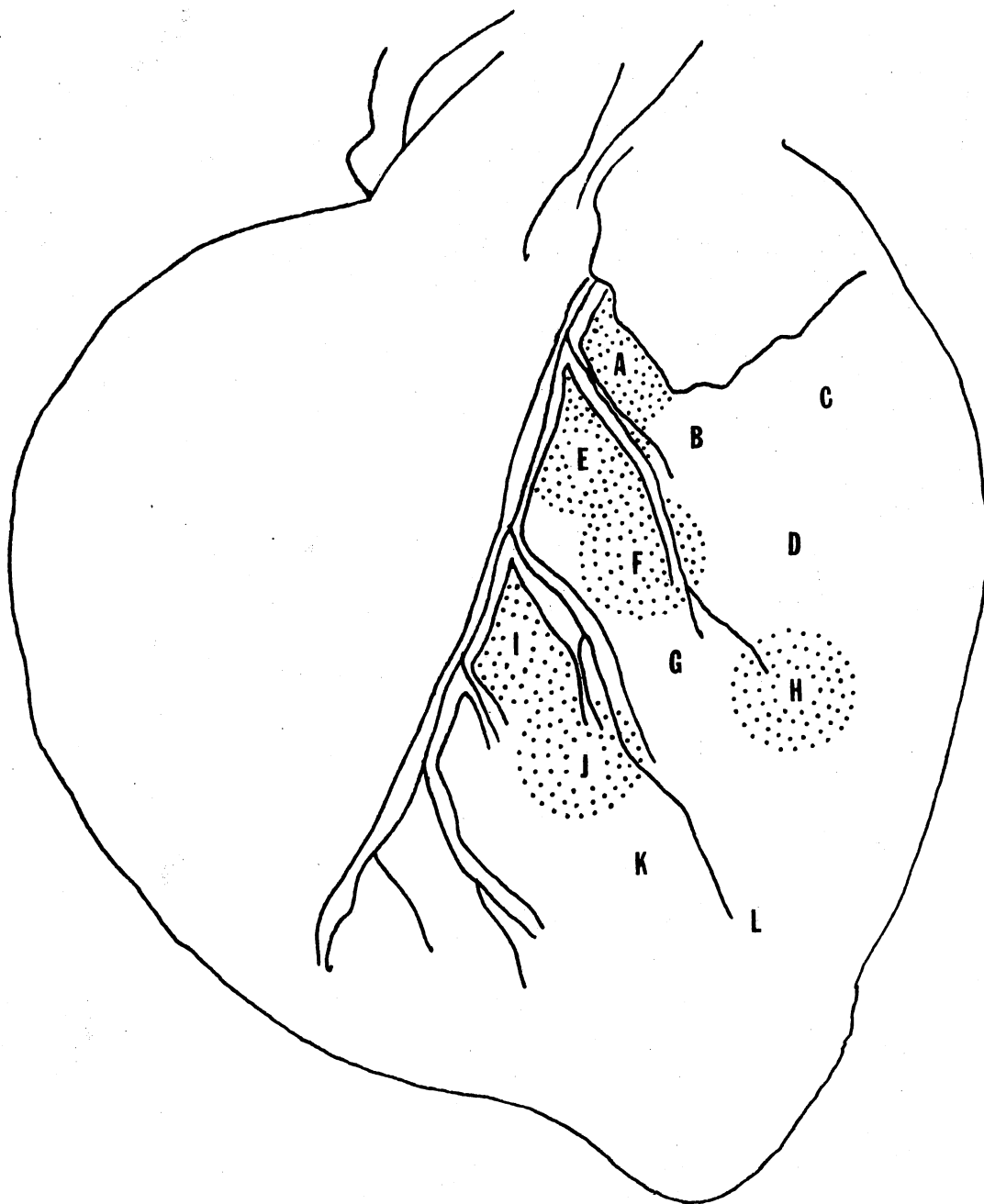
Figure 7. Areas of Significant Correlation Between dV/dt of the
R-spike Upstroke of the ECG and EG Prior to LAD Liga-
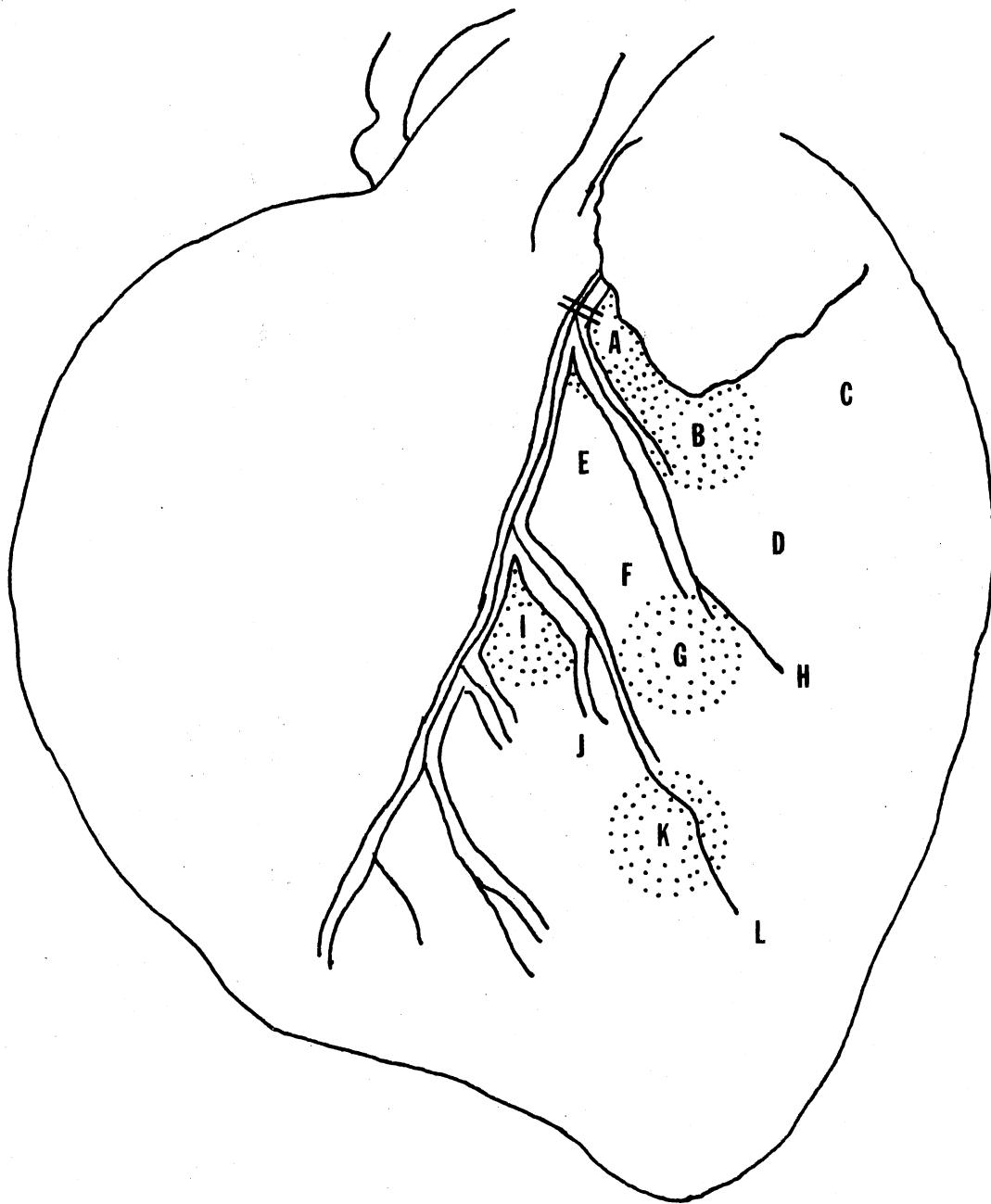tion Are Shown by Stippling in Dog #342, 18.2 kg.

Figure 8. Areas of Significant Correlation Between dV/dt of
the R-spike Upstroke of the ECG and EG After LAD
Ligation Are Shown by Stippling in Dog #342,
18.2 kg.

Point of ligation indicated by double line.

TABLE V

CORRELATION BETWEEN dV/dt OF R-SPIKE UPSTROKE OF LEFT VENTRICULAR
ELECTROGRAMS AND LIMB LEAD ELECTROCARDIOGRAM FOR DOG #342

		Pre-Ligation			Post-Ligation	
Point	n	r Value	Probability	n	r Value	Probability
A	11	0.8288*	0.0005 < p < 0.005	12	0.6635*	0.005 < p < 0.01
B	11	0.7844*	0.0005 < p < 0.005	11	0.7471*	0.0005 < p < 0.005
C	11	0.9255*	0.0001 < p < 0.0005	11	0.9171*	0.0001 < p < 0.0005
D	11	0.6114*	0.01 < p < 0.025	10	0.6818*	0.01 < p < 0.025
E	11	0.7339*	0.005 < p < 0.01	11	0.7777*	0.01 < p < 0.025
F	11	0.5409*	0.025 < p < 0.05	9	0.7227*	0.01 < p < 0.025
G	11	0.4695	ns	9	0.2867	ns
H	10	0.7037*	0.01 < p < 0.025	8	0.8897*	0.0005 < p < 0.005
I	11	0.3821	ns	10	0.4546	ns
J	11	0.4540	ns	9	0.4402	ns
K	11	0.4113	ns	11	0.3194	ns
L	11	0.3871	ns	9	0.4416	ns

Points with asterisk were shaded on the appropriate pre-ligation or
post-ligation map. Symbol n equals number of tracings analyzed for each
respective point.

TABLE VI

CORRELATION BETWEEN dV/dt OF R–SPIKE UPSTROKE OF
ELECTROCARDIOGRAM AND LEFT VENTRICULAR dP/dt
PRIOR TO AND AFTER LIGATION, #342

	Pre-Ligation		Post-Ligation	
	dV/dt	dP/dt	dV/dt	dP/dt
n	30	30	30	30
mean ± S.E	90.3 ± 3.1	1973 ± 62	112.5 ± 2.6	1281 ± 42
r	0.6469		0.2935	
t	4.4887*		1.6248	

Asterisk indicates significance at 0.05 level or better.

maintained at points close to the apex. The correlation was lost at most points after arterial ligation (Figure 10). However, points along the lateral border of the anterior wall did not lose their correlation, but the r values did decrease, as demonstrated in Table VII. As can be seen in Figure 10, arterial branches extended around from the posterior side and reduced the degree of ischemia along the lateral margin of the anterior wall. The correlation between dV/dt and dP/dt was significant in this animal also, and the r value appears in Table VIII.

Animal #377

The pre-ligation map of this animal showed a scattered area of high correlation (Figure 11). Points close to the septum showed greater correlation than points lying along the lateral edge of the anterior wall. The area adjacent to the distal edge of the left atrial appendage did not exhibit a significant correlation as in most of the other animals. The correlation at these points was lost after the ligation with the exception of one point lying along the septum and approaching the apex (Figure 12). Four other points (B, H, I, and N), which had not previously exhibited high r values, became significant in the post-ligation state, which can be seen in Table IX. As in the other animals, a significant correlation between dV/dt and dP/dt was demonstrated and the r value appears in Table X.

Composite of All Animals

By overlaying the maps drawn for each animal, a composite map (Figure 13) was constructed which identified the area of myocardium in which epicardial electrogram electrical activity was significantly
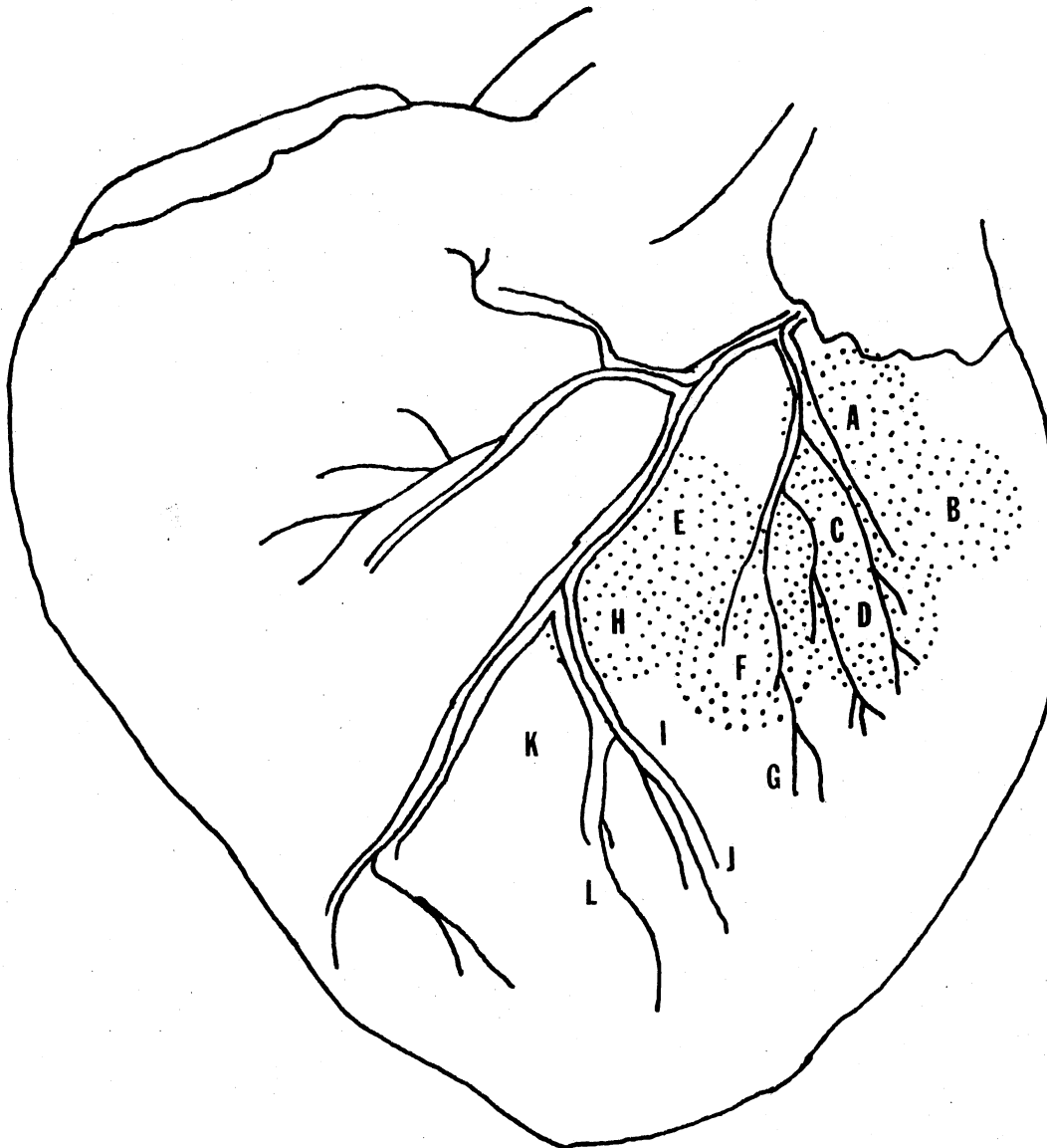
Figure 9. Areas of Significant Correlation Between dV/dt of the
R-spike Upstroke of the ECG and EG Prior to LAD Liga-
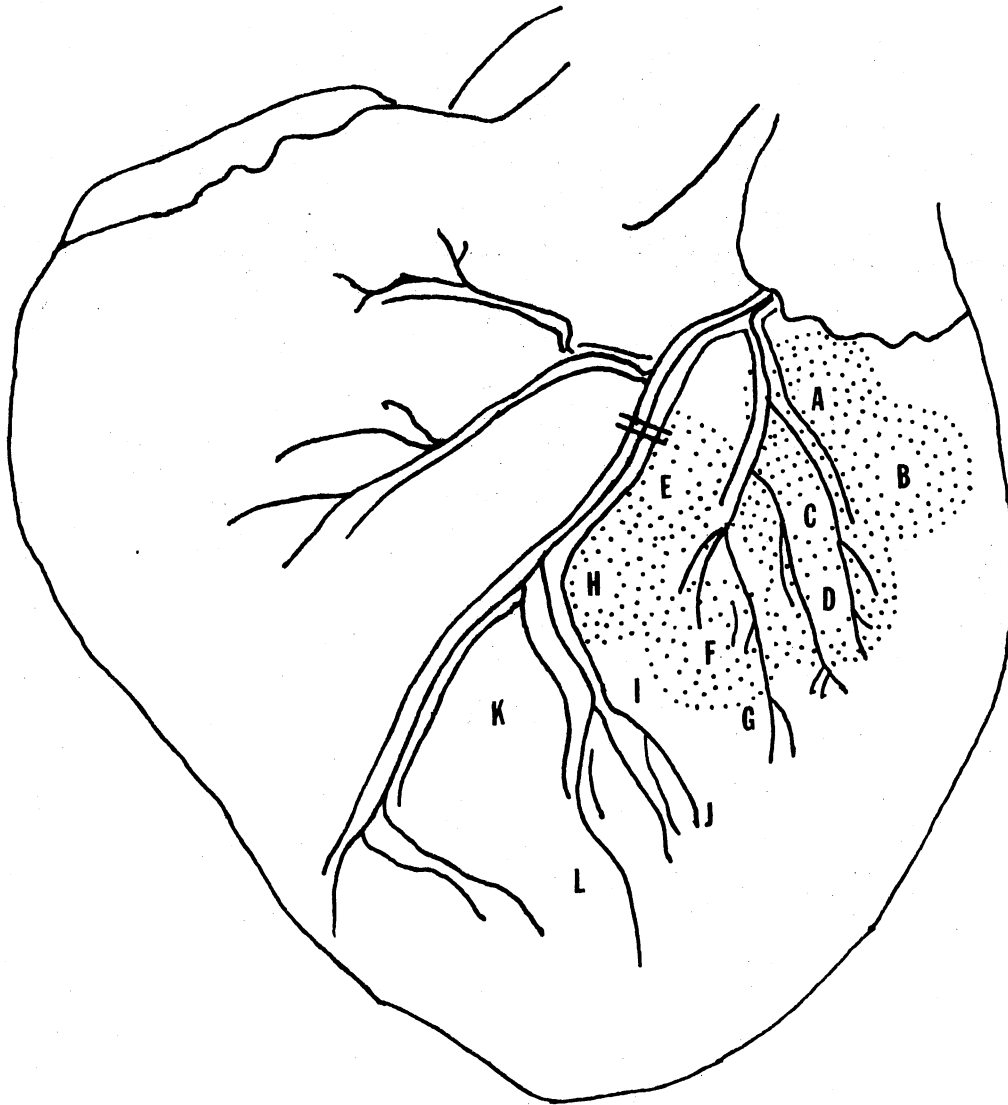tion Are Shown by Stippling in Dog #321, 28.0 kg.

Figure 10. Areas of Significant Correlation Between dV/dt of the
R-spike Upstroke of the ECG and EG After LAD Ligation
Are Shown by Stippling in Dog #321, 28.0 kg.

Point of ligation indicated by double line.

TABLE VII

CORRELATION BETWEEN dV/dt OF R-SPIKE UPSTROKE OF LEFT VENTRICULAR
ELECTROGRAMS AND LIMB LEAD ELECTROCARDIOGRAM FOR DOG #321

		Pre-Ligation			Post-Ligation	
Point	n	r Value	Probability	n	r Value	Probability
A	12	0.7073*	0.005 < p < 0.01	9	0.1013	ns
B	12	0.2301	ns	11	0.7504*	0.0005 < p < 0.05
C	12	0.7632*	0.0005 < p < 0.005	8	0.0223	ns
D	11	0.2417	ns	11	0.6319*	0.01 < p < 0.025
E	11	0.8248*	0.0005 < p < 0.005	9	0.5730	ns
F	11	0.7835*	0.0005 < p < 0.005	12	0.5981*	0.01 < p < 0.025
G	10	0.5839*	0.025 < p < 0.05	11	0.0306	ns
H	10	0.7753*	0.0005 < p < 0.005	11	0.1293	ns
I	10	0.7119*	0.01 < p < 0.025	12	0.6306*	0.01 < p < 0.025
J	9	0.7713*	0.005 < p < 0.01	13	0.0639	ns
K	10	0.5532*	0.025 < p < 0.05	11	0.4182	ns
L	9	0.9120*	0.0001 < p < 0.0005	11	0.1353	ns
M	10	0.7777*	0.0005 < p < 0.005	14	0.5520*	0.01 < p < 0.025

Points with asterisk were shaded on the appropriate pre-ligation or
post-ligation map. Symbol n equals number of tracings analyzed for each
respective point.

TABLE VIII

CORRELATION BETWEEN dV/dt OF R-SPIKE UPSTROKE OF
ELECTROCARDIOGRAM AND LEFT VENTRICULAR dP/dt
PRIOR TO AND AFTER LIGATION, #321

	Pre-Ligation		Post-Ligation	
	dV/dt	dP/dt	dV/dt	dP/dt
n	30	30	30	30
mean ± S.E	121.8 ± 3.0	3565 ± 231	138.6 ± 4.2	1259 ± 42
r	0.3238		0.0889	
t	1.8107*		0.4720	

Asterisk indicates significance at 0.05 level or better.
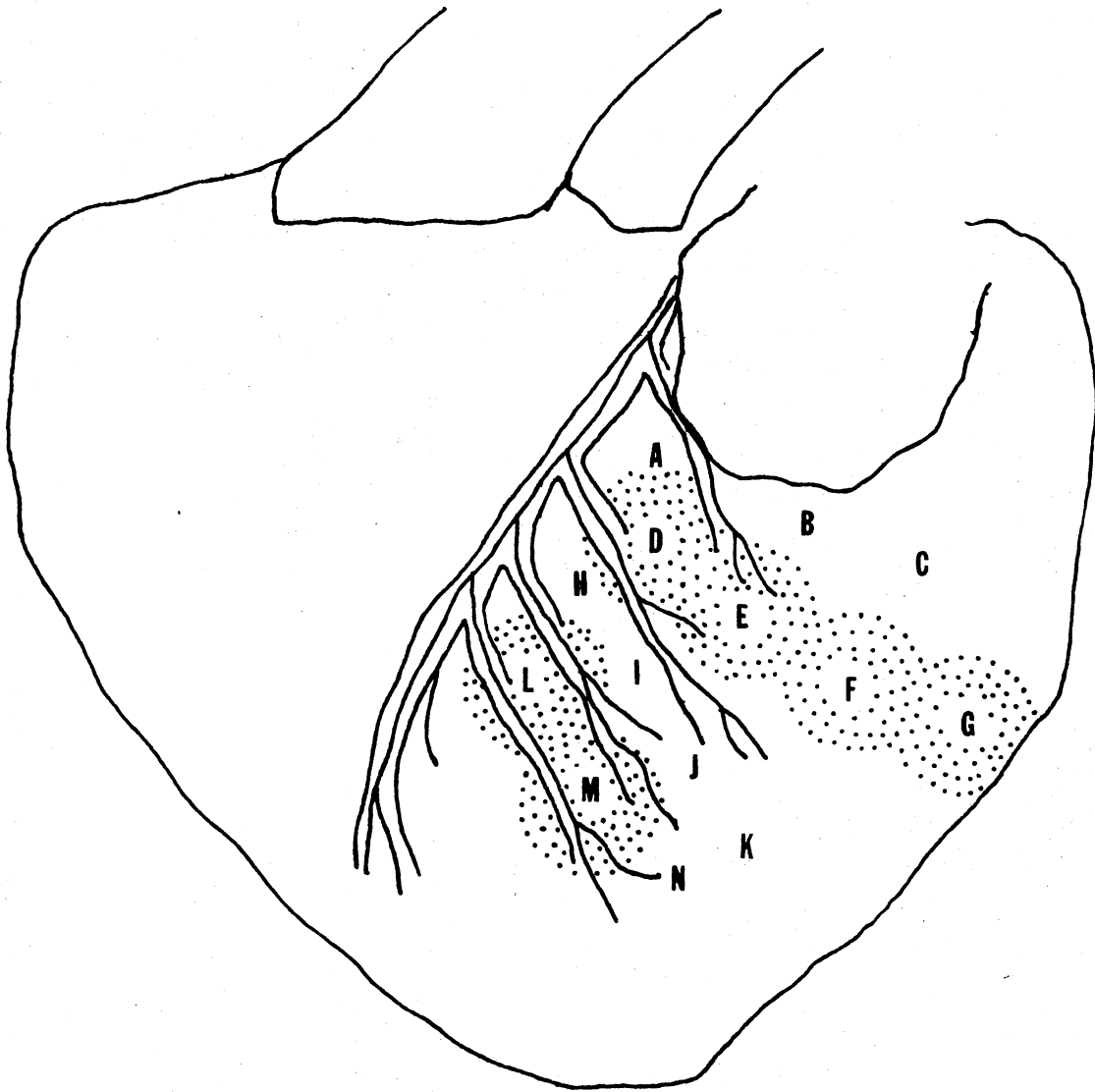
Figure 11. Areas of Significant Correlation Between dV/dt of the
R-spike Upstroke of the ECG and EG Prior to LAD Liga-
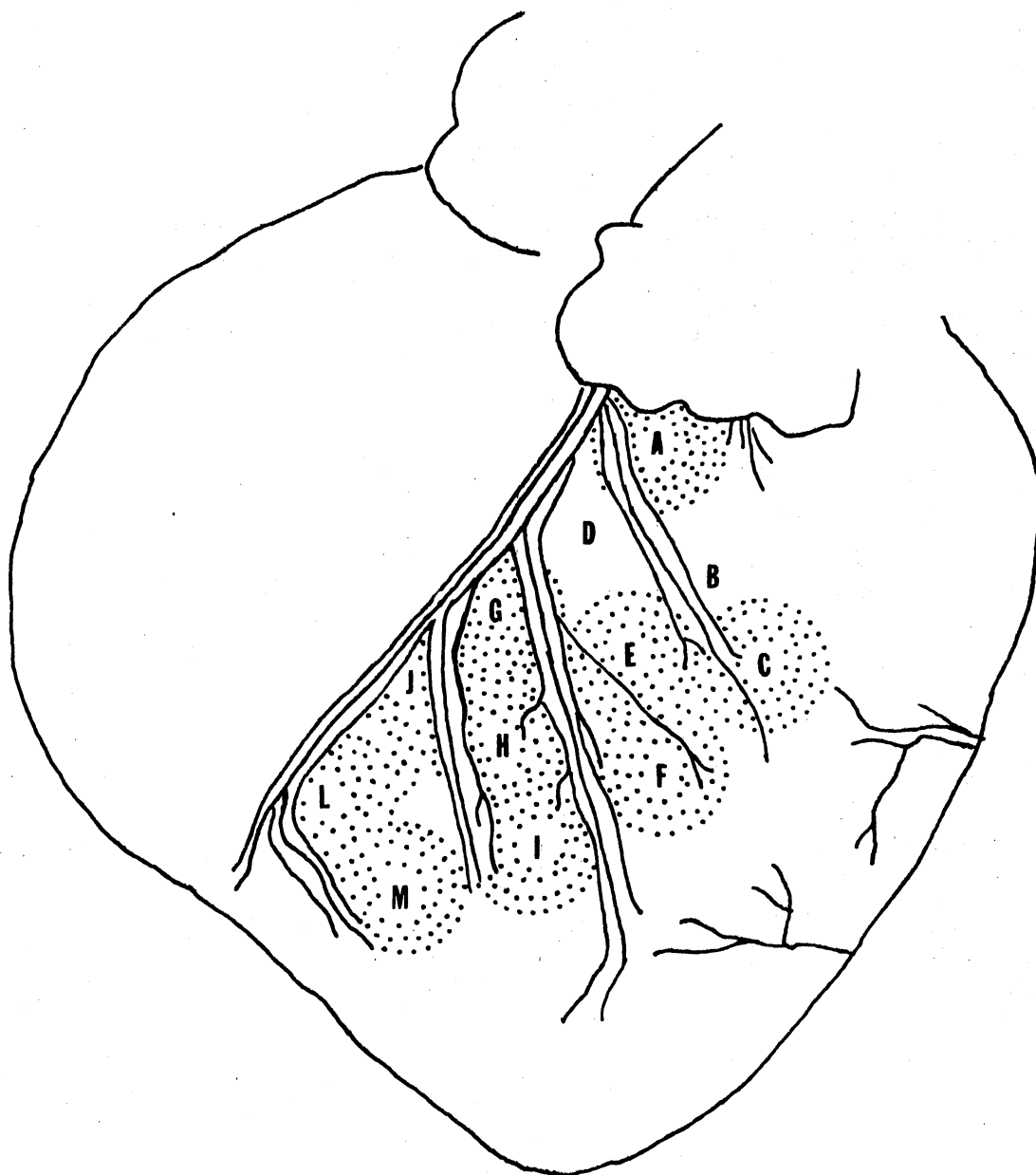tion Are Shown by Stippling in Dog #377, 10.4 kg.
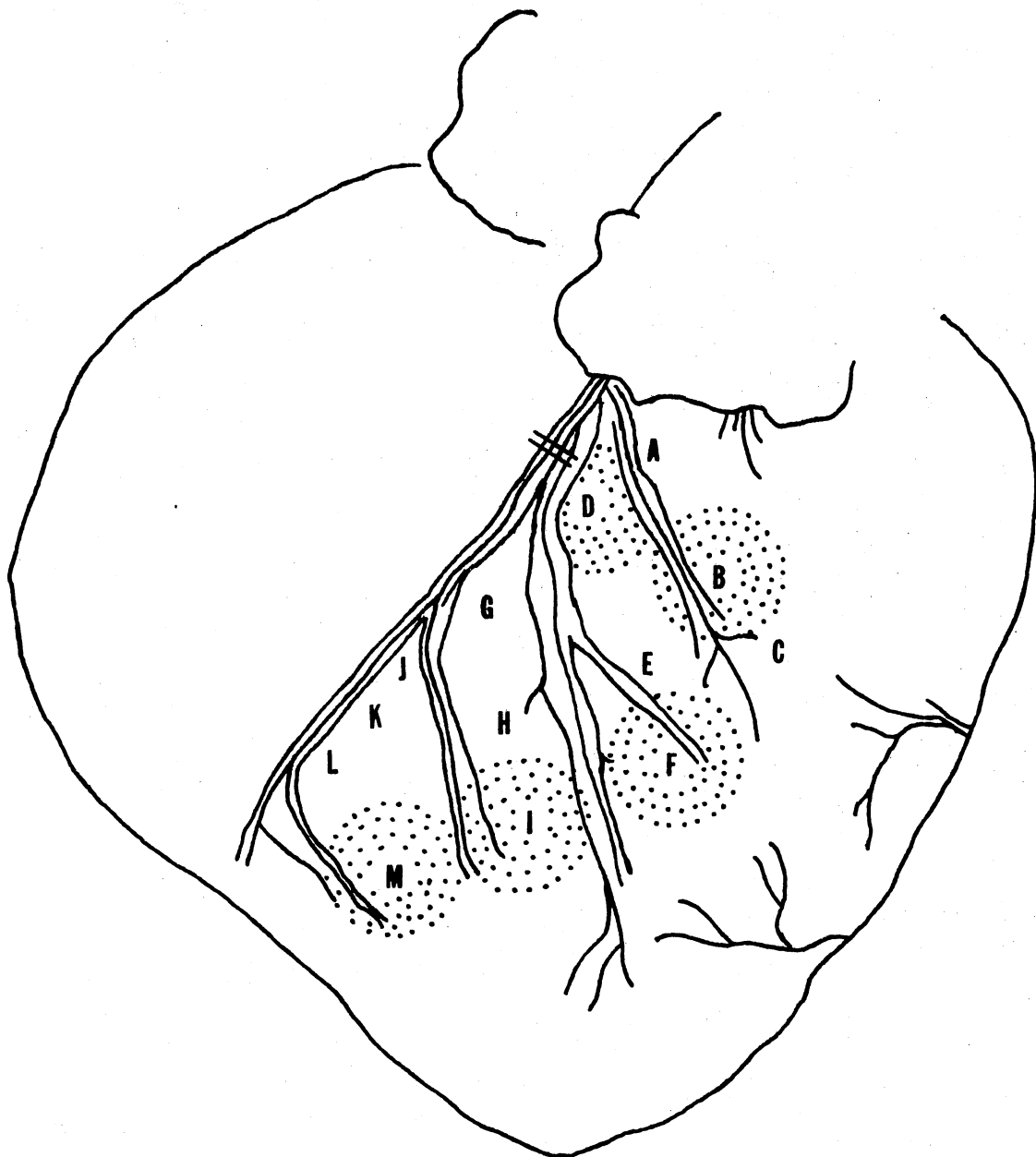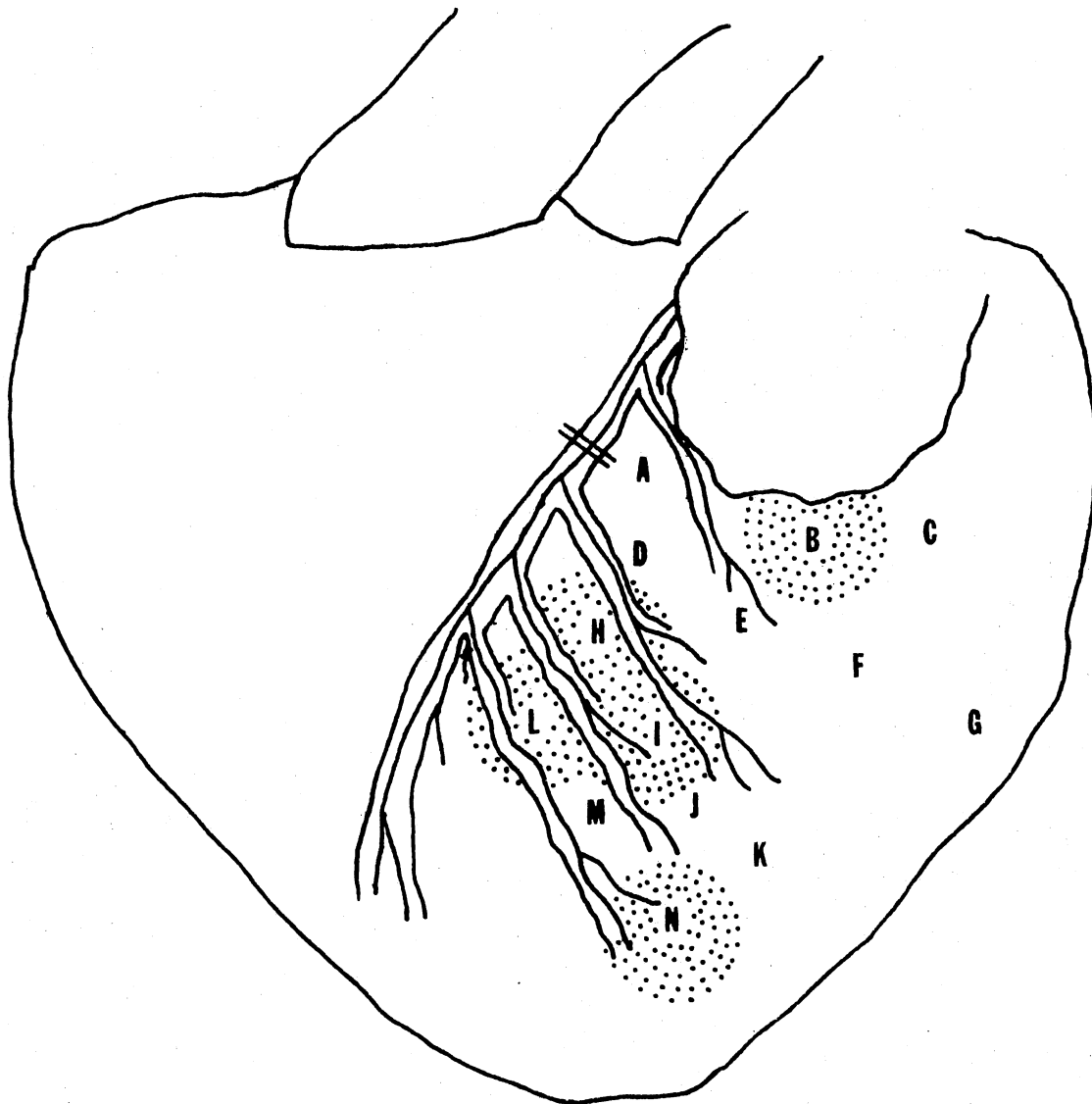
Figure 12. Areas of Significant Correlation Between dV/dt of the
            R-spike Upstroke of the ECG and EG After LAD Ligation
            Are Shown by Stippling in Dog #377, 10.4 kg.

Point of ligation indicated by double line.

TABLE IX

CORRELATION BETWEEN dV/dt OF R–SPIKE UPSTROKE OF LEFT VENTRICULAR
ELECTROGRAMS AND LIMB LEAD ELECTROCARDIOGRAM FOR DOG #377

		Pre-Ligation				Post-Ligation	
Point	n	r Value	Probability	n	r Value	Probability	
A	12	0.4400	ns	12	0.0923	ns	
B	12	0.0302	ns	12	0.6424*	0.005	$< p < 0.01$
C	12	0.3111	ns	12	0.4081	ns	
D	12	0.6816*	$0.005 < p < 0.01$	12	0.1060	ns	
E	12	0.7139*	$0.0005 < p < 0.005$	12	0.4664	ns	
F	12	0.5205*	$0.025 < p < 0.05$	12	0.0376	ns	
G	12	0.6842*	$0.005 < p < 0.01$	12	0.2702	ns	
H	12	0.0428	ns	12	0.5865*	0.01	$< p < 0.025$
I	12	0.3958	ns	12	0.5280*	0.025	$< p < 0.05$
J	12	0.0591	ns	12	0.3401	ns	
K	12	0.3347	ns	12	0.4182	ns	
L	12	0.8174*	$0.0005 < p < 0.005$	12	0.7508*	0.0005	$< p < 0.005$
M	12	0.6142*	$0.01 < p < 0.025$	12	0.2702	ns	
N	12	0.1788	ns	12	0.5500*	0.025	$< p < 0.05$

Points with asterisk were shaded on the appropriate pre-ligation or
post-ligation map. Symbol n equals number of tracings analyzed for each
respective point.

TABLE X

CORRELATION BETWEEN dV/dt OF R-SPIKE UPSTROKE OF
ELECTROCARDIOGRAM AND LEFT VENTRICULAR dP/dt
PRIOR TO AND AFTER LIGATION, #377

	Pre-Ligation		Post-Ligation	
	dV/dt	dP/dt	dV/dt	dP/dt
n	30	30	30	30
mean ± S.E	103.0 ± 4.6	2037 ± 97	96.2 ± 5.0	1854 ± 85
r	0.6596		0.4373	
t	4.6439*		2.5265*	

Asterisk indicates significance at 0.05 level or better.

PRE-LIGATION

Figure 13.   Composite Pre-Ligation Map of All Animals Used in the
Acute Study Showing Areas of Significant Correlation
Between dV/dt of the R-spike Upstroke of the ECG and
EG.

POST—LIGATION
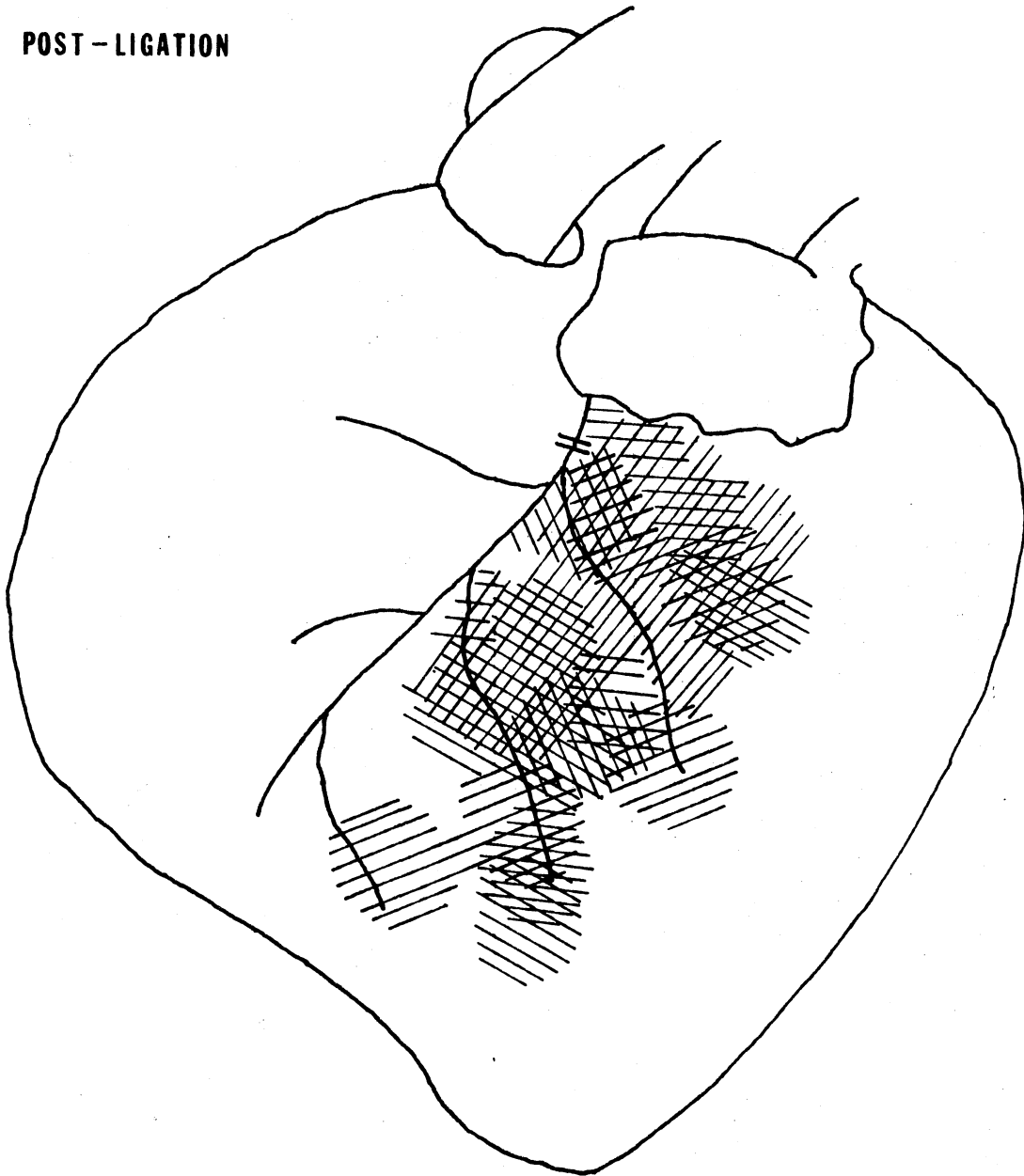
Figure 14. Composite Post-Ligation Map of All Animals Used in the
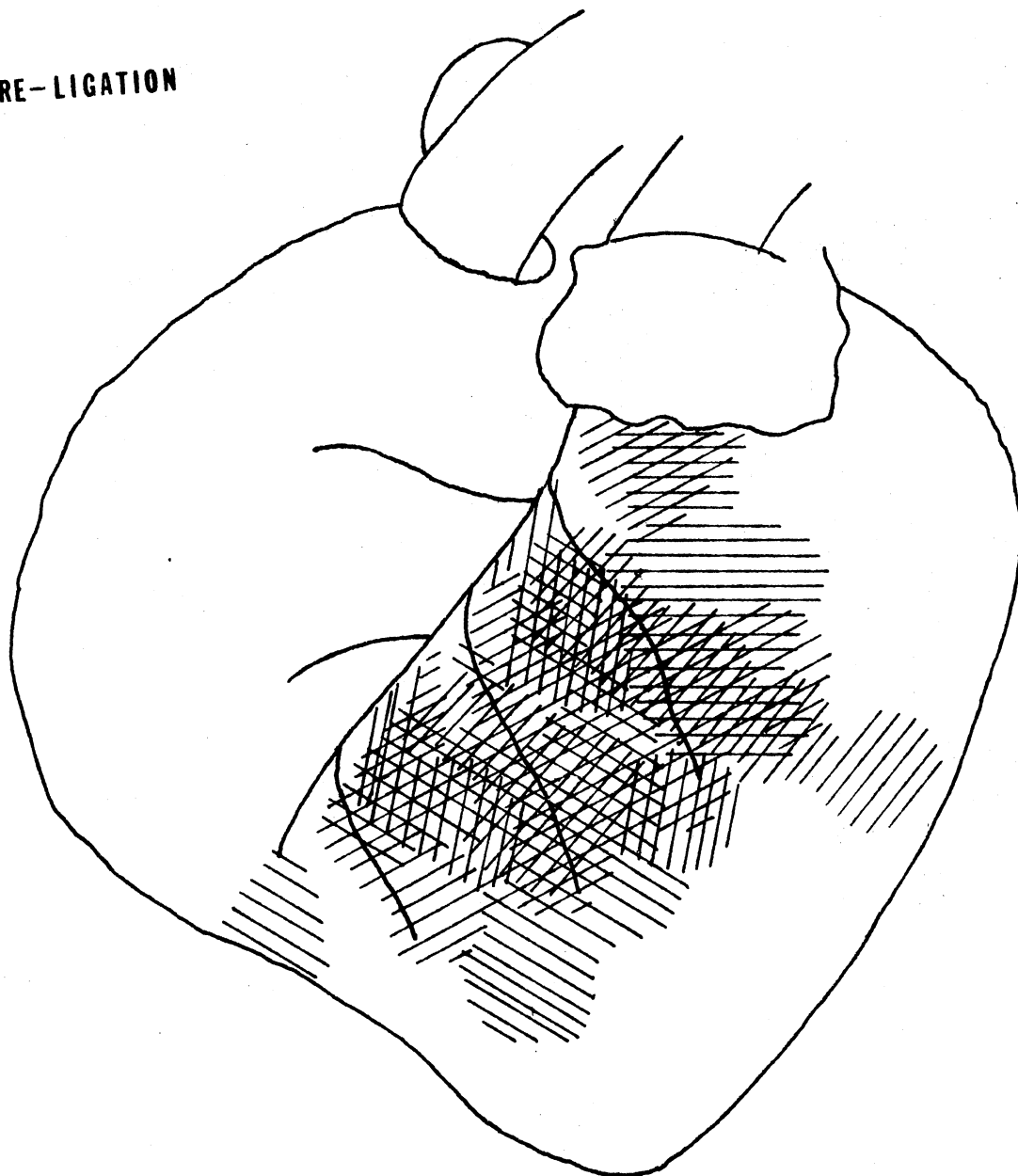Acute Study Showing Areas of Significant Correlation
Between dV/dt of the R-spike Upstroke of the ECG and
EG.

correlated with dV/dt in the ECG. The areas of correlation in different animals were slashed with diagonal lines, thus making the correlative area the most dense where it existed in several animals. This area included much of the anterior wall, extending from the edge of the left atrial appendage toward the apex of the heart. The correlation tended to decrease as the electrode was moved laterally away from the septum and also decreased as the electrode was moved distally down the left anterior descending coronary artery. This large area includes most of the purported ischemic zone produced by a ligation of the left anterior descending coronary artery done in the manner previously described. The composite map drawn from the post-ligation maps appears considerably different from that of the pre-ligation composite (Figure 14). The area of correlation is considerably smaller and scattered. There appears to be a shift in the density (correlated points) from the medial anterior wall to the more basal areas adjacent the area of ligation of the anterior descending artery.

Results of Chronic Study

Acute studies demonstrated that a significant correlation between dV/dt in the ECG and dP/dt in the left ventricle existed, and that dV/dt of the ascending limb of the R-spike was sensitive to changes in the electrical activity in selected portions of the anterior wall of the left ventricle. The design of the chronic study was to observe changes in dV/dt and dP/dt throughout a five-day post-ligation recovery period. Each animal developed an ectopic arrhythmia after the ligation which continued for a variable number of days. It was not possible to measure dV/dt in the ectopic beats, but this measurement was made in normal

beats. Left ventricular dP/dt was measured for both normal and ectopic beats.

Animal #338

The changes in dP/dt and dV/dt throughout the five-day post-ligation period are shown in Figure 15. Percent changes are also shown in the figure. Left ventricular dP/dt was decreased by half on the first day following the ligation. After another decrease on the second day, there followed two days which showed increases in dP/dt. On the fifth day, dP/dt was again depressed with a simultaneous increase in the ectopic frequency (Table XI).

TABLE XI

NORMAL, ECTOPIC, AND TOTAL HEART RATES* THROUGHOUT THE
POST-LIGATION PERIOD FOR DOG #338, 24.1 KILOGRAMS

Day	Normal	Ectopic	Total
Control	132	0	132
1	0	200	200
2	0	200	200
3	99	46	145
4	81	97	178
5	0	233	233

*Rates expressed in beats per minute and averaged over a five-minute period.

A steady decline in dV/dt in the ECG was observed during the post-ligation period. A significant correlation (r = 0.67) existed between dV/dt and dP/dt prior to ligation and is indicated by an asterisk in the dV/dt graph (upper panel) in Figure 15. The correlation was
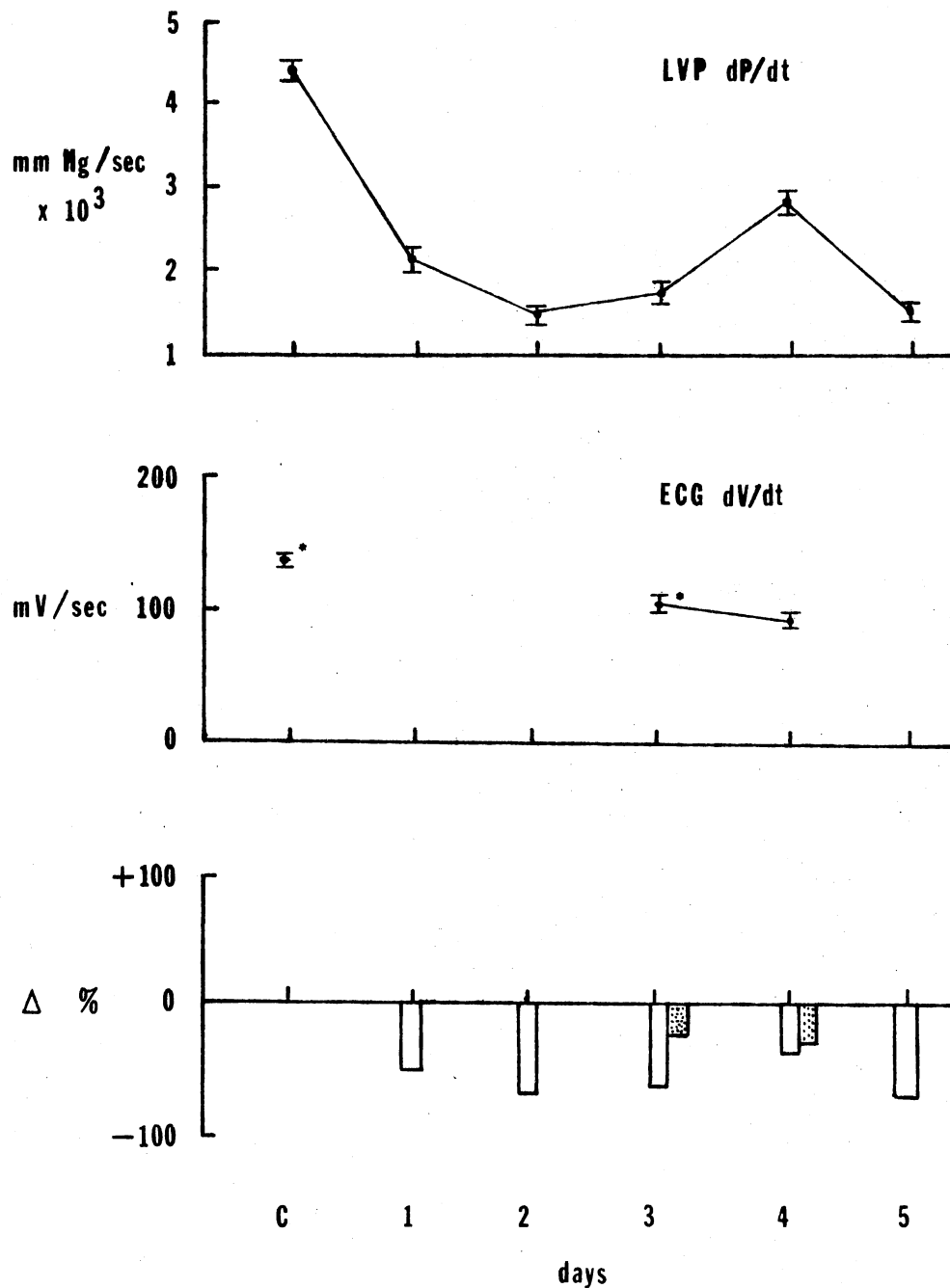
Figure 15. Upper Panel Depicts Changes in Left Ventricular Pressure Generation (dP/dt). Middle Panel Shows Changes in Voltage Generation (dV/dt) of R-spike Upstroke of ECG. Lower Panel Illustrates Percent Change From Control Day (C) for dP/dt (clear bars) and dV/dt (stippled bars). Dog #338, 24.1 kg.

All records for a five-day period after LAD ligation following control records at C. Asterisks in dV/dt graph indicate significant correlation between dV/dt and dP/dt on that day. Days in which dV/dt values are missing were days of complete ectopic rhythm.

maintained on the third day ($r = 0.69$), but was lost on the fourth day ($r = 0.05$). The change in mean dV/dt was in the same direction (middle panel) as the change in mean dP/dt which is presented as the percent change graph (lower panel) in Figure 15.

Animal #367

The results for this animal are presented in Figure 16. A large reduction in mean dP/dt is evident on the third day. Left ventricular pressure recordings were missed on the first and second day due to an occluded catheter. A recovery in dP/dt was observed on the fourth and fifth day with dP/dt remaining at about 50 percent of the control value (upper panel).

Instead of a decrease in mean dV/dt, this animal exhibited an increase, and the correlation between dV/dt and dP/dt remained throughout the post-ligation period. The mean change in dV/dt (middle panel) was opposite in direction to that of dP/dt on some days but directionally the same in others. Table XII presents the change in heart rate.

Animal #351

Mean left ventricular dP/dt was reduced to almost half of its control value on the first post-ligation day. A steady recovery in dP/dt was observed on subsequent recovery days with dP/dt reaching the control level by the fourth day (upper panel). The animal died before the fifth day's recording was taken. (Figure 17).

Prior to ligation, a significant correlation ($r = 0.68$) existed between dV/dt and dP/dt. This correlation was lost during part of the post-ligation period, but returned on the fourth day ($r = 0.71$). An

Figure 16. Changes in Left Ventricular dP/dt and ECG dV/dt (upper
two panels). Percent Change From Control Day (C) for
dP/dt and dV/dt. Dog #367, 12.3 kg.

Representations are as in Figure 15.

Figure 17.   Changes in Left Ventricular dP/dt and ECG dV/dt (upper
             two panels). Percent Change From Control Day (C) for
             dP/dt and dV/dt. Dog #351, 14.5 kg.

Representations are as in Figure 15.

increase was observed in mean dV/dt which again was in the same direction as the mean change in dP/dt (middle panel). Changes in heart rate are presented in Table XIII.

TABLE XII

NORMAL, ECTOPIC, AND TOTAL HEART RATES* THROUGHOUT THE
POST–LIGATION PERIOD FOR DOG #367, 12.3 KILOGRAMS

Day	Normal	Ectopic	Total
Control	92	0	92
1	0	243	243
2	0	202	202
3	164	0	164
4	110	1	111
5	103	4	107

*Rates expressed in beats per minute and averaged over a five-minute period.

TABLE XIII

NORMAL, ECTOPIC, AND TOTAL HEART RATES* THROUGHOUT THE
POST–LIGATION PERIOD FOR DOG #351, 14.5 KILOGRAMS

Day	Normal	Ectopic	Total
Control	131	0	131
1	12	161	173
2	9	118	127
3	84	5	89
4	101	4	105
5	––	––	––

*Rates expressed in beats per minute and averaged over a five-minute period.

Animal #315

Figure 18 depicts the mean changes in dP/dt and dV/dt for this animal. A decrease in dP/dt by more than half of its control value was observed on the first post-ligation day. A period of two days followed in which dP/dt began to increase, and was then followed by another decline for the succeeding two days (upper panel). This decline in dP/dt occurred with the resumption of ectopic activity after a day of entirely normal beats. (Table XIV).

This animal was one of two in which the pre-ligation dV/dt and dP/dt were not correlated (r = 0.05). On the third and fourth post-ligation day, significant correlations did exist (r = 0.76 and 0.36, respectively). A steady decline in mean dV/dt was observed, which followed dP/dt in direction (middle panel).

TABLE XIV

NORMAL, ECTOPIC, AND TOTAL HEART RATES* THROUGHOUT THE
POST-LIGATION PERIOD FOR DOG #315, 20.5 KILOGRAMS

Day	Normal	Ectopic	Total
Control	124	0	124
1	0	194	194
2	0	150	150
3	173	5	178
4	143	0	144
5	0	215	215

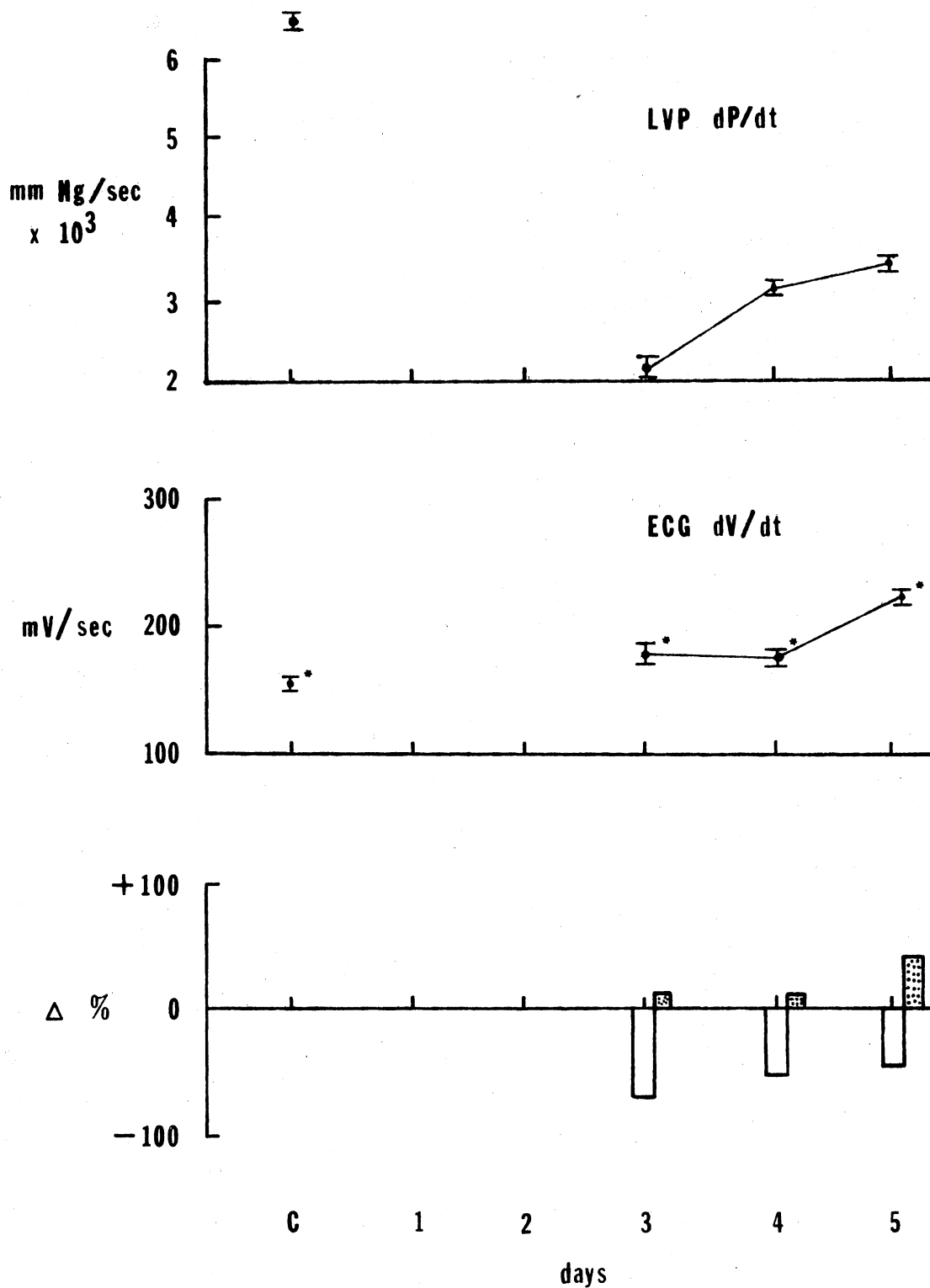*Rates expressed in beats per minute and averaged over a five-minute period.
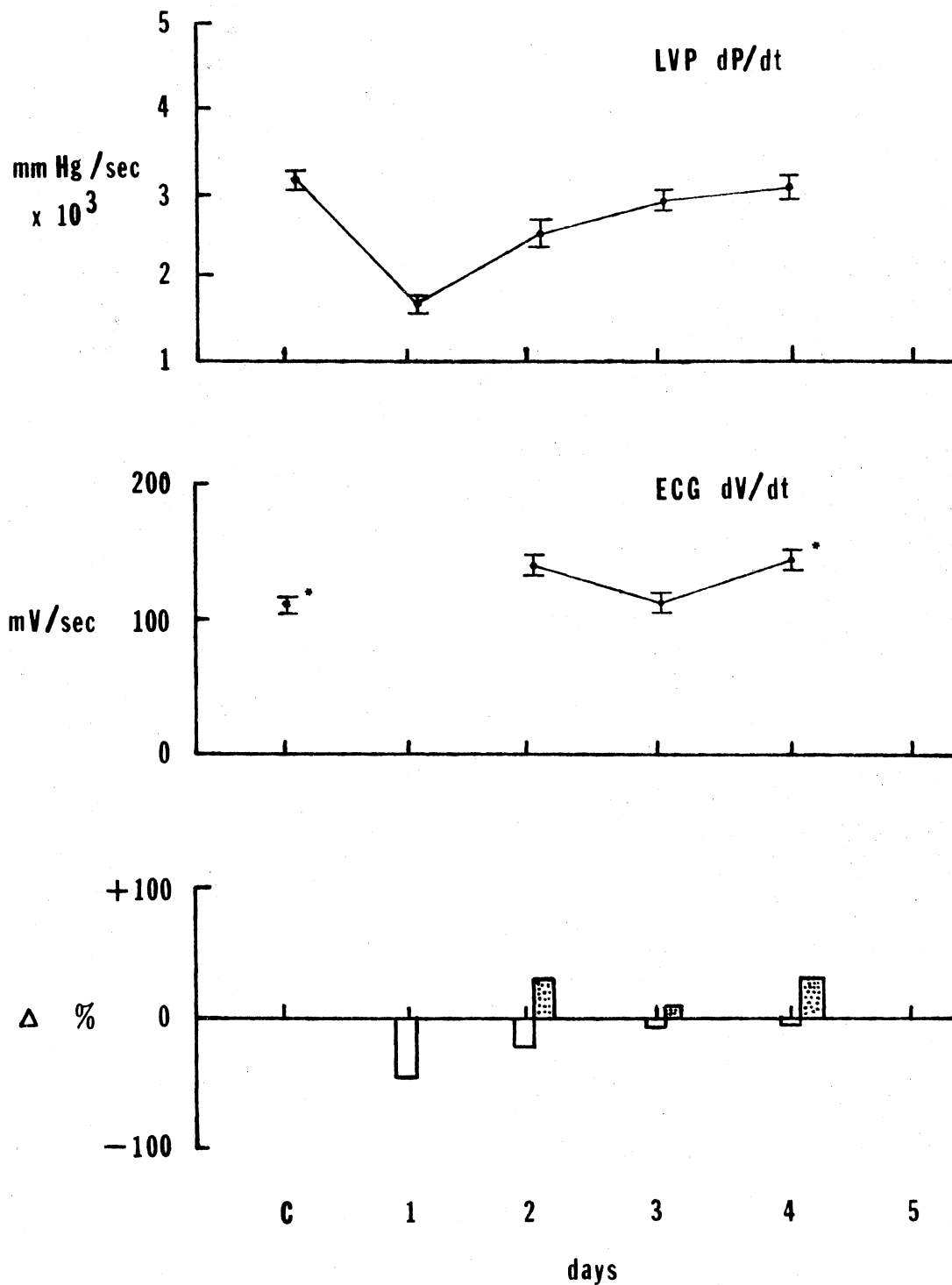
Figure 18.   Changes in Left Ventricular dP/dt and ECG dV/dt (upper
two panels).   Percent Change From Control Day (C)
for dP/dt and dV/dt.   Dog #315, 20.5 kg.

Representations are as in Figure 15.

Animal #380

A variation in the pattern of recovery was observed in this animal, in that a mean increase in dP/dt, rather than a decrease, occurred after the ligation (Figure 19). The increase continued for the first four days, reaching its peak on the fourth day, and then decreased to just slightly more than the control value on the fifth day (upper panel).

At no point during the days of normal rhythm following the ligation did the correlation between dV/dt and dP/dt lose its statistical significance. An initial decrease in mean dV/dt was observed on the third day when normal rhythm resumed, but was followed by an increase, approaching the control value on the fifth day (middle panel).

The increase in mean dP/dt produced a new pattern in the percent change graph. The mean changes in dV/dt and dP/dt, although opposite in direction, were reversed with dP/dt increasing and dV/dt decreasing (lower panel). Table XV presents the effects of ligation on heart rate and rhythm.

TABLE XV

NORMAL, ECTOPIC, AND TOTAL HEART RATES* THROUGHOUT THE
POST-LIGATION PERIOD FOR DOG #380, 29.4 KILOGRAMS

Day	Normal	Ectopic	Total
Control	142	0	142
1	0	191	191
2	0	175	175
3	60	65	125
4	113	0	113
5	120	1	121

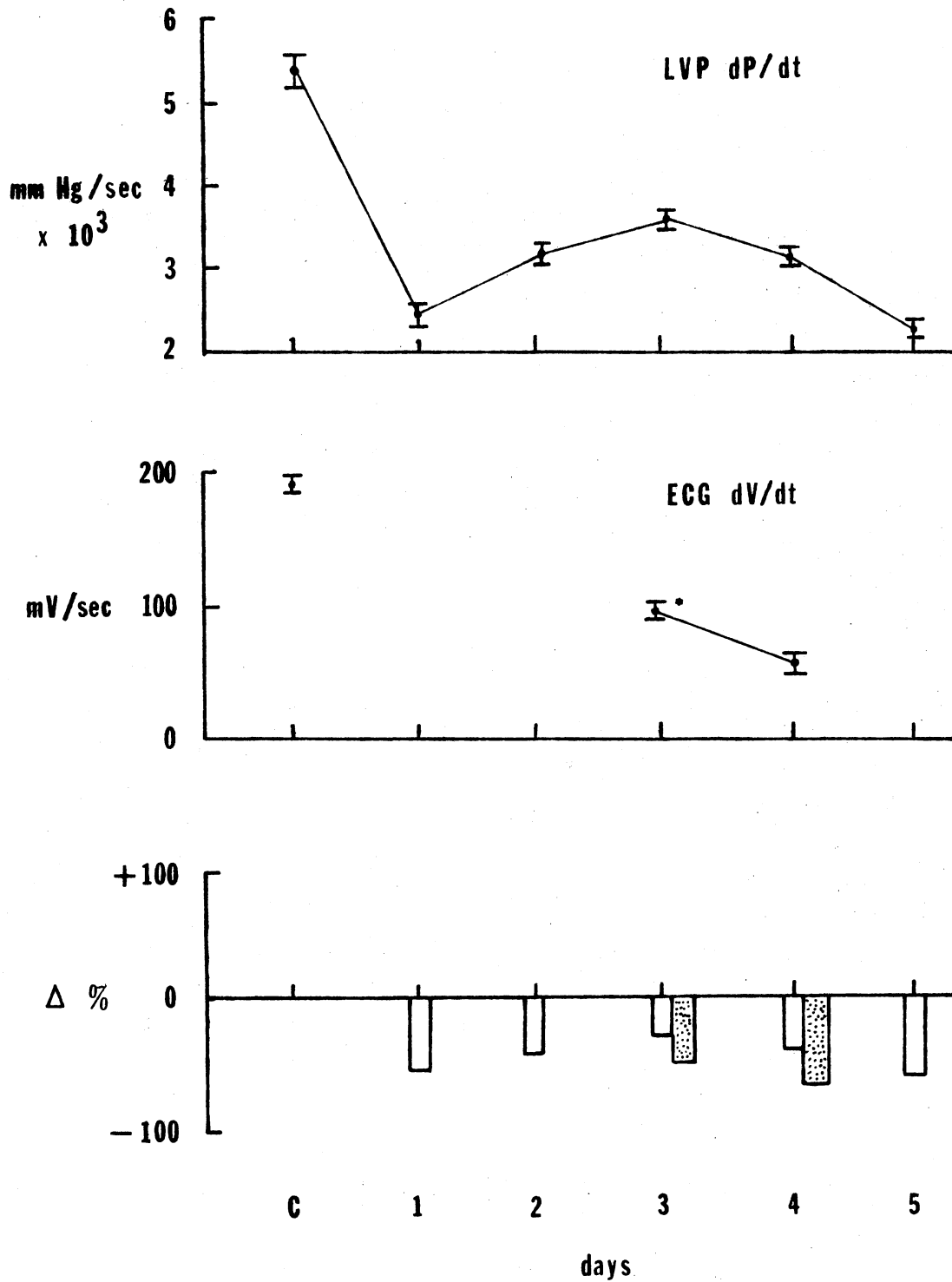*Rates expressed in beats per minute and averaged over a five-minute period.

Figure 19. Changes in Left Ventricular dP/dt and ECG dV/dt (upper two panels). Percent Change From Control Day (C) for dP/dt and dV/dt. Dog #380, 29.4 kg.

Representations are as in Figure 15.

Animal #303

This animal, like #315, did not show a significant correlation between dV/dt and dP/dt in the control condition (r = 0.02). After ligation, only one day of normal rhythm occurred, and dV/dt was correlated with dP/dt on that day (r = 0.49).

This animal also exhibited a mean increase in dP/dt after ligation which amounted to more than a doubling of the control value. A progressive decline in mean dP/dt followed this increase leaving the fifth day recording still above the control value (Figure 20, upper panel).

A mean decrease in dV/dt was observed resulting in the mean changes of dP/dt and dV/dt being opposed in direction (middle panel). The pattern was very similar to that seen in #303. Heart rate is presented in Table XVI.

TABLE XVI

NORMAL, ECTOPIC, AND TOTAL HEART RATES* THROUGHOUT THE
POST-LIGATION PERIOD FOR DOG #303, 17.2 KILOGRAMS

Day	Normal	Ectopic	Total
Control	135	0	135
1	0	185	185
2	27	184	211
3	26	126	152
4	88	29	117
5	27	116	143

*Rates expressed in beats per minute and averaged over a five-minute period.
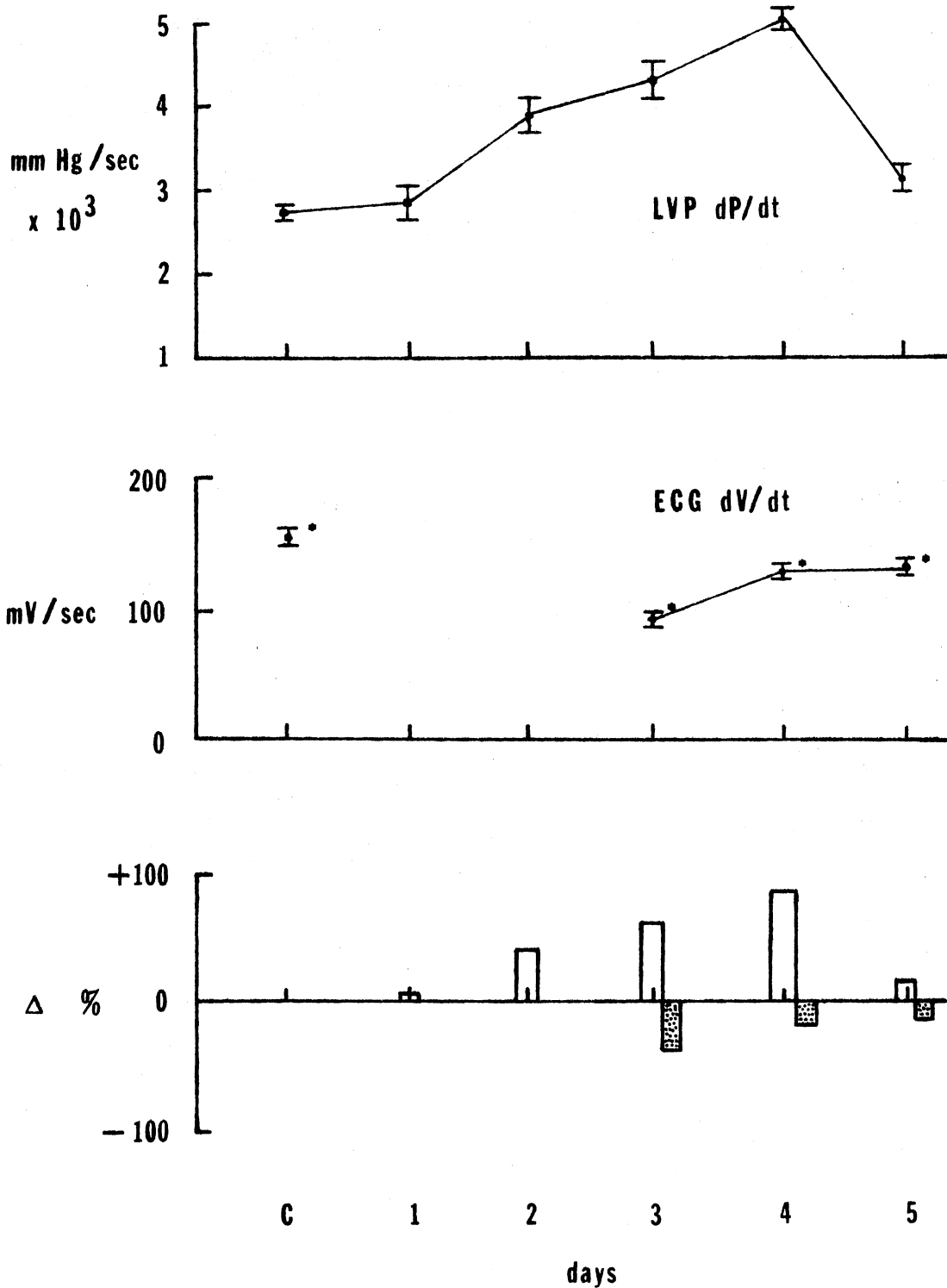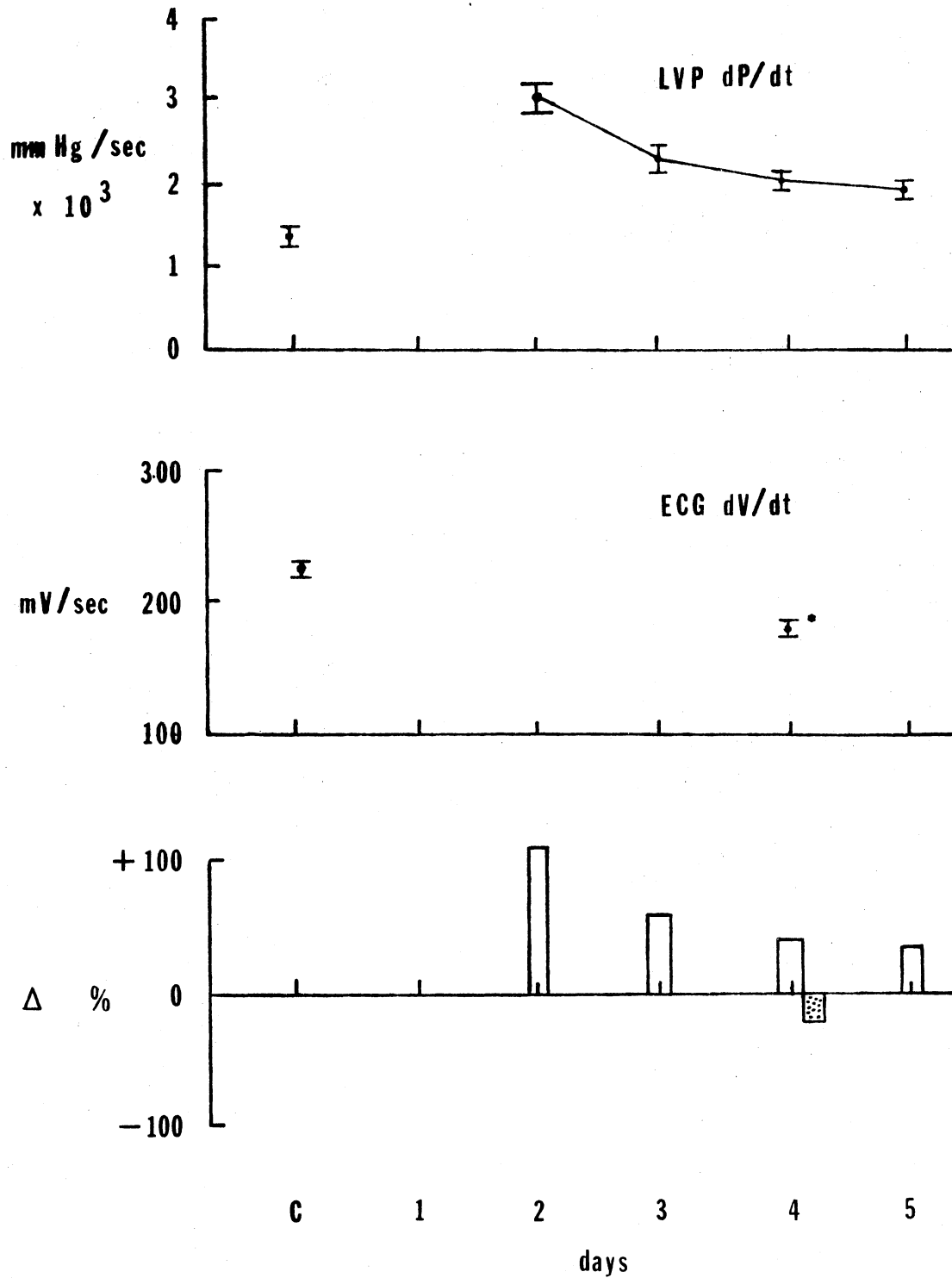
Figure 20.   Changes in Left Ventricular dP/dt and ECG dV/dt (upper
             two panels). Percent Change From Control Day (C) for
             dP/dt and dV/dt. Dog #303, 17.2 kg.

Representations are as in Figure 15.

Summary of Chronic Experiments

Six animals met the criteria for inclusion in the chronic study. Large infarcts were observed in all animals, and each exhibited a complete ectopic rhythm for one to two days following the ligation. All but one animal survived the entire five-day post-ligation period. Complications resulting in a loss of data points occurred in two animals in which left ventricular pressure could not be recorded due to an occluded catheter.

Four of the six animals exhibited a significant correlation between dP/dt in the left ventricle and dV/dt in the R-spike upstroke of the limb lead ECG prior to ligation. Correlation coefficients ranged between 0.67 and 0.86 for these animals. The other two animals which did not show a correlation both had r values less than 0.1. The correlation was occasionally lost after the ligation, but all animals did show a correlation during part of their recovery. Even the animals which did not show a significant correlation before ligation exhibited one during the recovery.

Mean left ventricular dP/dt was decreased after ligation in four of the six animals. Two animals exhibited an unanticipated increase in mean dP/dt. In both patterns of recovery, there was a tendency to return and approach the control value about the fourth or fifth day. Considerable variation between animals was observed in the control values of dP/dt, ranging from 1450-6584 mm Hg/sec.

Changes in dV/dt occurred in both directions with values decreasing in four animals and increasing in two animals. The development of ectopic rhythm following the ligation did not allow measurement of early

changes in dV/dt. There was less variation between animals in control values of dV/dt, with values ranging from 112.8–222.8 mV/sec.

Results of Anesthesia and Catecholamine Experiment

The animal used in this experiment had a conscious mean dV/dt value of 101.9 ± 1.8 (mean ± standard error). Thirty recordings were evaluated and measured. After anesthetization with the same dose of pentobarbital used in the other experiments, a mean dV/dt value of 96.3 ± 1.9 was recorded. A calculated t value of 2.1081 was obtained which was significant at the 0.05 level, demonstrating a depressant effect of pentobarbital anesthesia on dV/dt of the R-spike upstroke of the ECG.

Mean control values for both dV/dt and dP/dt were obtained after the catheterization of the left ventricle in the anesthetized animal mentioned above. Left ventricular dP/dt and ECG dV/dt were again measured and analyzed by linear regression analysis before and after the intravenous injection of epinephrine (1 mcg/kg). The results are presented in Table XVII. Mean left ventricular dP/dt was greatly increased by the epinephrine bolus, but mean dV/dt did not change significantly. The correlation was decreased slightly, but did not lose significance at the 0.05 level.

TABLE XVII

REGRESSION ANALYSIS OF CORRELATION BETWEEN dV/dt AND dP/dt
PRIOR TO AND AFTER ADMINISTRATION OF EPINEPHRINE*

	Control		Epinephrine	
	dV/dt	dP/dt	dV/dt	dP/dt
$\bar{x}$ ± S.E	113.4 ± 2.4	2483 ± 69	117.3 ± 3.4	5591 ± 230
n	30		30	
slope	17.0465		35.8956	
intercept	908.9751		1382.0590	
r	0.6033		0.5372	
probability	p < 0.0005		0.0005 < p < 0.005	

*Epinephrine was administered in a 1 mcg/kg intravenous bolus in dogs anesthetized with 32 mg/kg pentobarbital sodium.

CHAPTER V

DISCUSSION

Analysis of the amplitudes and duration of fixed intervals of the electrocardiogram (ECG) in various pathological states of the heart has been performed routinely for many years, but a measurement of the rate of voltage change (dV/dt) in the ECG has not been reported previously. Changes in the electrical activity of localized portions of the myocardium are manifested in the limb lead ECG (Ross, 1976), but assessment has been limited to ST-segment change and analysis of injury potentials by vectorcardiography. If changes occur in dV/dt of the monophasic action potential of myocardial fibers, it would be expected that the representation of the sum of this activity, the limb lead ECG R-spike, might reflect that change. With this assumption in mind, knowledge of that portion of the myocardium represented by the discrete phase of the ECG R-spike would perhaps allow localization of areas of electrical instability.

An attempt at localization of the areas of the myocardium which are able to exert changes in dV/dt of the ascending limb of the ECG R-spike was the first of two objectives. The second objective was to determine whether dV/dt could be used to assess changes in contractility. It is known that factors influencing contractility tend to alter dV/dt of the monophasic action potential of myocardial fibers in the same direction. A diagnostic and predictive quality was sought in

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dV/dt which would allow assessment of hemodynamic as well as electro-physiologic changes in healthy and diseased hearts. The relationship between ECG dV/dt and left ventricular dP/dt was studied in the acute animals prior to ligation and in the chronic animals throughout their five-day post-ligation recovery period. The results of the acute and chronic studies will be discussed separately.

<div align="center">Acute Study</div>

The results of the acute study indicate that a positive correlation exists between dV/dt of the ascending limb of the R-spike of the limb lead ECG and selected epicardial electrograms recorded from the anterior wall of the left ventricle. The areas of correlation did not include the entire wall, but were concentrated along the interventricular septum. The correlation decreased in areas extending laterally from the septum and toward the apex. This data compares favorably with maps of normal ventricular activation. Areas of earliest electrical activation are purported to be responsible for the inscription of the ascending limb of the ECG R-spike and include the anterior ventricular mass studied by electrogram recordings in these experiments. Undoubtedly, the variation from animal to animal was influenced by the different heart sizes (normalized for this study), the variation in the normal activation sequence in the area of interest, perhaps unknown micropath-ology, and circulating and local levels of catecholamines.

The second part of each acute experiment was to re-evaluate those areas of high correlation following the production of severe ischemia in the anterior wall. Ligation of the anterior descending branch of the left coronary artery has been shown to produce large infarcts in

the area of the anterior left ventricle immediately adjacent to the
interventricular septum (Harris, 1954). This area includes most of the
epicardial surface exhibiting significant ECG and EG dV/dt correlation
prior to ligation. A loss of correlation was observed in the ischemic
area in almost all dogs. The alteration of electrical activity in the
ischemic area produced changes in dV/dt of both the electrograms and
ECG, and it also reduced the correlation between them. This loss of
correlation was more complete in some of the animals than in others.
It is probable that the degree of ischemia may have been related to
this loss. The fact that areas proximal to the ligation did not nor-
mally lose their correlation suggests this reasoning as a viable
hypothesis. The existence of visible vasculature reaching around the
lateral edge of the ventricle from the left circumflex artery may have
prevented the loss of correlation in areas near these vessels. Colla-
teral circulation, known to be functional in variable degrees in man,
may have also been a factor moderating the degree of ischemia produced
by arterial ligation. More importantly, however, is the condition of
the myocardial cell's electrical stability. It is known that hypoxia,
definitely a relevant factor in this study, leads to a decrease in the
resting membrane potential, which may oscillate between normal and
rather low values. Studies with individual myocardial fibers demon-
strate that the higher this potential, the greater is the rate of rise
of zero phase depolarization. The obverse is also true. In essence,
the instability of the cells in the ischemic zone will exhibit greater
variation in their collective dV/dt measured either in the surface EG
or the ECG. It is probable that the influence of this instability will
be visualized to the greatest extent in the EG while the ECG, being an

average of normal and unstable areas, may be influenced to a lesser degree.

Areas that became correlated only after ligation may be the result of a functional change in the normal activation sequence. The ischemic area with its inherent instability may lead to localized refractoriness and "skirting" of the normal but ischemic pathway in favor of viable adjacent tissue.

Left ventricular dP/dt and ECG dV/dt were correlated prior to ligation in three of the five animals used in the acute study. The results of these correlations will be discussed along with the results in the chronic animals.

Chronic Study

The primary objective of the chronic study was to determine whether dV/dt in the limb lead ECG can be used to assess changes in contractility. Left ventricular dP/dt was thus correlated with limb lead ECG dV/dt to determine if a significant relationship does exist, and what happens to the relationship after experimental myocardial infarction.

Eleven animals, five in the acute study and six in the chronic study, were used to determine if a significant relationship between dV/dt and dP/dt exists normally. Seven of these animals showed a significant correlation between dV/dt and dP/dt in the control condition, with correlation coefficients ranging between 0.47 to 0.86. It is not well understood why the other four animals failed to show this correlation. However, all of the chronic animals did exhibit a significant correlation at some point during their recovery.

The existence of a significant correlation between dV/dt and

dP/dt does provide a predictive ability to the ECG on a beat-to-beat basis, but this ability remains somewhat limited. It is possible to detect directional changes in contractility using dV/dt from beat-to-beat, but the wide variation of dP/dt between animals as described by Mason (1969) will not allow a prediction of the absolute value of dP/dt by the ECG alone. Further, in the pathological state (i.e. infarction in our experiments), dV/dt was not always correlated on any particular day. Although changes in dV/dt were observed after the ligation, the slope of the regression line and its intercept had changed from the pre-ligation value even on those days of significant correlation. This would suggest that dV/dt and dP/dt are sensitive to the changes produced by infarction to different degrees and may not change in the same direction, and yet remain significantly correlated in the post-ligation state.

Another complication developed in interpretation of the results in that four of the six animals showed changes in dV/dt and dP/dt which were opposite in direction. Two of these animals showed a decreased dP/dt with an increased dV/dt after ligation, while the other two demonstrated a reverse trend. Nevertheless, a significant positive correlation existed during at least part of the post-ligation period. With the regression line slopes and their intercepts changing day to day, it was not possible to predict an absolute value for dP/dt. Indeed, a family of regression lines was generated for each animal after the ligation. Even if a significant correlation existed on every post-ligation day, a change in dV/dt from the control value would not allow an estimation of contractility with changes occurring in the regression line.

Two different patterns of recovery emerged in the chronic animals. Four of the six animals exhibited a marked decrease in dP/dt after ligation which was generally followed by a progressive return toward the pre-ligation value. The other two chronic animals showed a paradoxical increase in dP/dt after ligation. These animals had the lowest control values of dP/dt of all animals used in this investigation. It is possible that the hearts of these animals were operating at some "lower end" of a contractility range in the control condition. Coronary artery ligation, even though reducing the mass of functional myocardium, may have induced some type of reflex compensatory adjustment, possibly through the sympathetic nervous system. This adjustment, in compensating for the ischemic and infarcted tissue, may be reflected in the enhanced level of contractility. The temporary increase in dP/dt should not imply a "healthy" state because the beats generating those pressures were often ectopic in origin. In both animals, dP/dt returned toward normal after reaching a peak during the post-ligation period.

It was also observed that these two chronic animals who exhibited the increase in dP/dt after ligation had the highest pre-ligation heart rates of the entire group of animals. Left ventricular dP/dt in the control condition was higher in animals with slower heart rates. It is doubtful that these high rates were fast enough to encroach seriously on filling time such that cardiac output would have been depressed, but small changes in ventricular filling will indeed alter end-diastolic fiber length (preload) and influence dP/dt in this manner. If these animals were exhibiting a depressed mean dP/dt in the control condition, it is possible that a change in the preload conditions, even after the ligation, may have increased mean dP/dt.

Anesthesia and Catecholamine Experiment

Pentobarbital anesthesia was observed to have a depressant effect on dV/dt in the ECG. The t value obtained was significant at the level, $0.01 < p < 0.025$. The difference, although statistically significant, amounted to approximately a six percent change from the control value. Control records of the ECG in all experiments of this study, from which dV/dt was calculated, were taken in the anesthetized state. Anesthesia was necessary in order to catheterize the ventricle so a simultaneous record of left ventricular pressure could be obtained. The error due to comparing control records taken in anesthetized animals with post-ligation records taken in conscious animals was introduced into our results. It is doubtful if the absence of anesthesia would have changed the pattern of recovery, assuming only a six percent change in absolute value between the control and anesthetized dV/dt values. However, the presence of the barbiturate in the control situation may have depressed the reactivity of the myocardial cells which would be reflected in the dV/dt parameter. Since the cellular mechanism of barbiturates is not known at present, possible effects are necessarily speculative. The possible error introduced by anesthesia was accepted as being inherent in our protocol, and the advantages of attempting to remove it were considered to be outweighed by the possible disadvantages necessary to remove it.

The intravenous bolus of epinephrine produced an anticipated marked increase in mean dP/dt. Mean dV/dt exhibited no significant change. However, dV/dt was correlated with dP/dt in both the control condition and after the epinephrine injection. Left ventricular dP/dt and dV/dt

apparently show different sensitivities to catecholamines, though their new response curves are correlated.

Catecholamines are known to be released and circulating levels raised after myocardial infarction. This release would tend to alter dP/dt to a greater extent that dV/dt and change their relationship (i.e. the regression line would be altered from the control.) When this occurrence is compounded with the effects of infarction on dP/dt itself, the relationship becomes complex and difficult to interpret, as evident in the relationship between dV/dt and dP/dt in the chronic animals. Interaction of unrelated factors may depress dV/dt while enhancing dP/dt and vice versa. Complicating the problem is the differential sensitivities of the two parameters to various interventions. A day-to-day prediction of contractility changes from dV/dt in the ECG would be very difficult without knowing what conditions are influencing both parameters. It is possible using this method to obtain a directional change in contractility on a beat-to-beat basis, but the utility of this information may be limited.

Further investigations may elucidate other features of the relationship between dP/dt and dV/dt. The establishment of normal ranges for dV/dt and the factors which influence this value may be helpful in clarifying its relation to dP/dt.

CHAPTER VI

SUMMARY AND CONCLUSIONS

An attempt to develop a non-invasive method of locating and ass-
essing myocardial damage using the limb lead electrocardiogram (ECG)
has been discussed. The electrocardiographic parameter measured and
evaluated as a predictor was the rate of voltage change (dV/dt) of the
ascending limb of the R-spike of the QRS complex in Lead II. Two pro-
tocols were designed to study dV/dt on an acute and chronic basis after
coronary artery ligation.

It was demonstrated that dV/dt of the ECG was significantly corre-
lated with dV/dt of R-spike upstrokes of epicardial electrograms
recorded from a large part of the anterior wall of the left ventricle.
After ligation of the left anterior descending coronary artery, the
correlation was lost in much of the area and appears to be related to
the degree of ischemia produced. An acute change in the electrical
activity of this area of the myocardium, as in myocardial infarction,
would be expected to produce a change in dV/dt of the limb lead ECG.
The assumption is made that only a small area of the left ventricle is
responsible for the upstroke of the R-spike in the ECG. The area of
damage may then be localized in the anterior wall.

In each animal, dV/dt in the ECG was correlated with the corres-
ponding rate of pressure rise (dP/dt) in the left ventricle. Seven of
the eleven animals used in this study exhibited significant correlations

prior to ligation.

Six animals were allowed to recover and were monitored for five days following the ligation. Two patterns of recovery emerged: (1) four animals showed a marked decrease in dP/dt after ligation, and (2) two animals showed an increase. A possible compensatory adjustment to explain these two aberrant animals was discussed.

Even though mean dP/dt and mean dV/dt often changed in opposite directions, significant correlations were maintained throughout the post-ligation period. A new regression line was developed each day, disallowing a prediction of dP/dt to be made using the line generated on the control dog. Directional changes in contractility could be predicted on a beat-to-beat basis, but accurate quantitation with this method is not possible.

Pentobarbital anesthesia (32 mg/kg) was demonstrated to have a depressant effect on dV/dt. Its effect in these experiments appears to have little effect on the absolute values and would probably have no effect on the pattern of recovery, though it may influence the correlation of ECG dV/dt with EG dV/dt by unknown effects on the rate of voltage generation. The timing of this experiment may have induced a problem in comparing these results with the other experiments. The ECG was monitored immediately after the administration of the anesthetic in this experiment, while an hour or more had elapsed before recording the ECG in the other animals. It is probable that an exaggerated effect of the drug may have been observed under these conditions.

An intravenous injection of epinephrine (1 mcg/kg) produced a marked increase in dP/dt, but did not significantly alter the correlation between dV/dt and dP/dt. The slope of the regression line was

doubled from the control condition.

The significance of these findings is at best speculative, in that these experiments could not rule out all the known and unknown variables which may have influenced the mean changes of dV/dt and dP/dt as well as their relation to one another.

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