CHANGES IN ELECTRICAL STABILITY AND MYOCARDIAL CONTRACTILITY FOLLOWING RESTORATION OF BLOOD FLOW TO ACUTELY INFARCTED MYOCARDIUM

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PREFACE

The work reported in this thesis was carried out in the University Surgical Clinic of the Montreal General Hospital. It was supervised and directed by Dr. P.E. Blundell of the Department of Thoracic and Cardiovascular Surgery.

Among those not involved in directing this project I am very grateful to Dr. C.J. Chiu for his suggestions and encouragement during the year. Mrs. A. Goggin and her staff did all they could to make operating room work run smoothly, and Mr. A. Mott gave personal attention and excellent care to my animals. The histologic slides were prepared by Miss C. Labelle. Statistical analysis of the results was carried out with the help of Mr. F.D.K. Liddell and Miss J. Swift of the Department of Statistics, McGill University.

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ABSTRACT

Arrhythmias and pump failure remain the main causes of death from acute myocardial infarction. Aorto-coronary bypass offers the possibility of early restoration of blood flow to the ischemic myocardium. These experiments attempt to clarify the critical time factor associated with reversible changes in electrical stability and myocardial contractility following revascularization of the ischemic tissue.

I. Electrical Stability

Ventricular fibrillation thresholds (VFT's) were measured in dogs using Shumway's modification of the original method by Wiggers. Three groups of animals were investigated:

1) One hour occlusion
2) Two hour occlusion
3) Permanent ligation

Measurements were made prior to and at 15 min. intervals up to three hours after occlusion. Within 15 min. of occlusion, VFT's dropped below 40% of control values. In groups 1 and 2 the VFT rose to 90-100% of control within an hour of release of occlusion, but in Group 3 it remained below 50% throughout the

experiment. Conclusion: Restoration of blood flow following two hours of myocardial ischemia is associated with recovery of electrical stability as measured by ventricular fibrillation thresholds.

II. Myocardial Contractility

Peak dp/dt and Vmax were measured in four groups of anesthetized cats; hourly during the initial four hour study, and again at six weeks.

Groups:
1) Sham operation
2) Two hour temporary occlusion of LAD coronary artery
3) Four hour occlusion of LAD coronary artery
4) Permanent ligation of LAD coronary artery

Mortality from congestive heart failure and pneumonia (in the 70 cats studied) was: 22.2%, 50.0%, 63.6% and 69.2% respectively. Of the cats awaiting operation, 10.0% either died of natural causes (preop) or were too sick to be kept.

In those surviving six weeks, Vmax and Pdp/dt dropped to below 80% of preocclusion values immediately after occlusion, but after that showed considerable variation within groups and little difference between groups, both during the four hour study and at six weeks.

Because of the small number completing the study period, variability within groups, and self-elimination of those dying with congestive heart failure, inferences from the study of myocardial contractility should be made with caution. However, the mortality rates suggest that restoration of circulation within less than four hours of ischemia may save some myocardial function which would otherwise be lost by a permanent occlusion.

Variations de la Stabilité Electrique et de la Contractilité Myocardique Survenent Aprés une Revascularisation de l'Infarctus Aigue

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Les arythmies et la defaillance de la pompe cardiaque demeurent les principales causes de mort aprés un infarctus du myocarde. Le pontage aorto-coronarien offre la possibilité d'une restauration precoce du debit sanguin à un myocarde atteint d'ischemie. Les expériences suivantes essayent de clarifier le facteur tempe critique associé à des variations reversibles de la stabilité électrique et de la contractilité myocardique survenant aprés une revascularisation du tissue ischémié.

I. La stabilité électrique:

Le seuil de fibrillation ventriculaire (SFV) a été mesuré chez les chiens par la methode de Shumway qui est une modification de la methode originale de Wiggers. Trois groupes d'animaux ont été investigués:

1) 1 heure d'occlusion
2) 2 heures d'occlusion
3) ligature permanente

Les mesures ont été faites 15 minutes avant et à une intervalle de 15 minutes durant trois heures aprés l'occlusion. En moins de 15 minutes d'occlusion le seuil de fibrillation ventriculaire a chuté au dessous de 40% de valeur de control. Dans les groupes let 2 le SFV s'est élevé jusqu'à 90-100% de valeur de control en moins d'une heure aprés le relachement de l'occlusion, mais dans le groupe 3 la valeur demeurait au dessous de 50% durant toute la duré de l'experience. Conclusion: La restauration du debit sanguin aprés 2 heures d'ischemie myocardique. est associé aun retour àla normale de la stabilité électrique comme elle a été mesurée par la methode de SFV.

II La Contractilité du Myocarde:

Le pic dp/dt et le Vmaximum ont été mesurée chez quatre groupes de chats anesthésiés. La mesure a été faite chaque heure durant les quatre premiéres heures d'étude puis de nouveau aprés six semaines.

Groupes: 1) Opération de Sham
2) Occlusion temporaire de l'artère coronaire gauche descendente auterieure (GDA) pendant 2 heures
3) 4 heures d'occlusion
4) Ligature permanente de l'artere GDA

La mortalité par decompensation cardiaque et pneumonie (chez les 70 chats etudiés) était respectivement de 22.2%, 50.0%, 63.6% et 69.2%. Chez les chats attendant une opération 10.0%

mouraient d'une couse naturelle (préopératoire) ou bien étaient trop malades pour être gardé.

Chez les chats qui ont survecu six semaines le Vmax et Pdp/dt ont chuté au dessons de 80% de la valeur initiale avant l'occlusion immédiatement après l'occlusion, mais aprés ceçi ont montré une considerable variation à l'interieur du meme groupe et une petite différence entre differentes groupes, tous les deux durant les 4 heures d'étude et aprés 6 semaines.

À cause du petit nombre étudié pendant la periode d'etude, la variante à l'intérieur du groupe même et l'elimination automatique de ceux qui sont mort par defaillance cardiaque; les déductions de l'étude de la contractilité du myocarde doivent être faites avec prudence. En tout cas le taux de mortalité suggere que la restauration de la circulation en moins de 4 heures d'ischémie peut sauver certaines fonctions du myocarde qui pouvaient être perdues aprés une occlusion permanente.

ILLUSTRATIONS

CHAPTER I

GENERAL INTRODUCTION

1. THE AMERICAN WAY OF DEATH

Coronary heart disease has assumed such serious proportions in North America that it has been called "The American Way of Death", (1). The lay press has fairly accurately reported etiologic theories (2), clinical course (1,2), and recent advances in its management (3).

In the form of angina pectoris and myocardial infarction, coronary artery disease was "relatively rare" at the time Sir William Osler wrote about it in 1910 (4), but has since burgeoned resulting in over 625,000 deaths annually in the United States, at the turn of the last decade (5). The estimated economic cost of this problem was 2.6 billion dollars in direct and 28.1 billion dollars in indirect costs for the year 1962 alone (4).

At the level of the individual, however, this is overshadowed by personal incapacitation and disruption of the family.

If we follow an asymptomatic population of males (ages between 45 and 54 years), every year 1% become symptomatic of coronary artery disease: half have an acute myocardial infarction, about one third angina pectoris, and almost one quarter die suddenly (6). Of the intermediary

syndromes (unstable angina, rest pain), annually, 3% will die suddenly, and 15% will have an acute myocardial infarction of which 4% will die. Examining the problem from a different angle, we find that out of 100 patients with an acute myocardial infarction (7), 20 will die outside the hospital (usually within four hours from the onset of symptoms), and of the remainder, 20 will die in hospital with conventional treatment: 10 of pump failure (myocardial insufficiency), and eight of arrhythmias.

In large hospitals with well equipped coronary care units the number dying of arrhythmias is lower, and with the use of mobile coronary care units (8), it should be possible to save some of the twenty dying before reaching hospital. Despite these improvements, we are still left with the two main causes of death from coronary artery disease which have been recognised for a long time (9): arrhythmias and pump failure.

2. SUDDEN DEATH OR PUMP FAILURE

Coronary disease can cause death by gradual progressive myocardial insufficiency, the heart becoming increasingly inadequate in its performance as a pump, or suddenly, by arrest or the development of ventricular fibrillation (10).

Sudden death (usually defined as instantaneous death

to death within an hour or two from the onset of terminal symptoms) is most commonly associated with underlying coronary disease (11,12), and comprises half or more of all deaths of persons with symptomatic coronary artery disease (13,14). It is thought to be caused by ventricular fibrillation (15,16,17) or cardiac arrest (17). Indeed in one coronary care unit (18), ventricular fibrillation occurred in 5.5% of patients with acute myocardial infarcts admitted within 4 hours after the onset of symptoms.

As noted earlier (6), 20% of all persons developing symptomatic coronary atherosclerosis in one year present with sudden death, and prior to the aggressive treatment of arrhythmias this accounted for approximately one third of the deaths from myocardial infarction (19), the most critical period being the first two days. Several theories have been proposed to explain ventricular fibrillation (11,20-23), but the exact mechanism is still unclear.

With the development of modern coronary care units in large centers, the early hospital mortality rate has been reduced from over 30% to 12-14% (26,27), mainly because of advances in treatment of fatal arrhythmias. These accounted for almost half the hospital deaths prior to intensive coronary care. At present, the main cause of hospital deaths is pump

failure (for which medical treatment is ineffective), the mortality rate for cardiogenic shock being 80-90% with present therapy (24).

3. MEDICAL MANAGEMENT OF THE ACUTE MYOCARDIAL INFARCTION

Until recently, management of the patient with acute myocardial infarction has been primarily medical, certain aspects of which (such as bed rest) dating back several centuries. Indeed, digitalis was formally introduced into medicine for the treatment of heart failure in the late 1700's when Whithering discussed its use "in cases of dropsy, especially when of cardiac origin" (25), although it had been used earlier for a variety of purposes. At present, the treatment includes hospitalization, rest, relief of pain, oxygen, antiarrhythmics, and the management of heart failure if it is present (26). There is variable acceptance of the use of anticoagulants or glucose-insulin-potassium.

The assessment of the effectiveness of medical management of acute myocardial infarction should not be based only on early and late mortality rates. The persons surviving are left with a precarious coronary supply to the heart which might decrease still further, causing more damage. In addition

to this, the infarcted muscle will scar, compromising ventricular function.

Rahimtoola studied cardiac performance in 16 patients 3 - 8 weeks after an acute infarct (28). Although all appeared to be clinically recovering well, and were not in overt congestive failure, 14 of the 16 had abnormal ventricular function. Feild found abnormally contracting segments in 24 of 25 patients 2 - 12 months following myocardial infarction, even though 16 of them were clinically without heart failure (29).

It would appear, therefore, that medical therapy of acute myocardial infarction falls short in two basic areas: (1) it is inadequate in the treatment of pump failure (cardiogenic shock); (2) it does not prevent damage to the heart produced by the acute ischemic episode, which will, in the long term, compromise heart function.

4. SURGICAL MANAGEMENT OF CORONARY ARTERY DISEASE

Cardiac surgery has advanced considerably since Billroth in 1833 wrote: "A surgeon who would attempt such an operation (cardiac suture) should lose the respect of his colleagues" (30). Surgical treatment of coronary artery disease probably started after Francois-Franck, a Professor of Physiology in Paris, suggested that cervical sympathectomy might be beneficial

for relief of angina pectoris. This procedure was carried out by Jonesco (31) in 1916 producing some symptomatic relief. The next indirect surgical approach to coronary disease followed the report of subsidence of congestive failure in patients with hyperthyroidism after thyroidectomy (32). This was followed by a series of total thyroidectomies which apparently decreased heart work, but so depressed metabolism that the patients were less capable of functioning normally than prior to operation.

It was not until 1935 that Claude Beck reported attempts to improve myocardial blood supply, by abrading the epicardium and suturing a pedicle of pectoralis muscle to the myocardium (33). The relief of pain in the patient reported led to the use of a series of different pedicle grafts. Beck later suggested the arterializing of the coronary sinus in an attempt to provide retrograde arterial blood flow (34). In 1946, Vineberg reported evidence that with time, the internal mammary artery implanted in the wall of the left ventricle communicated with the coronary system (35), and he later reported a series of patients who underwent the operation with an operative mortality of 5% and late patency of over 75% (36). Others subsequently reported higher patency rates. Animal experiments showed pulsatile flow and response to vasodilators,

not unlike that occuring in the native circulation. Coronary endarterectomy was first performed in 1957 by Bailey and associates (37), but further work showed a continued high mortality (range of 25%). In the Cleveland clinic these were abandoned, as were the pericardial patch-grafts, which in the case of the left coronary artery had a mortality of 65% (38). The next step following the development of coronary arteriography (37), was the use of saphenous vein grafts in direct coronary reconstruction (39), and then the aorta-coronary vein bypass which is the most widely used procedure at present.

5. RESULTS OF SURGERY

Over the last 4 - 5 years, bypass operations have been performed with increasing frequency, presently at a rate of over 20,000/yr (3). Coronary bypass surgery is performed most commonly for angina, and is generally attended with good subjective response. It is thought that myocardium viable enough to produce angina under stress will respond to improved blood supply. Symptomatic improvement is noted by 80 - 90% of these patients (40,41), although objective improvement is less frequent. Improved ventricular function was associated with graft patency (40). 75 - 80% of the grafts were patent

12 months after operation, and most of these were still patent when studied two and three years later (38,40,42). On the other hand, the low operative mortality of less than 5% (30, 41,43) is coupled with a variable number (5-10%) of early postoperative infarcts (40,42). Furthermore, the five year survival of the "low risk" group (44), or patients with single vessel disease and good left ventricular function (45), under medical management, is not unlike that of the ones bypassed.

A recent less optimistic report from the Johns Hopkins Hospital suggests that despite relief of angina, a significant number of patients showed poorer heart function (46), consistent with the hypothesis that pain relief may be related to destruction of the pericoronary nerve plexus or further muscle damage (47), associated with progressive occlusive changes in the native circulation (48). Results of the bypass surgery for unstable angina are less clear. The title itself leads to some confusion, variably called "preinfarction angina" or "impending myocardial infarction" and but generally refers to recent change in quality or quantity of angina, or angina at rest. Some reports have been encouraging, with early mortality of 7 - 8% (49,52), followup studies showing improvement of ventricular function in the early postoperative cineangiogram and pressure studies (52,53).

On the other hand, results are partly related to preoperative heart function (49), and the life expectancy may not be increased by operation for the whole group. Krauss, following 100 patients of this group, treated medically, noted six myocardial infarcts in hospital and one hospital death, and the one year survival rate was 85% (54). Until recently, operation in the early stage after an acute myocardial infarction has been regarded as prohibitively dangerous. Hattler and Sabiston, writing on myocardial revascularization in 1969, noted that "other than recent infarction, there are few absolute contraindications to surgical treatment" (37).

Mundth reported on the use of this procedure in cardiogenic shock in combination with preoperative circulatory assistance in seven patients, with three survivors at three weeks to seven months (56), and Bolooki later reported the operation in six, with four survivors (56). In general, bypass surgery in the acute infarction stage has been considered when the patient would probably otherwise not survive.

Emergency revascularization for acute evolving infarction without shock is very controversial. Most of these patients survive the acute episode, and many people regard the operation at this period as dangerous and unnecessary. In spite of this, there are a few reports of this procedure in

uncomplicated acute infarction. Faveloro (51) found good ventricular function in four, and abnormal or undamaged function in three patients of a group of seven survivors. Operative mortality was a bit higher than in those of the angina group. In another group of 20 patients (including 11 with impending infarction and two with impending infarction with cardiogenic shock, the others being early infarcts with or without shock), there were 19 survivors after bypass operations, with variable left ventricular function in those with shock prior to operation (57).

The most encouraging results were those of Dr. Cohn, who reported no deaths in a group of eight patients bypassed shortly after in-hospital coronary occlusion, with reversal of electrocardiographic abnormalities in 6, and no significant morbidity (58), concluding the "immediate coronary bypass for acute coronary occlusion in this clinical setting (documented in-hospital occlusions) is not only feasible but is the treatment of choice".

However optimistic some of these reports may be, they should be considered with caution. The final proof of the value of such surgery will be in improved function and survival shown by long-term follow up.

6. PROBLEMS ASSESSING SURGERY

Three main problems face us in assessing results of surgery:

(A) Controls and the Placebo Effect

In any assessment which is based on symptomatic improvement (this is especially true of the angina group) we encounter the placebo effect. This was well demonstrated in the study of patients with internal mammary artery ligation popular in the 1950's (59,60). Patients were randomly assigned to an artery-ligation or an open-and-close operation, and the results showed that 12 of 17 patients who had sham operations improved subjectively, and 2 of 9 had objective evidence of improved exercise tolerance.

Henry Beecher, in his essay Surgery as a Placebo, makes the point that the magnitude of the placebo effect is directly related to both the associated emotional stress and the surgeon's enthusiasm (61).

In a recent study, David Spodick, reviewing trials of medical and surgical therapy for cardiac disease reported over a twelve month period in 1971, found that while about half of the 21 medical trials were controlled, none of the 49 surgical trials were controlled using single-blind, double-blind,

or placebo measures (62).

(B) Methods of Assessing Results

There are many methods of assessing the heart and the value of the operation, one or more being used by the different workers. Operative mortalities are of value but a far cry from the long term survival. Electrical, chemical, and metabolic studies are enlightening, but still fall short of quantitative functional measurements. Many patients are now being assessed angiographyically for graft patency and movement of the ventricular wall; and from pressure studies as well as cineangiograms we may obtain some measurement of the mechanical function of the heart. The use of different methods (including clinical) to evaluate patients post-operatively makes comparison of patient groups difficult.

(C) Variability of Patients

Patients come to surgery at different stages in the disease with different degrees of coronary occlusion, variable ventricular function, and at a variable interval from the acute episode (in the case of early revascularization) - so that each patient is his only true control. The results correlate well with maintained patency of the grafts (40,41). Patency of the grafts is influenced by the size of the coronary artery anastomosed (63), the handling of the vein, and other technical

factors (64), and, more importantly, the run-off, a flow of over 40 ml/minute being associated with patency of 90% at 1 - 2 yrs (65). Increase in the occlusive process in the native circulation after successful bypass (46,48) may be associated with recurrent angina, or impairment of ventricular infarction, or both.

In all revascularization procedures, the most favorable results were among patients with the best preoperative heart function (66), itself being related to the extent of disease in the arteries, the single vessel group usually characterised by a shorter history of symptoms and lower frequency of heart failure, while the patients with diffuse disease were characterised by many hemodynamic abnormalities (67).

In the case of the acute infarct, the time interval from onset of ischemia to revascularization appears to be important. The duration of ischemia was thought to be significant by the Cleveland group (51). We should also note that six out of eight of Cohn's patients were bypassed within 3 hours of the occlusion (58). The importance of the duration of ischemia on the resultant heart function is also evident in animal experiments, Banka and co workers (68) reporting reversibility of abnormal contraction with restoration of

circulation within 45 mins. in dogs, and Maroko's group demonstrating some improvement in function in hearts revascularized at 3 hours, in contrast with those permanently occluded (69).

This concept of the possiblity of reversal of potential damage caused by ischemia within a critical time interval has a pathophysiologic basis.

7. THE TIME FACTOR AND THE UNSTABLE ZONE

With interruption of blood flow to the myocardium a series of changes are observed in myocardial cells which die when the flow is reduced to below that required to maintain vital functions. Within 10-15 seconds, the myocardium becomes cyanotic and cooler, and within 30 - 60 seconds, the injured area ceases to contract. Electrocardiographic changes appear, and hydrogen ion accumulates, as the affected cells shift from aerobic to anaerobic metabolism. In studies in which the posterior papillary muscle (in dogs) was rendered ischemic by occlusion of the circumflex branch of the left coronary artery (70,71), minimal morphological changes were noted with occlusion of 15 mins or less. There was a progressive loss of glycogen and relaxation of myofibers which were gradually followed by extreme myofibrillar relaxation, marked nuclear chromatin

margination, widespread mitochondrial changes, disorganization of sarcoplasmic reticulum and disruption of the sarcolemma. These latter changes are associated with irreversible cell damage despite minimal light microscopic changes (71).

In animals surviving the initial period of ischemia, it was observed that no dead cells could be found in papillary muscles ischemic for less than 20 mins. With longer periods of ischemia, the scattered dead cells increased in number, such that most were dead by 60 minutes. Other investigators have not found areas of necrosis even after 30 mins ischemia (72). This may be because the artery (in this case LAD) was occluded more distally, producing a smaller ischemic area, or because of difficulty locating focal areas of necrosis noted with shorter periods of ischemia. Presumably a very small area deprived of normal blood supply may survive on nutrients from the peripheral tissue. This may play a part in the case of well developed collaterals around the area supplied by the occluded vessel.

In any case, it would appear that when the duration of ischemia exceeds 20 mins, focal areas of irreversible change begin to appear in the center of the region supplied by the occluded vessel. If the myocardium is ischemic for 60 mins or longer, these areas spread to reach a final "maxi-

mum" area of infarction equal to that produced by permanent occlusion. It is also evident from these studies, that restoring blood flow before this "maximum area" has developed will prevent progression of the extension of irreversible change, and preserve some viable muscle.

In another study (72), ischemia of less than 45 mins, produced by occluding the LAD coronary artery in dogs, showed no histologic evidence of necrosis. Using nitroblue tetrazolium to stain the ischemic heart, O'Brien (73) concluded that histochemical changes occurring during a one hour period of occlusion were reversible by a two hour period of restored blood flow.

Arno King (74) studied the cat heart with intravital staining and showed that all ischemic areas seen within 5 mins of release of 30 mins LAD occlusion recovered 15 - 60 mins after revascularization in all hearts, whereas with 60 mins ischemia recovery was noted in only 50%. With 120 min ischemia, all were abnormal when studied up to 6 hours post revascularization. This study thus showed less residual damage with earlier revascularization. Arnold (also studying cats) found an increasingly larger area of permanent damage (examining hearts at six weeks after occlusion) with increasing duration of ischemia,

till about 6 - 8 hours of ischemia, at which the damaged area nearly equalled that produced by permanent ligation (75). Implicit in these observations is the development, with ischemia of increasing duration of a gradually expanding central area of necrosis, surrounded by a zone of reversible change, which is gradually decreasing in size.

Maroko (69) mapped out the area of injury using the S-T segment of the E.C.G. as an index, and found that at one week it was 60% of the size predicted from the acutely injured area (permanent occlusion), whereas in those reperfused at 3 hours it was only 10% that size. Using dehydrogenase enzyme staining to determine the evolution of this zone, Cox (76) found a significant area of reversibly damaged tissue at 18 - 24 hours, while (by electron microscopy) Wilcken demonstrated signs of regeneration of myocardium as long as three weeks after the onset of ischemia (77).

This potentially reversible zone could be salvaged by early revascularization, preserving some functioning muscle. Hence the importance of investigating the critical time interval during which the value of preserving functioning heart muscle will outweigh the dangers of the operation.

8. THE CRITICAL TIME FACTOR FOR REVERSING THE EFFECTS OF ISCHEMIA ON THE HEART

With these thoughts in mind, we have planned to study the effect (on the heart) of the restoration of blood flow after variable periods of ischemia. Since the two main causes of death from myocardial infarction are arrhythmias and pump failure, we have followed the response of the heart in two ways:

(1) Studying changes in electrical stability of the canine heart using Shumway's method for determining ventricular fibrillation thresholds (78). The threshold for fibrillation was measured prior to coronary artery occlusion, during a period of occlusion of variable duration, and following release of the occlusion.

(2) Evaluating mechanical changes in heart function (studying the heart as a pump), using a measure of contractility derived from the left ventricular pressure curve. This second part was first carried out in our laboratory a year ago by Dr. J.F. Symes using cats (79). Symes performed thoracotomies on five groups of cats: a control group in which no coronary artery was occluded; three temporary ischemia groups in which the left anterior descending artery (LAD) was occluded (just

distal to its origin) for periods of a half, two, and four hours; and a permanent occlusion group in which the LAD was permanently ligated. The left ventricular pressure record was obtained by means of a catheter inserted into the left ventricle, and was studied during the period of occlusion and for a half hour after release of occlusion in the temporary ischemia groups. The control and permanent ligation groups were studied for a period of one hour. At the end of this initial study the chest was closed and all animals saved for restudy at six weeks.

He found that at six weeks the impairment of contractility produced by ischemia of 30 mins was completely reversed. A significant difference was found in comparing contractility of the control and two hour ischemia groups, and this was more marked in the four hour ischemia group. The hearts permanently ligated showed impaired function of the same degree as those ischemic for four hours. Symes concluded that revascularization of the infarct at 30 mins of ischemia completely reversed the effects of ischemia. Revascularization partially reversed the effects of two hours ischemia, but affected the heart very little if the period of ischemia lasted four hours.

This experiment was repeated in order to extend the study of cardiac mechanics during the early post-revascularization phase, and to equalize the duration of the initial operation in all groups. Seeing that this present study was meant to complement the one already done, we have kept close to the original protocol, even though it appeared, during the course of the experiment, that a somewhat different method (particularly with regards anesthesia) would have been preferable.

In the following chapters we shall deal separately with the Study of Ventricular Fibrillation Thresholds, and the Study of Cardiac Mechanics.

CHAPTER II

VENTRICULAR FIBRILLATION THRESHOLDS

1. INTRODUCTION

Ventricular fibrillation frequently follows coronary artery occlusion in dogs, especially a high occlusion (80), the ventricular ectopic activity being maximal during the first few hours (81), with ventricular fibrillation (VF) usually occuring within 48 hours (80). Ventricular fibrillation thresholds (VFT's) were studied by Wiggers and Wegris about forty years ago, comprising the first quantitative study of electrical stimuli applied directly to the heart, and adjusted to fall in the vulnerable period of the cardiac cycle (82), the VFT being the smallest electrical stimulus applied directly to the heart (in this case the canine heart) precipitating VF. At that time, procaine was shown to raise the VFT.

This model was modified by Shumway, resulting in effect in a circuit (connected to stimulating electrodes) triggered by the electrocardiogram of the animal, producing a stimulus of known strength and duration, the position of which in the cardiac cycle could be adjusted (78).

Using this method, studies have demonstrated fairly constant thresholds with repeat testing for the same dog, under constant conditions (83). A direct relationship was noted between temperature and the VFT from 23 - 40°C (83), and a

drop in the VFT with acidosis (pH in area of 7.1) (84). Cigarette smoke lowered it in dogs (85), as did caffeine in large intravenous doses (86). Lignocaine and bretyllium were demonstrated to raise the VFT (87), the effect of the intravenous lignocaine rather brief (10 - 15 min), as the blood levels of the drug dropped rapidly.

The drop in VFT following coronary occlusion was partially reversed by an infusion of destrose insulin and potassium (88), corresponding well with its suggested effect decreasing infarct size (89).

A previous "revascularizing" procedure (e.g. Vineberg) minimized the drop in VFT with LAD coronary artery occlusion (90), as has infarctectomy (91). The rise in VFT in chronic experiments (two months post ligation) might be secondary to impaired conduction in the area of fibrosis (92).

No studies of the early period covering the release of occlusion (i.e. revascularization) have been reported, and in this study we have attempted to show the effect (on the VFT) of restoring blood flow after LAD occlusions of one and two hours in dogs, compared with VFT's measured during a three-hour occlusion.

2. METHOD

Twenty-nine mongrel dogs of both sexes, weighing 9 - 23 kg were anesthetised with nembutal (30 mg/kg), and ventilated with 100% oxygen using a Harvard Pump, while an IV with normal saline was kept open. Additional anesthetic was given during the procedure when necessary, in doses of 50 mg amounts. Temperatures were measured using an esophageal thermometer and maintained within 1 1/2°C of the preoperative temperature. A thoracotomy was carried out through the left fifth interspace, the pericardium opened, and VFT's measured following Shumway's method (78).

The apparatus (Fig 1) consists of an S_4 grass stimulator triggered by the QRS of the animal, firing a DC stimulus of known strength after a preset delay. The stimulus impulse and electrocardiogram can be viewed simultaneously by means of the oscilloscope which receives the QRS impulse and feeds it into the trigger circuit. The use of this apparatus is further described in the procedure.

The model is shown in Fig 2, with the subject and operator in the centre, the stimulator and oscilloscope on the left, and the grass polygraph in the background. Stimulation of the heart was carried out in the area supplied by the coronary

artery (LAD) ligated (Fig 3) using stimulating electrodes consisting of two 30-gauge needles imbedded 1 cm apart in a silastic block leaving the terminal 2 mm of the needles bare. The LAD coronary was occluded using a snare with a loop of 0-silk, approximately 2.5 cm from its origin. ECG leads were connected and the ECG tracing monitored on a two channel oscilloscope. This signal was fed into a grass model S_4 stimulator, which then fired a stimulus (DC) of known amplitude and duration, at a preset delay from the QRS of the ECG tracing. Fig 4 (a) is a picture taken of the two tracings on the oscilloscope, the lower stimulus potential inducing a spike in the upper ECG tracing. By gradually increasing the current strength, and sweeping the interval of the cardiac cycle (which was done for each determination, to ensure applying the stimulus during the vulnerable period), we can obtain a measure of the smallest stimulus producing ventricular fibrillation (VF). This is the threshold stimulus producing VF, or the ventricular fibrillation threshold (VFT). The duration of the stimulus was a constant 12 mscc, and the amplitude was measured in millimeters on the oscilloscope screen (the impulse could be recorded on photographic film during the procedure, (Fig 4 (b)) and the current calculated from the formula:

$I = \frac{E}{R}$, where I = current in amps

E = scope height of stimulus in cm

R = constant circuit resistance (10 ohm)

Following the production of VF, the heart was immediately defibrillated using an AC defibrillator (1/10 sec, 125-175 v), no drugs being used in resuscitation. After the determination of the control VFT for each heart, the LAD artery was occluded for a variable period of time, and VFT's were repeatedly measured every 15 - 30 mins throughout the three-hour period during which the hearts were studied.

The animals in this study were divided into the following groups:

1 - Permanent occlusion (5 animals)

2 - 60 minute occlusion (6 animals)

3 - 120 minute occlusion (5 animals)

The remaining 13 animals were excluded because they either failed to resuscitate after the control or first post-occlusion VFT determination (8 animals), or else had been studied for occlusion periods which did not fit into the above groups (5 animals: no occlusion, 15 min, 30 min, 45 min, and 135 min occlusions).

Blood gasses were measured at the start of each experiment and prior to alternate determinations. The animals were sacrificed at the end of the experiment.

3. RESULTS

A. Permanent Occlusion Group: (Fig 5)

In this group, as in all the others, VFT's are plotted as percentages of the control value (for each heart) against time, the occlusion following immediately after zero-time. In this group the VFT dropped initially to 30 - 40% of the control value, rose a bit after the first hour, and then remained at around 50% during the period of study (3 1/2 hour post occlusion).

B. 60 Minute Occlusion Group: (Fig 6)

In this group the drop in VFT during the occlusion period is comparable to the corresponding period of the permanent occlusion group, but, following release of the occlusion (at 60 min), the VFT rose progressively towards control values, reaching 90 - 100% at three hours.

C. 120 Minute Occlusion Group: (Fig 7)

Here, again, the VFT's remained at levels comparable to those of the permanent occlusion group during the period of occlusion, but rose to 90-100% of the control during the hour after release.

In Fig 8 the mean values for each 30 min interval

(for each of the groups) are plotted, giving a composite graph, demonstrating the changes in VFT with revascularization of the infarct. A significant difference is seen between the hearts permanently occluded and those revascularized ($P < 0.01$ for permanent v/s temporary occlusion, using the Kruskal-Wallis Test). There was a tendency for easier resuscitation in the lighter dogs (Fig 9) ($P < 0.05$, using the Rank Sum test for unmatched groups). It should be remembered that these were mongrels and the population small.

D. Blood Gas Studies:

Average for groups: pH 7.36; PO_2 368.5, PCO_2 28.4. Only one animal was markedly acidotic, with an average pH 7.09 and lowest 6.99. This was in the 60 min occlusion group and survived till the second post-release determination, VFT's being similar to those measured for other animals over the same period.

4. DISCUSSION

While the number in this series is small, all the hearts in the temporary occlusion groups followed closely the trend of reversal of ischemic electrical instability towards normality, soon after revascularization of the one or two hour old infarct. Clinically, patients do not present with an identical level of occlusion or a standered preinfarction functional level. They have different degrees of coronary artery disease before the episode of acute infarction, differences in collateral circulation, and differences in the basal level of electrical stability. Hence, extrapolation of these findings to the situation in humans should be made with caution.

In the study of the effect of glucose-insulin-potassium on the VFT's in permanent coronary occlusion, Danielson found that the controls showed a rise of the VFT to close to 75% of preocclusion values after occlusion of four hours, (88). It has already been observed that in chronic coronary occlusion (92) VFT's were normal at six weeks, (probably because of fibrosis of the infarct), so the importance of reversing instability would be in the acute stage. Ecker reported the successful use of coronary revascularization in treating in-

tractable ventricular tachycardia (VT) in a 61 year old man, two months after an acute myocardial infarction (93A). In the coronary care unit, more than 20% of patients with acute myocardial infarction developed VT, and almost a quarter of those with at least one episode of VT developed ventricular fibrillation (93B). Drug therapy can be expected to convert 78% of cases of VT to normal rythm (93C). Cline recently reported aorto-coronary bypass procedures carried out in two patients following resuscitation from ventricular fibrillation occurring during the early stages of treadmill testing. Postoperatively, they were able to perform moderate exercise without electrocardiographic abnormalities (93D).

Our model demonstrates the effect of aorto-coronary bypass on changes in electrical stability caused by acute infarction. This model can also be used to study the effect of drugs and metabolic and environmental changes on the electrical stability of the heart during acute infarction, and with revascularization.

CHAPTER III

STUDY OF CARDIAC MECHANICS

The aim of this study was to investigate the effect of early revascularization of the acute infarct on contractility of the heart, studying it during the ischemic and early post-revascularization periods, and again after healing of the infarct.

A similar study was carried out in our laboratory a year ago by Dr. J.F. Symes (79), who found, using cats, that at 6 weeks the impairment of contractility produced by ischemia of four hours was almost equal to that produced by a permanent occlusion, (see section 8 of INTRODUCTION). The basic purpose of this part was to complete that work, and, in particular, extend the study during the early post-revascularization period.

Seeing that this present study was meant to complement the one already done, we have kept close to the original protocol, even though it appeared, during the course of the experiment, that a somewhat different method would have been preferable.

Any differences between protocols will be pointed out in the section on "Methods", and again reviewed in the "Discussion".

1. EXPERIMENTAL DESIGN

A. Choice of Experimental Animal

While most studies of myocardial ischemia have been carried out with dogs, they are not ideal subjects for all types of experiments for a number of reasons. They show considerable variation in distribution of coronary arteries, so that occlusion of a major artery at a fixed point from its origin will produce infarcts varying in size in different animals (94). In addition, dogs develop ventricular arrhythmias very frequently after coronary occlusion, especially a high occlusion (80), VF occurring in 40% of hearts with LAD coronary occlusion and over 50% with left circumflex occlusion.

Our study requires an infarct large enough to produce significant hemodynamic changes without resulting in fatal arrhythmias. Krug chose the cat for his experiments because he found it less vulnerable to electrical instability (74). Studies done by Dr. I. Arnold in our laboratories two years ago suggest that fairly reproducible infarcts could be produced in cats with ischemia of equal duration (75). Because of this apparently uniform response to coronary ligation and the increased cardiac electrical stability, the cat was chosen as the experimental animal.

B. Assessment of Ventricular Function

A considerable amount of research has been done to find valid and accurate means of measuring ventricular function quantitatively. Despite considerable refinements in techniques, the ideal parameter of ventricular function still eludes us (95), and the different clinical and research workers select from a large variety of parameters available.

In general these fall into two main groups: those describing the heart as a pump, such as end diastolic pressure (EDP), dp/dt, stroke volume, stroke work, cardiac output, ejection fraction, and ventricular function curves. These are all influenced by the leading conditions of the heart, reflex mechanisms, endogeneously produced inotropic infarcts, and heart rate. The need to study the contractility of the heart uninfluenced by so many variables led to the study of the heart as a muscle (often using a papillary muscle) with the aim to arrive at a parameter, mainly, if not solely, dependent on myocardial contractility. Some of these measures of contractility based on studies of isolated papillary muscle have lately been applied to the heart as a pump (studying LVP curves), a not completely logical step.

As EDP was clearly influenced by factors other

than contractility (96), in particular venous return, the rate of rise of ventricular pressure (dp/dt) (Fig 10) was regarded for a while as an adequate measure of left ventricular function. However, dp/dt increases with a rise in EDP (equivalent to preload in isolated muscle experiments), with an increase in aortic systolic pressure (afterload), with an increase in heart rate, or with inotropic agents (increasing contractility) (97). If the action potential is not transmitted through the normal conducting system (e.g. arrhythmia or ventricular pacing), the ventricle is depolarised less uniformly and the contraction less efficient (dp/dt drops).

This led to the calculation of the maximum intrinsic velocity at zero load by Sonnenblick in 1962 (98) who called it Vmax and described it further a few years later (99).

Deprivation of Vmax

A.V. Hill's work on skeletal muscle forms the basis of the early work on muscle mechanics. He originally proposed a two-component muscle (Fig 11A) which was later modified to from Maxwells three-component muscle (Fig 11B) consisting of:

(1) A contractile element (CE) - Freely extensible at rest but which can develop force to shorten when activated;

(2) A passive elastic element (SE) in series with CE;

(3) A parallel elastic element (PE) in parallel with CE + SE, and responsible for maintaining the resting length of CE (100).

In using this model to study contractility, it is assumed that the model can be applied to cardiac muscle and that during the period of isovolemic contraction, alterations in ventricular geometry are minimal. Based on these assumptions Vmax is calculated as follows (98,99). During isovolumic contraction, the rate of force development (dp/dt) is equal to the velocity of shortening of the contractile element (VCE) times the rate of stretch of SE (VSE) or,

(1) $dp/dt = VCE \times VSE$;

Experiments in skeletal muscle and cardiac muscle have shown that the stress-strain characteristics of SE form a curve, the shape of which is a linear function of developed pressure (p). Developed pressure in this case equals isovolumic pressure minus end diastolic pressure. Thus,

$VSE = KP + C$, where K and C are constants

Substituting in equation (1) and solving for VCE:

(2) $$VCE = \frac{dp/dt}{KP + C}$$

The value of C is very small in comparison with KP and can

thus be ignored. K is a constant of known value and has been shown to be equal to 30 in cat papillary muscle (101). Therefore, for our purposes, the contractile element velocity (VCE) can be calculated, by knowing the values for dp/dt and P during isovolumic contraction. The force-velocity relation is then derived by plotting VCE against P at various time intervals over the course of the isovolumic portion of contraction (Fig 12 top). From the curve thus plotted (Fig 12 bottom), the peak VCE can be determined, and when it is extrapolated to P = 0 (no load), the maximum velocity of contraction (Vmax) is obtained, and is apparently not affected by a change in load, although inotropic agents clearly raise it. Vmax thus calculated is still affected by heart rate (direct relationship) (102).

Criticism of Vmax

While Vmax has been applied to clinical situations (103,104), recent work suggests it is not the long sought-for ideal measure of contractility.

According to Pollack (105), Sonnenblick's data (98) assume that AV Hill's two-element muscle could be applied to cardiac muscle, and when these data were reanalysed adjusting for a three-element model (106) hyperbolic force-velocity curves were rarely found in cat papillary muscles. Pollack

found that Vmax of the CE, unlike that of muscle fibers, is not independent of fibre length but increases at least 50% for a 25% increase in fibre length (105).

In addition, when force-velocity points measured at different times in the contraction are used, different amounts of internal shortening of the CE will have occurred at the time the muscle begins to shorten, so that force-velocity points, although measured at nearly the same muscle length, pertain to different CE lengths (107). Using a quick-release method, Noble (106) found the Vmax was length dependent, and that hyperbolic relationships were not found at lengths appreciably below Lmax (muscle length at which peak isotonic systolic force minus diastolic force is a maximum). This appears to agree which the observation that at the length at which maximum active tension is developed, the passive tension applied to the preparation of skeletal muscle is about zero, whereas in cardiac muscle it is 50 - 80% (or more) of the active tension (108). Recently, Brutsaert has reported studies on isolated cat papillary muscles at close to Lmax (107).

We should remember that these measurements are based on studies of isolated papillary muscles and not on the whole heart.

The calculations have been greatly simplified by the use of computers (109).

More recently, other measures of contractility have been suggested for the whole heart, such as Emax (110) which is proportional to the ratio of the time varying instantaneous pressure P (t) to instantaneous volume V (t). It has also been suggested that in clinical practice the mean velocity of circumferential shortening (Vcf) by cineangiography allows better distinction of normal from abnormal patients, with less overlap than obtained by Vmax measurements (111). This measure of left ventricular performance is readily obtainable during diagnostic cardiac catheterisation (112).

The weight of these opposing views was appreciated more towards the completion of the study of cardiac mechanics, and for this reason, as well as the fact that the initial plan for this study was to complement the previous one, the parameter of Vmax was retained and followed together with changes in dp/dt.

2. EXPERIMENTAL METHOD

A. Procedure

Seventy cats of both sexes, weighing between 1.5 and 4.5 kg were used. Each cat was anesthetised with intravenous nembutal at a dosage of 30 mg/kg body weight. Seeing that the operations were considerably longer than in the experiment reported last year (79) (see section below on Groups), additional anesthetic was invariably needed and given as a quarter to three-quarters of an ml of nembutal (50 mg/ml). The cats' temperature was maintained by the use of a heating pad as well as periodic instillation of warm normal saline in the chest cavity. The cats were intubated and ventilated with 100% O_2. All procedures were carried out under sterile conditions. 20 cc of 5% dextrose in water were injected subcutaneously before operation and again after skin closure.

With the animal positioned on its right side, the chest was entered through an incision over the left fifth interspace. The use of a small rib retractor allowed good exposure without the necessity for rib resection. The pericardium was then incised and the edges sutured to the chest wall to form a "pericardial cradle" affording ready access to the anterior descending coronary artery and the left

ventricle. The bifurcation of the coronary artery was then carefully dissected and a ligature of 2-0 silk placed around its anterior descending branch just distal to the bifurcation. By means of a snare it was possible to occlude and release this vessel at will. An 18 guage needle was then inserted into the cavity of the left ventricle by direct puncture and connected via a #90 polyethylene catheter to a Statham P23Db pressure transducer by means of which the left ventricular pressure pulse was recorded on grass multichannel recorder at a paper speed of 100mm/sec. The catheter was intermittently flushed with heparinized saline to maintain patency.

End diastolic pressure was measured directly from the high fidelity left ventricular pressure pulse. In addition, by means of a resistance-capacitance differentiating circuit, the instantaneous first derivative of the pressure pulse dp/dt was recorded simultaneously on an adjacent channel. Thus, from the isovolumic period of each contraction, the peak contractile element velocity and Vmax could be determined as described previously.

In each experiment, control recordings were made and followed by the appropriate interventions. Recordings were carried out for a period of four hours starting with

the onset of ischemia. The chest was then closed in layers and the animal saved for follow-up study at 6 weeks. At that time repeat measurements were made, again with the chest open, and the animal then sacrificed. At post-mortem each heart was evaluated grossly and histologically for the presence and degree of myocardial damage. Animals dying before the six week period was up were autopsied, and the lungs and heart were studied in an attempt to explain the cause of death.

B. Groups (fig 16, Table 1)

Group A - SHAM OPERATION (12 cats) - The entire procedure was carried out but the coronary artery not occluded, to determine the effect of the operation on ventricular function. In this group, as in the others, the chest was left open for 4 hours (after insertion of the catheter-needle into the left ventricle) during which LVP and dp/dt were recorded. In the experiment previously reported (79) the chest was left open for a total of only one hour in the SHAM OPERATION and the PERMANENT LIGATION groups and long enough to take readings up to 30 minutes following release of the occlusion in the temporary ischemic groups (i.e. one-hour in the 30 minute occlusion group, two-and-ahalf hours in the two-hour occlusion group and four-and-ahalf hours in the four-hour occlusion group). This

resulted in a brief study of the early post-release period, as well as markedly different duration of operation in the different groups, bringing in an extra variable - that of duration of open chest operation.

Group B - PERMANENT LIGATION (18 cats) - in which the artery was permanently ligated with 3-0 silk to provide comparison with the next two groups.

Group C - TWO-HOUR OCCLUSION (19 cats) - occlusion released after two hours ischemia.

Group D - FOUR HOUR OCCLUSION (21 cats)

The last two groups were chosen to cover the minimal ischemic period which was thought practical in terms of clinical application of the procedure. All the cats operated on have been included in the above groups (including early deaths from anesthesia or arrhythmias, and late deaths from congestive heart failure and pneumonia) because all must be used in the analysis, even though the initial study plan was meant to investigate the long term results of the operation - hence the unequal numbers in the different groups.

C. Antibiotics

Chloramphenicol (10 mg/kg) was injected intramuscularly before operation (in most animals, but in a few

immediately after), and once a day for the first two post-operative days. In the event the animals developed a respiratory infection, this was given for a further 4-5 days, as recommended by Dr. Lord (113). Towards the end of the experiment, we became aware that in dogs the combination of chloramphenicol and nembutal is associated with prolonged anesthesia (114). Because of excessive drowsiness in the cats postoperatively (lasting 2-3 days), and a number of early postoperative deaths presumed to be caused by respiratory depression, the chloramphenicol was discontinued during the operative period and replaced by tetracycline (115) or Penicillin G. This was carried out in the last 15 animals which will be reported separately. The antibiotic used by Dr. J.F. Symes was a tetracycline (116).

D. Modifications in Anesthesia

Because of an unacceptable number of (presumed) anesthetic deaths, the procedure was reviewed during the course of the experiment, at which time it became apparent that in the previous experiment using cats, there was high mortality rate in the group (4 hour occlusion, see GROUPS above) with an operative duration comparable to that of our groups (116). Many of these animals had received additional

doses of nembutal. It should be remembered that cats, unlike dogs, sleep for 24-72 hours after nembutal anesthesia (117).

For these reasons, a number of modifications were instituted in the method of anesthesia and postoperative care*:

(1) prolonged postoperative ventilatory assist (up to 5-6 hours),

(2) the use of methohexital (ultrashort acting barbiturate with almost 25%/hour metabolism in humans (118)) in a dose of 5 mg/kg IV if additional anesthetic was needed, given as seldom as possible. These changes were made for the last fifteen animals.

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* These modifications had to be minimal in order to maintain an acceptable degree of similarity between procedures carried out in all animals, so that they could all be analysed together, and so the recommended inhalational anesthetic (Halothane and nitrous oxide) to be used in combination with a short acting non-barbituate inducing agent such as ketamine (119) could not be instituted, despite its superiority over our existing method of anesthesia.

E. Arterial Patency

The question arises as to whether or not the vessel occluded to produce temporary ischemia is truly patent after release of the occlusion, and functionally so during the postoperative period. It is conceivable that with occlusion, trauma to the intima, or clotting distal to it (occlusion), should result in a degree of permanent obstruction. This would make valid comparison with the "permanent ligation" group impossible.

In the previous experiment (79) vinyl acetate was used to inject the arteries at 6 weeks. This hardens rapidly and so requires force in injection. With forcible injection the material may be seen to emerge from the venous side of the coronary circulation. While this may dislodge a thrombus in the arterial tree, it should not traverse a completely organized solid length of artery.

Latex solutions have been used similarly (120). Using a somewhat different approach, microspheres could be injected in the coronary artery, chosen to have a diameter that would preclude passage through capillaries. In this case, gross examination of the heart would hold no advantage over vinyl acetate or latex injections which would also be

seen to fill surface vessels. However, a suspension of particles small enough to leave the capillary bed would allow us to visualize the perfused tissue. Autoradiography (121) would be costly and the technique require considerable experience for consistent results to be obtained.

Arterial patency (after release of occlusion) was evaluated in two ways:

(1) during the initial operation: with release of the occlusion, the artery (LAD) distal to it was observed to distend, and the previously bluish muscle became pink again. This occurred within 1-2 seconds in the case of the 2 hour occlusions, but a few seconds later in the 4 hour occlusions, where the area was left with a brownish discoloration.

(2) at six weeks: vinyl acetate or latex were used to inject the left coronary artery of the animals with 2 hour, 4 hour, and permanent occlusions. Those occluded temporarily were patent at 6 weeks by these methods. In addition, a suspension of charcoal particles of diameter 20-30 mμ ("Pelikan Ink") was used.

Ink injection study: One cc of the suspension was injected into the root of the aorta in vivo (at the time of the second operation) (Fig 13 is a diagrammatic

representation of observations with this method; Figs 14 A-D are pictures of in vivo injected hearts). When this is done in the normal heart, the ink passes into the coronary arteries at physiologic pressures, and passes through the capillary wall staining the perfused muscle (black). This occurs within 1-2 heartbeats from the time of injection. Within another 4-5 beats it is cleared from the tissue spaces leaving a grossly normally coloured heart. Microscopically the "dark" heart shows charcoal particles lying diffusely between the muscle fibres (Fig 15).

In a heart with acute LAD artery occlusion, a pale area is left in the distribution of the occluded artery during the perfusion phase. During the clearing phase the rest of the heart clears as in the "normal", while the pale area darkens as particles spread into it. Then follows the clearing phase for the ischemic area which takes 10-15 mins, probably because of poor flow and contraction.

In a heart with a chronically occluded LAD artery, the infarct remains pale as the rest of the heart clears. Microscopically a few particles may still be seen in the infarct (if the heart is excised before it clears completely) the quantity varying with the degree of fibrosis.

Hearts with temporary coronary occlusions, studied at 6 weeks all showed the "normal" picture (see above), indicating unimpaired perfusion.

3. RESULTS

A. General Findings

In the sham operated group, the procedure was well tolerated generally, and no significant changes in the appearance of the heart nor the parameters measured were seen.

In contrast, occlusion of the LAD artery in the three ischemia groups was generally followed within a few minutes by marked changes. The area of the ventricle supplied by the LAD quickly became cyanosed and within 2-3 minutes lost contractile activity. Paradoxical bulging was not noted in any of the animals.

Release of the occlusion in the two temporary ischemic groups resulted in restoration of blood flow, which was readily apparent from distention of the artery and clearing of cyanosis following some initial hyperemia.

At the time of the six week follow-up, a few adhesions were found in the chest but no visible myocardial damage was seen in the control animals. In the occluded animals, in addition, pleural effusions (2-10cc) were found, and whitish

fibrotic patches in the area of distribution of the LAD coronary artery. These "final infarcts" covered 1/10 - 1/3 of the anterior surface of the heart with microscopic findings corresponding with an infarct of that age, the scar replacing a quarter to almost full thickness of the ventricular wall, and occasionally extending into the septum.

In hearts with permanent LAD ligation, the gross infarct was a half to two thirds the size of the initial cyanotic area ("initial infarct") not unlike Maroko's observation in dogs (69). In those temporarily occluded (2 and 4 hours) the final infarct was 1/10 - 1/3 the size of the initial one.

While these observations were made generally in the animals studied, variations were also noted, significant both in frequency and in degree, and the linear relationship between infarct size and duration of ischemia (up to 6 hours occlusion) described by Arnold (75) was not demonstrated in those studied at 6 weeks.

Variations

There were variations in the relative sizes of the branches of the left coronary artery, occasionally

marked (1/10), the left circumflex branch appearing on the left heart border, extending anywhere from half of the border to the whole of the left heart border including the apex, the LAD branch being proportionally smaller. Similar variations were described by McNamara et al (122) recently in a comparison of monkeys and man. In both groups, the LAD artery was non-dominant (ending above or at the ventricular apex) in about 55%, and dominant (extending into the posterior interventricular groove) in about 45% of hearts studied. There were also corresponding variations in the sizes of the initial cyanotic area ("initial infarct") and the final infarct, so at this point we would expect proportional changes in the resultant functional defect. As a matter of fact, out of two consecutive "PERMANENT" occlusions done on the same day (#61,#62), one barely showed a cyanotic area, while the other showed a large clear infarct and expired on the table with edema fluid pouring out of the tracheal-tube.

This poses a problem, because we want to compare long-term changes in contractility produced by saving functioning myocardium by early revascularization (with the to result in a smaller final infarct), but are starting out

with "initial infarcts" of markedly variable size.

B. Morbidity and Mortality

The overall mortality (all groups from all causes) was 72.8%. This can be analysed by group and by cause of death.

Causes of Death

1. Ventricular Fibrillation (VF): 25.8% of all animals in the ischemic groups died of VF. Deaths from VF made up 29.4% of all deaths from all causes. These include animals fibrillating on the operating table (observed) as well as those dying in the immediate postoperative period while still on the respirator at which time it was felt that an arrhythmia (including arrest) was the most likely cause of death. VF usually occurred within 1-2 hours of coronary occlusion, but two (in the 2 hour group) occurred within 15-20 mins of release of occlusion.

2. Anesthesia: (23.5% of all deaths). Post-operative respiratory depression was presumed to be the cause of death in those dying within 24 hours (and usually 1-2 hours) of being taken off the respirator. These almost invariably had received additional doses of anesthetic during the procedure, were very drowsy postoperatively, and examination

of the lungs at autopsy did not show evidence of pulmonary edema or pneumonia. Clearly, some arrhythmias belong to this group, and in any case, would feature in death from respiratory depression. The percentage of deaths from all causes classed as "anesthetic" deaths in the first 50 cats was 29. Of the last 15 animals, for which additional precautions were taken (see Modifications in Anesthesia, under METHODS), it was only 10%.

3. Congestive Heart Failure (CHF) (25.4% of all deaths): These animals usually showed marked shortness of breath on exertion without nasal discharge, and, at autopsy, cardiac enlargement and pleural effusions, with typical microscopic appearance of pulmonary edema in the lungs (Fig 18 shows the appearance of normal cat lung and Fig 19 the high power view with pulmonary edema). This group lessens the validity of analysis of the survivors - we wish to compare heart function at 6 weeks, but those with the poorest function are eliminating themselves from the study.

4. Pneumonia (17.6% of all deaths): These animals had serous to mucopurulent nasal discharges while still living, and on examination of the lungs (at postmortem), gross and microscopic evidence of pneumonia (Fig 20 A,B).

Mortality by Group

On reviewing the deaths, (Fig 21) it was apparent that those classed as "anesthetic" showed no predilection for any group, and that the incidence of VF was also unrelated to the duration of coronary occlusion. In an attempt to separate out deaths that could readily be related to the coronary occlusion, mortality was calculated per group, not counting deaths due to anesthesia or arrhythmias. This leaves us with deaths with CHF (logically associated with coronary occlusion) and pneumonia (which is more frequent, and more poorly tolerated in the presence of CHF).

The highest mortality (69.2%) occurred in the permanent ligation group followed very closely by the 4 hour occlusion group (63.6%). Mortality in the two hour group was 50.0% to be compared with 22.2% mortality in the Sham operated group. Very interesting to note was the number of deaths of animals not subjected to any operative procedure or anesthesia. 10% of all animals brought to the lab died of natural causes within 2-3 days of arrival. Most of these fit clearly into the "PNEUMONIA" group, one of them having multiple lung abcesses, as seen in Figs 22 A-C. While these cannot form a true "second control" group they

give us an impression of the physical condition of the animals used in this experiment.

C. Mechanics

Only animals surviving the six week period are included here (viz, 7,4,4,4, in Sham, 2 hr, 4 hr and Permanent groups respectively). Two of these (one 2 hr occlusion, one 4 hr occlusion) were excluded because of technical difficulty analysing the pressure tracing.

In Fig 23, Peak dp/dt is plotted against time, control readings taken before occlusion which occurred at zero time. Each point represents the average for all animals in a particular group at that time, readings (calculated in triplicate) taken before occlusion, immediately after occlusion, hourly for 4 hours after occlusion and again at 6 weeks. The sham operated animals showed a slight drop of Pdp/dt over the period of study. The ischemic groups all showed an immediate drop of Pdp/dt (by about 30%), and then some fluctuation, all ending somewhat lower than at the start. However, there is considerable variation at 1 and 2 hours, even though the three ischemic groups should be comparable during this period.

The Vmax course (Fig 24) is not unlike that of

peak dp/dt. Again, there is an immediate drop (about 20%), followed by a rather variable course. While the group permanently ligated showed lowest Vmax at 6 weeks, we should note that those animals also showed lowest Vmax at 2 hours occlusion, at which time values for the 2 hour and 4 hour groups compared favorably with values of the sham group, even though the three ischemic groups had all been subjected to ischemia of equal duration at that time.

4. DISCUSSION

In this section I shall discuss the methodological differences between this experiment and the one reported by Symes (79) with the aim to explain differences in the results; next the problems encountered in the experiment, the sources of error, difficulties in interpretation, and factors detracting from its statistical validity; and, finally, the results, and suggested changes to be considered in any future study of this type.

(A) Methodological Comparison of Two Experiments;

1. Length of operation: As described under METHOD, animals were studied for a period of 4 hours after the control readings were made, resulting in a "chest-open" duration of about 5 hours, in contrast with the previous study where (other than in the group with 4 hour occlusion) "chest-open" time ranged from 1-2 1/2 hours only. This lengthened operative time alone is expected to result in greater deterioration of the animal (predisposing to a higher mortality), apart from the problem of the invariably required additional doses of anesthetic in the longer operations.

The longer "early" study, and, more important, the

extension of operative time to be equal in all groups to that of the longest study (4 hour occlusion) to provide valid comparison between groups, was thus carried out at expense of an increased mortality rate in an already "critical" preparation.

2. Inclusion in results of mortalities: All animals studied are included in the results (see Morbidity and Mortality - RESULTS), allowing us to appreciate the significance of causes of death in animals not surviving the six weeks, and, in particular, the importance of those dying with CHF. The group of non-survivors was not reported in the previous studies, despite comprising one third of the animals operated on (116). The importance of this point is well brought out by the advice of R. Palmer Howard (123):

> "The great value of the examination of the diseased body after death is not sufficiently recognised. It and often only it, reveals the truth or error of the diagnosis formed. It and only it, will sometimes account for an anomaly observed during life, or explain the failure of treatment observed by the most experienced."

3. Drawing of the Vmax curves: Extrapolation to zero load (Fig 12) by means of a straight line, as opposed to the previously used curved line (convex upwards) which is more vulnerable to technical error and bias of the investi-

gator.

4. Preoperative health of animals: The high incidence (10%) of death from natural causes (see RESULTS - Morbidity and Mortality) was not noted previously (116), and suggests a population of experimental animals less capable of surviving the trauma of thoracotomy and coronary occlusion.

(B) Problems In Procedure and Interpretation:

1. The large number of deaths: This is better understood when we consider the "critical" nature of our preparation: coronary occlusion and thoracotomy of over five hours ((2)-(A)) in an animal vulnerable to respiratory disease. To this we must add: the rather feeble strain of the cats admitted to the lab (see D above), and the anesthetic hazard. The anesthetic hazard was discussed in the method under antibiotics and modifications in anesthesia, and includes the need for additional doses of anesthetic, and the synergistic effect of chloramphenicol on nembutal in an animal already very sensitive to nembutal anesthesia. With the discontinuation of chloramphenicol, the modifications in anesthesia, and the improvement in postoperative (respiratory) support, the %

of deaths from all causes presumed "anesthetic" dropped from 29% to 10% in the last fifteen animals.

2. Variations: (see Variations - RESULTS (1) General Findings). There was significant variability in the degree of dominance of the LAD artery with corresponding variability in the size of the infarct, the initial infarct ranging from an unclear minute cyanotic patch, to an area extending over 2/3 of the anterior surface of the heart. When we consider that the aim in this experiment is to demonstrate the functional (mechanical) change associated with a change in size of the infarct induced by early revascularization, it is apparent that variations of this degree and frequency preclude meaningful assessment of the course of functional change in these animals.

This is compounded by the deaths with CHF.

3. Elimination of animals dying with CHF: The self elimination of animals dying with CHF from the study of the long-term effects of early revascularization, deletes from the study those with the largest infarcts and the poorest heart function. We are thus left with animals with smaller infarcts and lesser derangements of cardiac function, the

size of the infarct and degree of functional impairment in turn related to the duration of ischemia, and the pre-existing variations in the coronary circulation.

At this point, the study loses statistical validity (124). Also, the variability noted in the course of dp/dt and Vmax, and the poor separation of groups (Fig 23, 24), is readily understood.

4. The measurement of contractility: This problem has two aspects: (i) the validity of the use of Vmax, and (ii) the technical part of derivation. The basis for Vmax has been questioned (105,106) - the value varying with heart rate and still dependent on EDP (preload). This has been discussed under EXPERIMENTAL DESIGN - Criticism of Vmax, where other suggested measures of contractility were reviewed. Technically speaking, the line to be extrapolated to zero (Fig 12) is not always straight, nor clear in direction, giving some leeway in the choice of the point of intersection.

The practice of calculating it in triplicate minimizes the error somewhat, but as each value falls between 1-30% (usually within 10%) of the mean of the three values calculated, the source of error is apparent. In our study,

the paper speed of the grass polygraph was set at a maximum (100 mm/sec), considerably below the optimum speed (200 mm/sec) needed for easy comparison of LVP and dp/dt curves. These errors would be consdierably minimized by the use of computers (109).

(C) Results

Because of the small numbers completing the study, variation within groups, poor separation of groups, and those dying with CHF, the course of contractility depicted in Figs 23, 24 must be considered with reservations and inferences made with extreme caution.

From the mortality rates, it would seem that a period of ischemia of four hours or longer is associated with as much functional loss as with a permanent coronary occlusion. In other words, restoration of circulation within less than four hours of ischemia, appears to preserve some heart function which is reflected in the survival of the animal.

(D) Suggested Changes

On reviewing this experiment, it is apparent that a number of changes in method would help us enhance the consistency and validity of our results.

The animal. As advised by Dr. Lord (113), the use of cats prepared for chronic experiments would improve survival rates generally. Also, from the practical standpoint, it should be remembered that cats are more susceptible to respiratory disease in the winter months, and thus would withstand operative trauma better in the spring and summer.

The anesthetic. As discussed in the METHOD, an inhalation anesthetic with a non-barbituate inducing agent would less likely be associated with marked postoperative respiratory depression, than repeated doses of barbituate during a long operation.

The evaluation of contractility. The best measurement for use is still unknown, though under these conditions a derivative of the left ventricular pressure pulse may still be most appropriate. The use of computers in deriving the measure of contractility would save a considerable amount of time that would otherwise be spent analysing individual curves, and, in addition, produce more consistent and reproducible results.

SUMMARY

In this paper we have briefly reviewed two important complications of coronary artery disease - namely, arrhythmias (and, in particular, ventricular fibrillation), and pump failure, and trends in management of the acute myocardial infarction.

Two animal experiments, investigating the effect of revascularizing the acute infarct on heart function and electrical stability, are reported. As with all animal experiments, relating conclusions to the clinical situation is difficult. Clinically we deal with subjects of different ages, with different extracardiac diseases, a variable extent of coronary artery disease, and different degrees of impairment of cardiac function. So, results must be viewed critically, and extrapolation of principles of management to human subjects be undertaken with caution.

The study of ventricular fibrillation thresholds in dogs suggests reversibility of the effect of ischemia on the electrical stability of the heart, with revascularization one and two hours after coronary occlusion. Because of the small numbers completing the study, as well as the variations

within groups, and a significant number dying with congestive heart failure, inferences from the study of the effect (on cardiac mechanics) of early revascularization of the acute infarct in cats must be made with reservations. It would appear, however, from the mortality rates, that revascularization of the acute infarct within less than four hours from the onset of coronary occlusion is associated with a significant improvement in survival.

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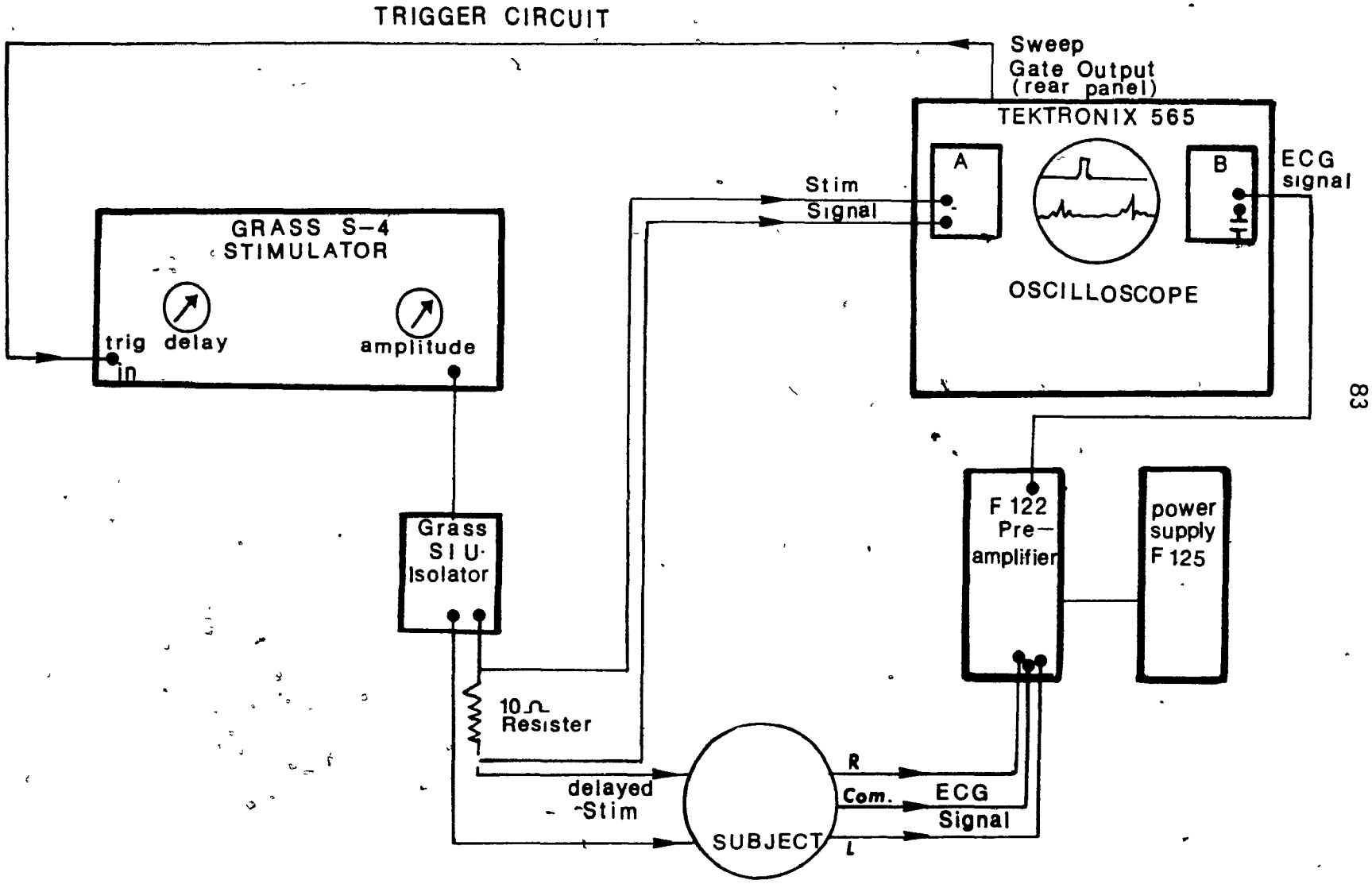


fig. 1 Apparatus used for VFT determination

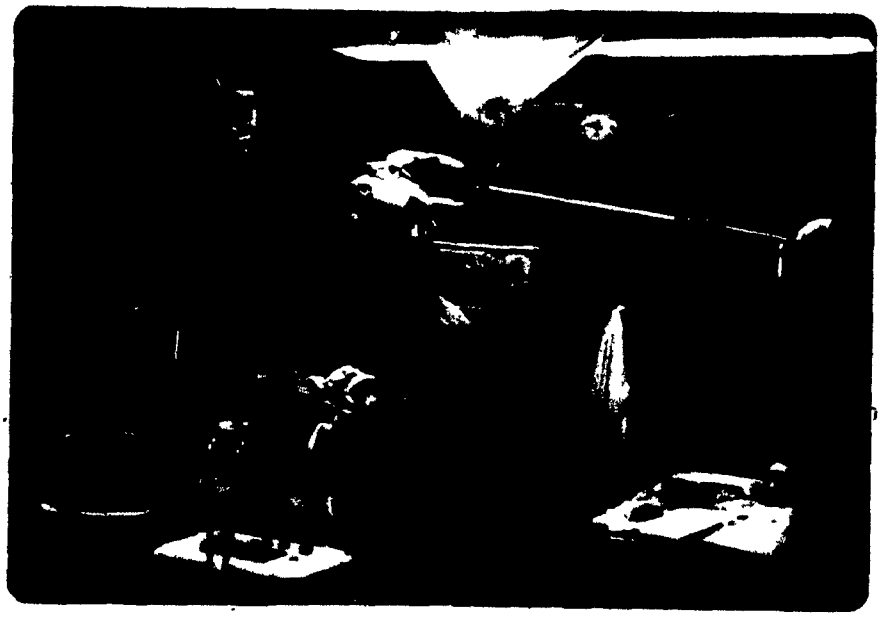


FIG 2
model for
VFT experiment

FIG 3
VFT experiment
heart, snare,
stimulating electrodes

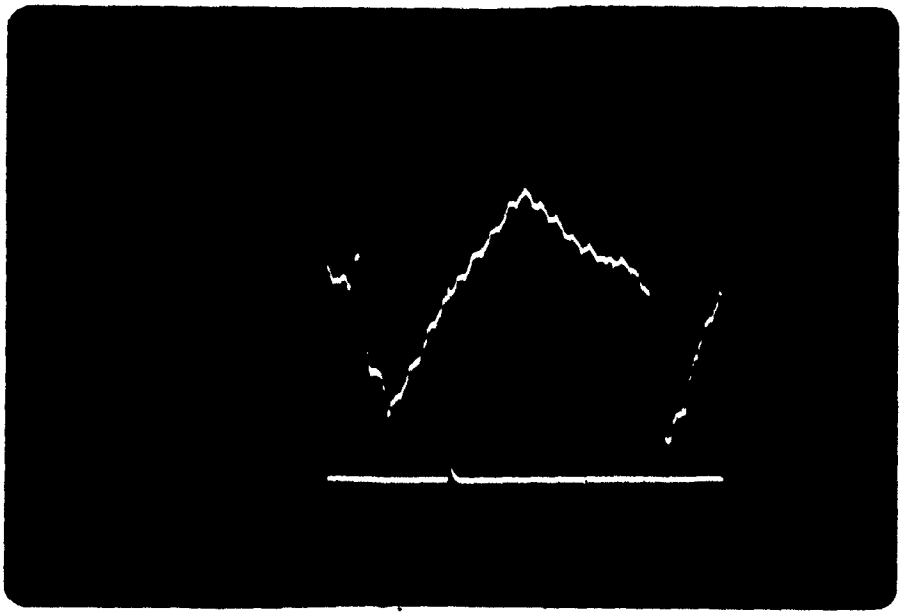


FIG 4(a) Oscilloscope Tracing

EKG (above) & Stimulus (below)

FIG 4(b) Photograph Taken by Oscilloscope Camera

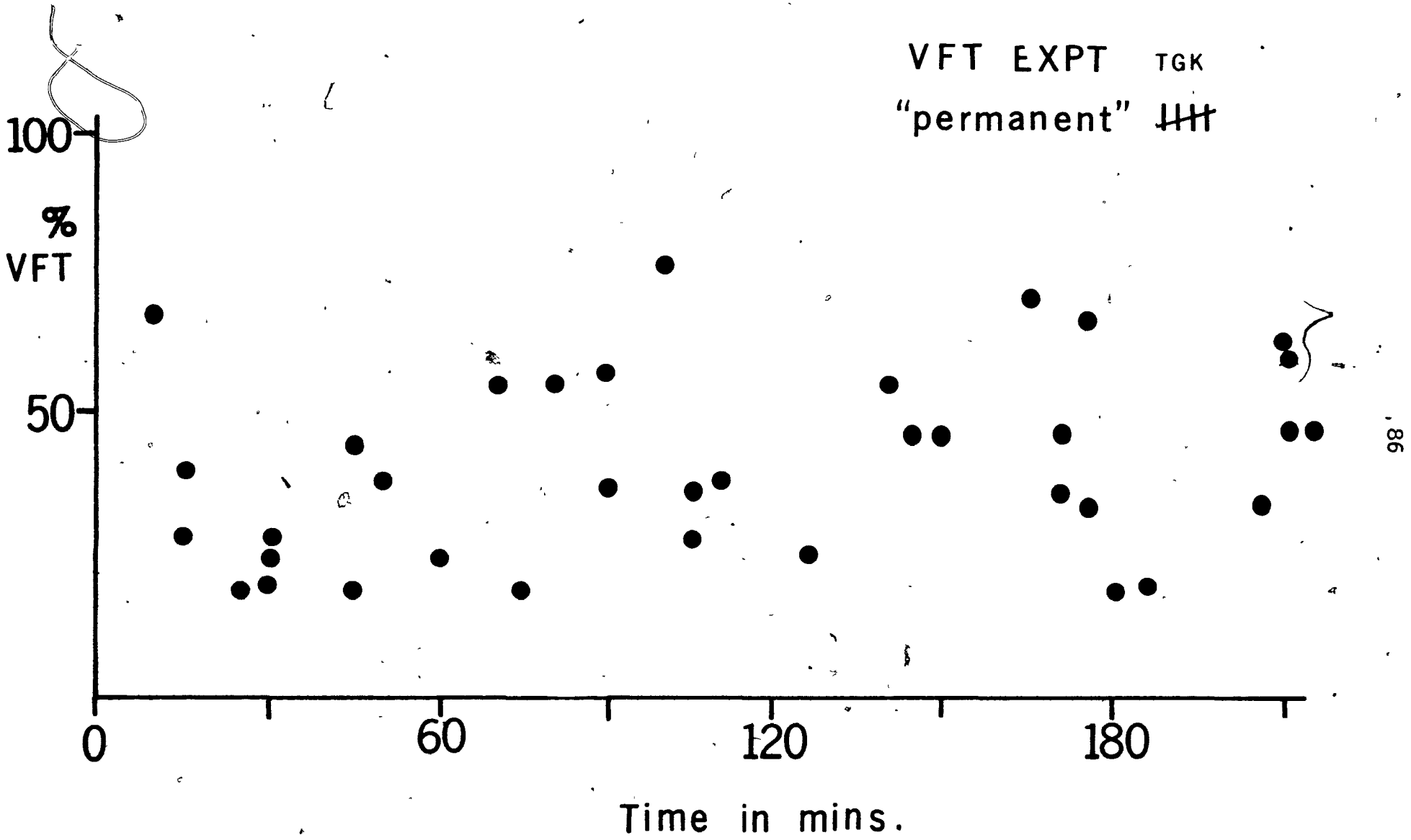

VFT EXPT TGK
"permanent" ~~IIII~~
100
%
VFT
50
0
60
120
180
Time in mins.

fig.5

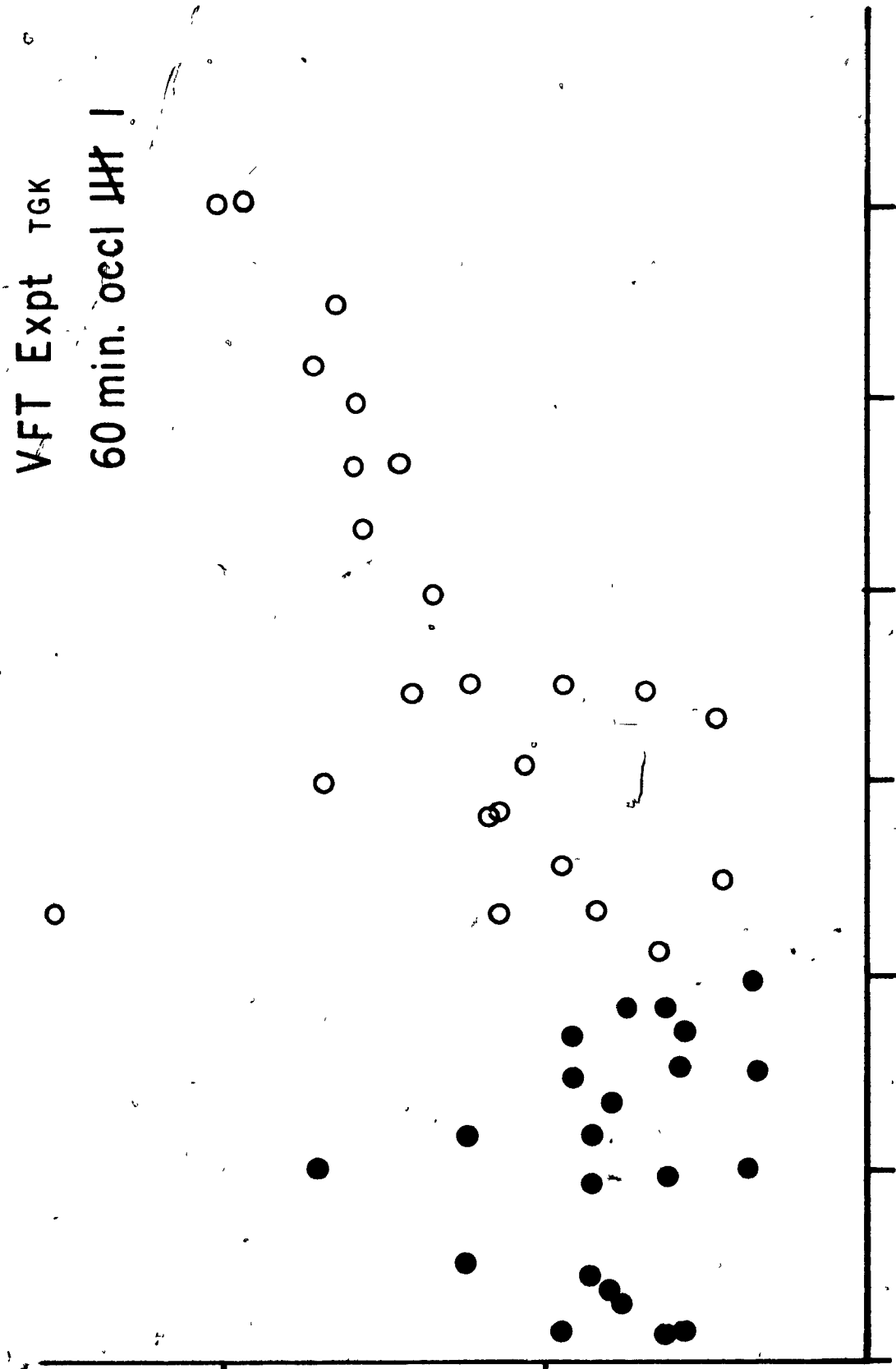


fig 6

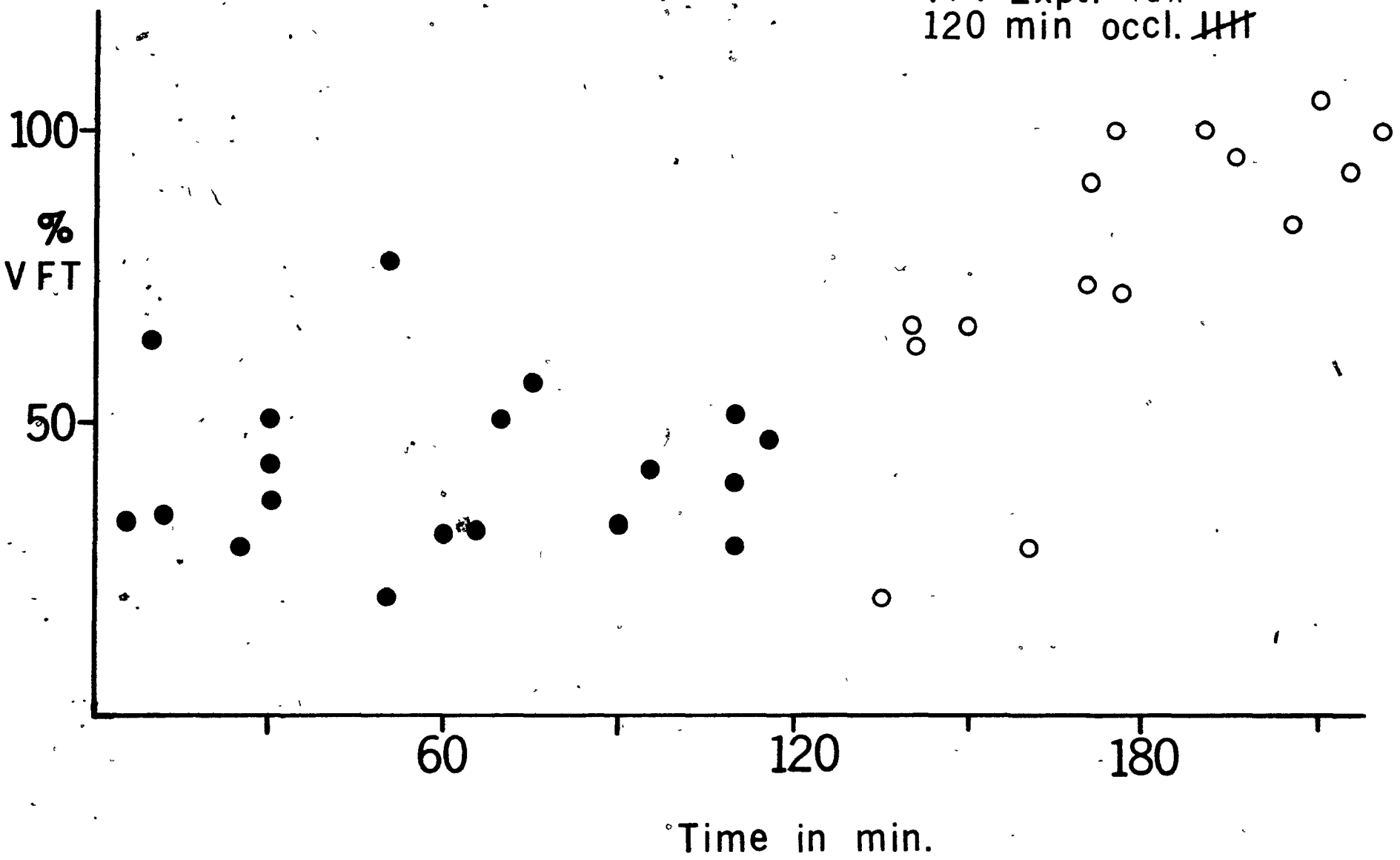


fig. 7

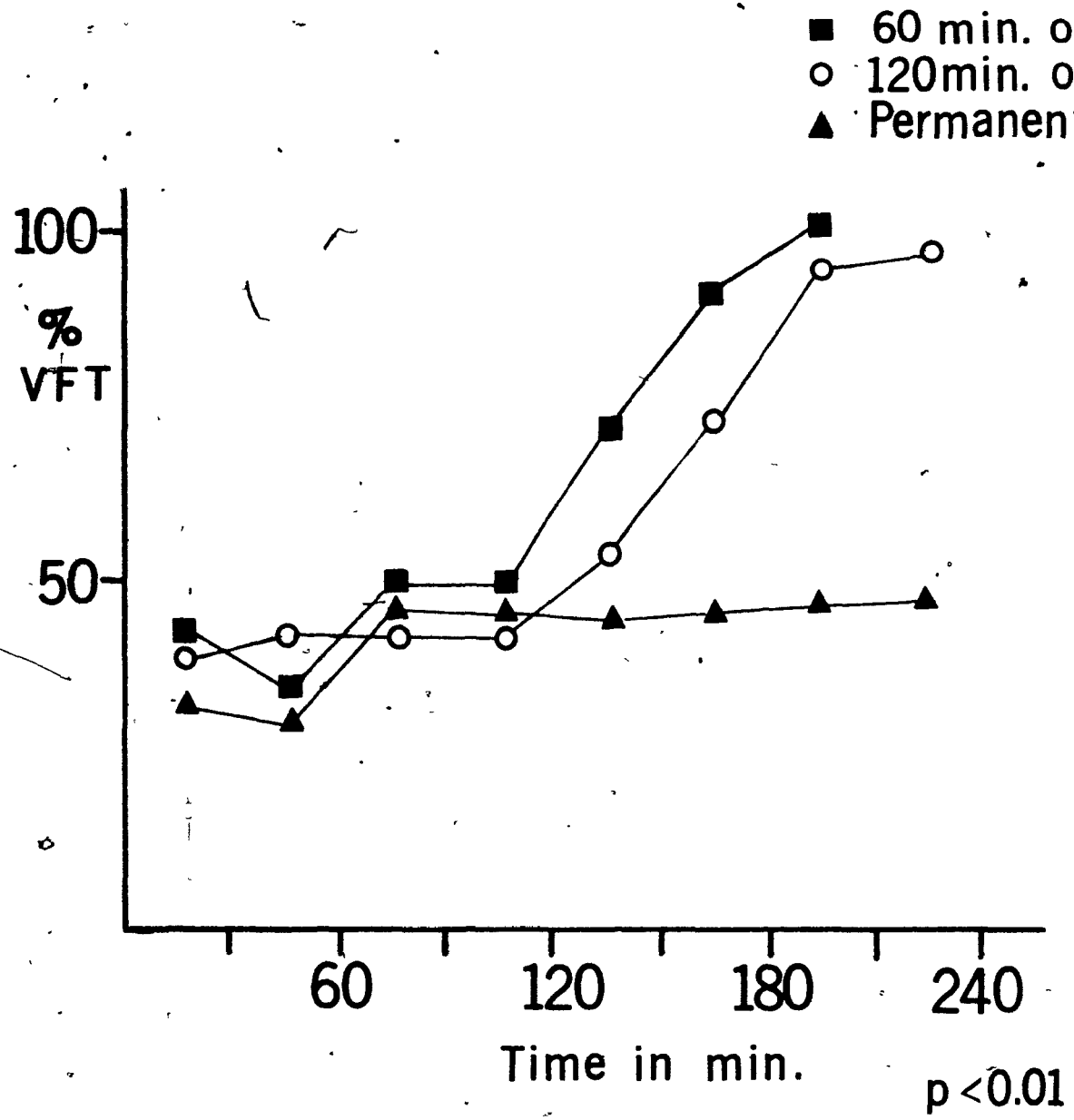
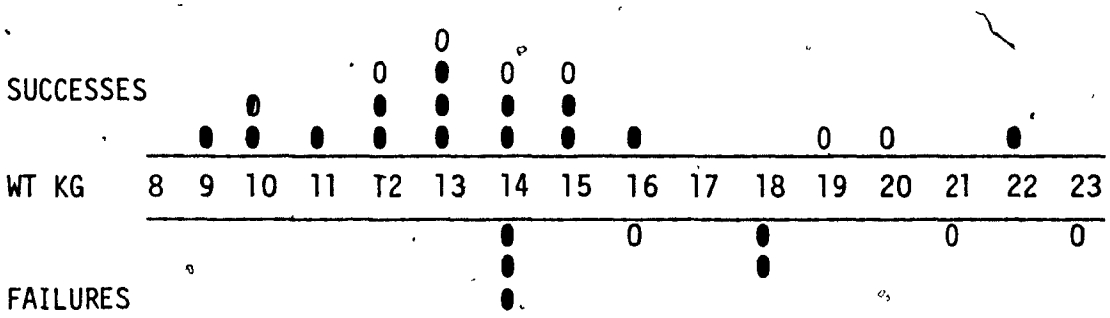

60 min. occl.
120min. occl.
Permanent "
100
%
VFT
50
60
120
180
240
Time in min.
p <0.01

fig. 8

VENTRICULAR FIBRILLATION THRESHOLDS



0 Female
● Male
0 Sex?

Variation in weights between successes X failures Sig. at at 5% level

FAILURE = Inability to resuscitate within 1st 30 min of Experiment

FIG 9

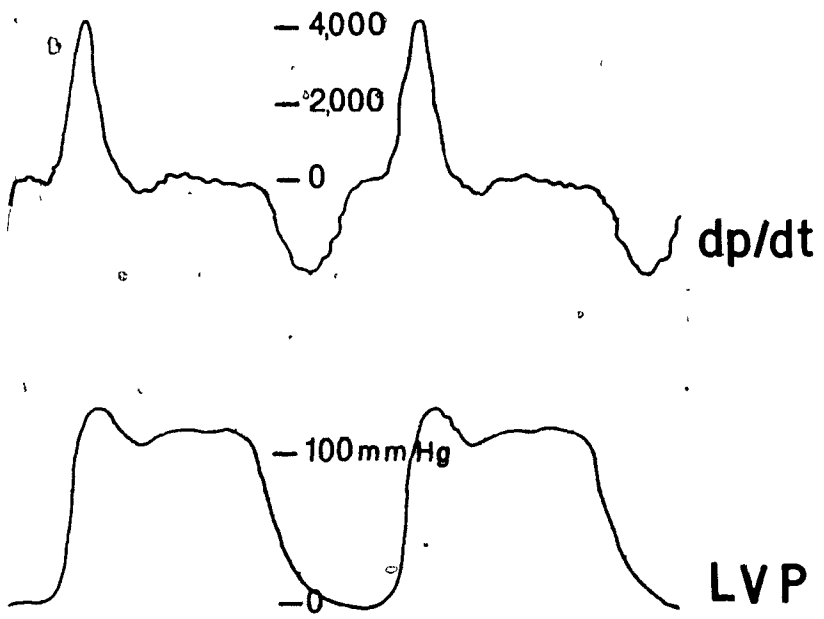


fig.10 Polygraph tracing of dp/dt & LVP curves; paper speed: 100mm/sec.

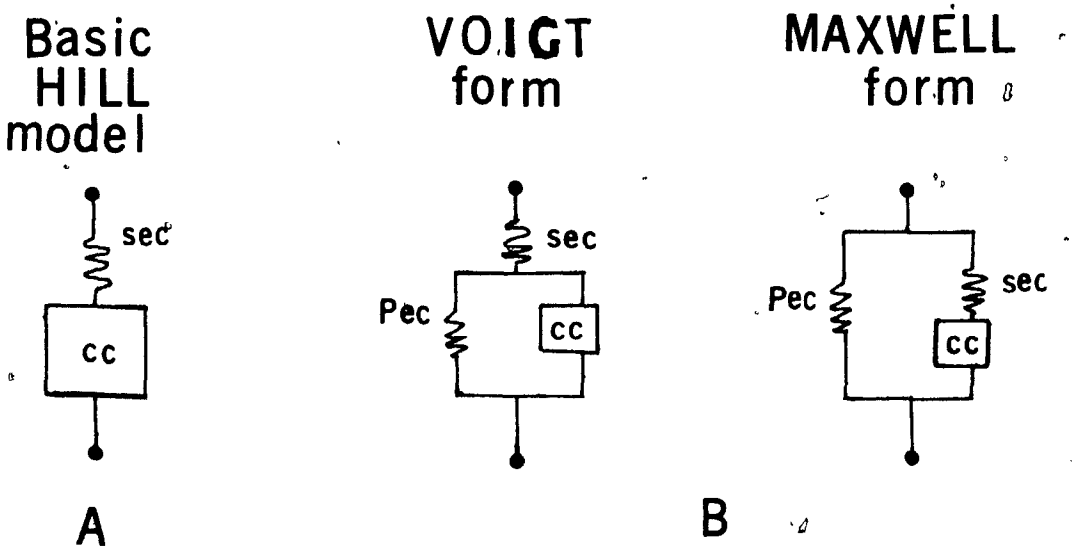


fig.11 - A –Two-component, B –Three-component, muscle models

sec = series elastic component
cc = contractile component
Pec = Parallel elastic component

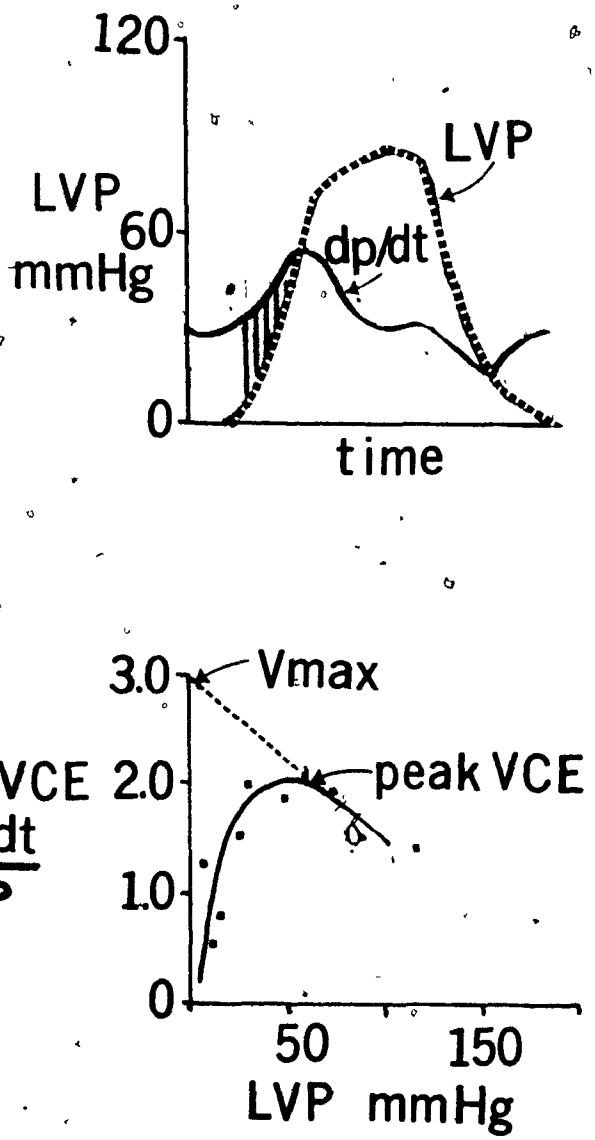


fig.12 Derivation of Vmax :-

Curve plot : calculated VCE against Isometric pressure at corresponding Time

: dotted line shows extrapolation of Vmax

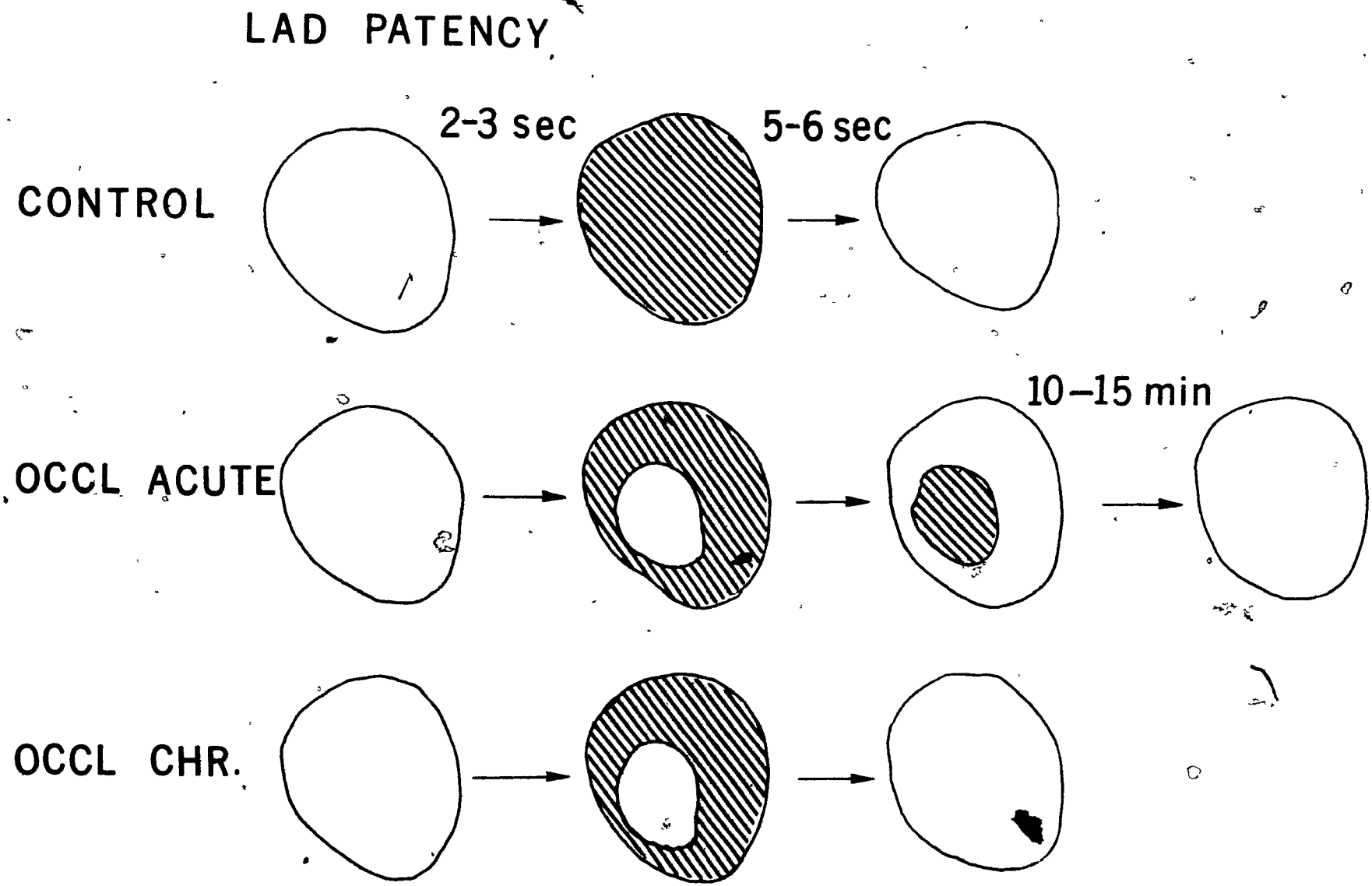

LAD PATENCY
2-3 sec
5-6 sec
CONTROL
10–15 min
OCCL ACUTE
OCCL CHR.

fig.13

FIG 14 Evaluation of Arterial Patency

By Ink Injection

(a) Cat Heart Before Ink

(b) Acute LAD Occlusion After Ink

(see text)

14(c) Sham Operation at 6wk After Ink

14(d) Permanent LAD Occlusion at 6wk After Ink

FIG 15 High Power View of Myocardium,
Showing Ink Particles
Between Muscle Fibres

MYOCARDIAL REVASCULARIZATION EXPERIMENT

	STUDY					
GROUP	IMMED.	1HR	2HR	3HR	4HR	6WK
A SHAM	X	X	X	X	X	X
B PERM	X	X	X	X	X	X
C 2HR	X	X	X	X	X	X
D 4HR	X	X	X	X	X	X

FIG 16 TABLE I

Groups and study times in

Cardiac Mechanics Experiment

CAUSE OF DEATH

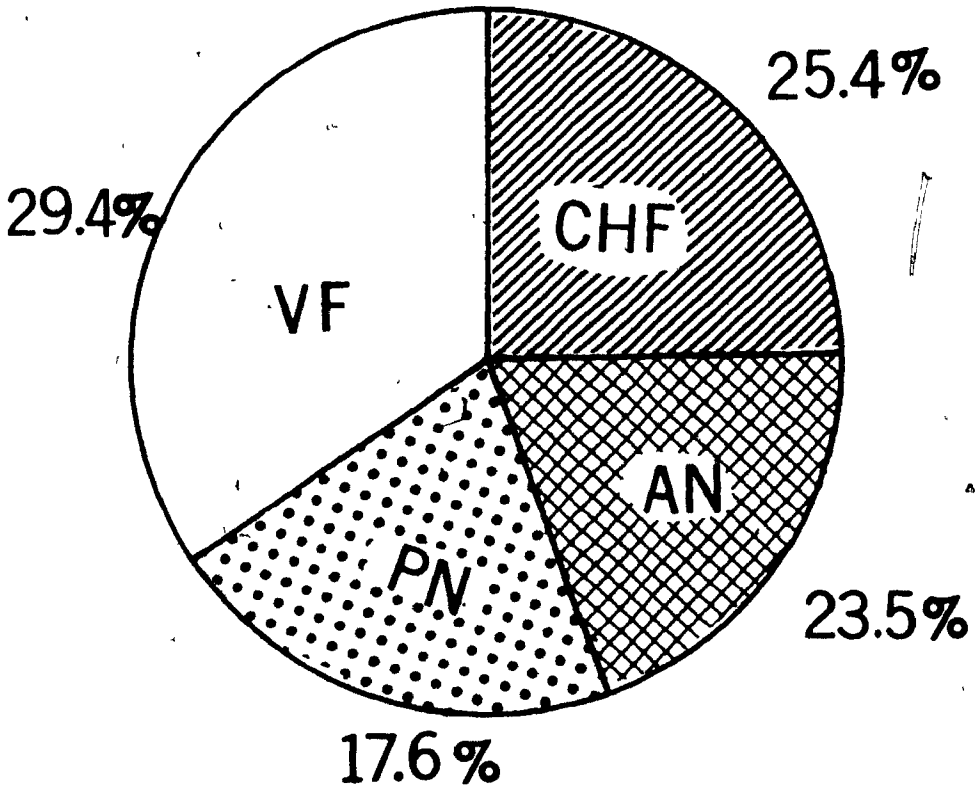


fig. 17

VF = Ventricular Fibrillation
CHF = Conjestive Heart Failure
AN = Anesthetic
PN = Pneumonia

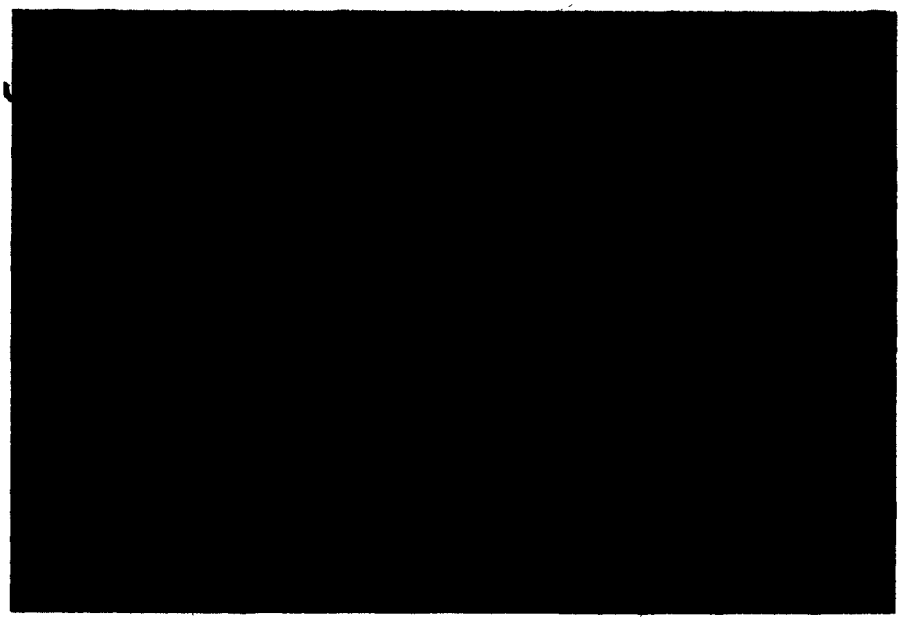


FIG 18 Normal Cat Lung (LP)

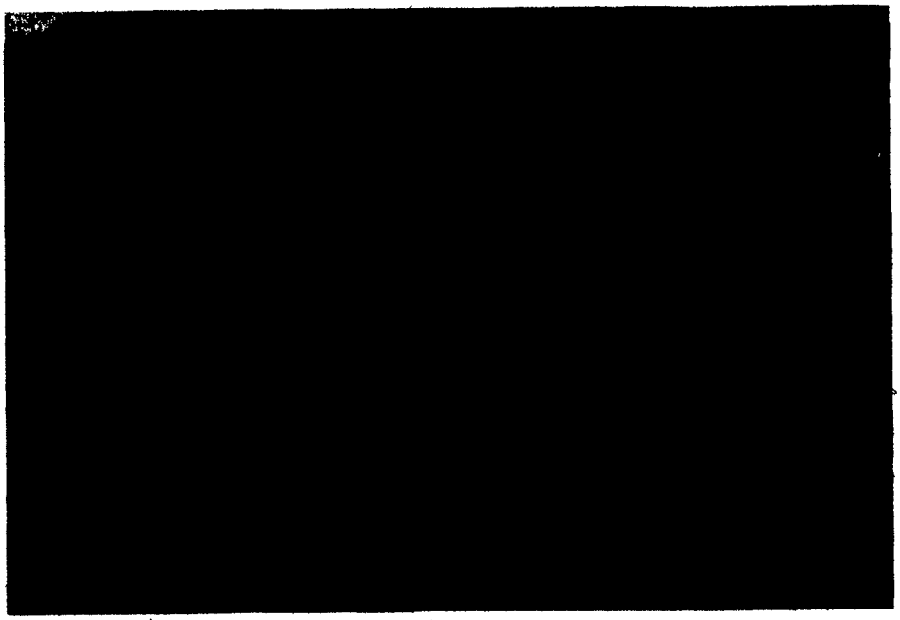


FIG 19 Pulmonary Edema (HP)

FIG 20 (a) Pneumonia (LP)

FIG 20 (b) Pneumonia (HP)

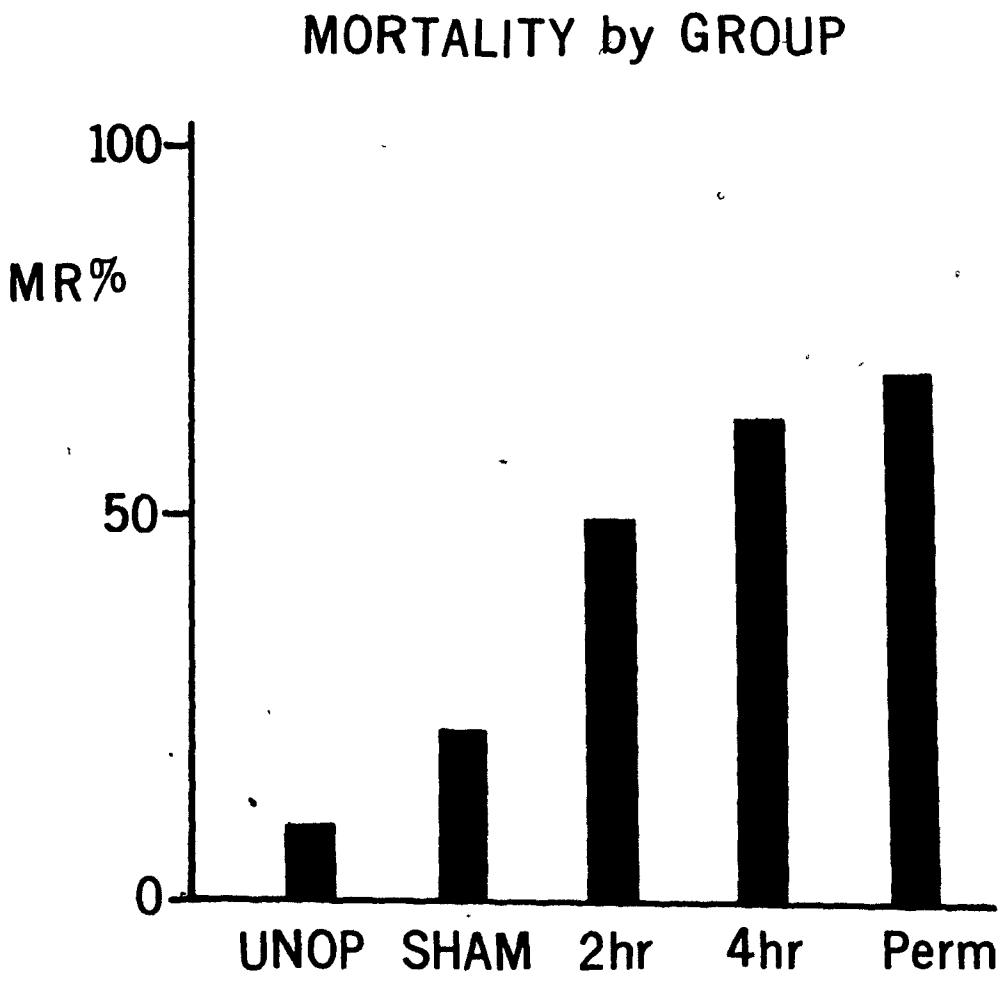
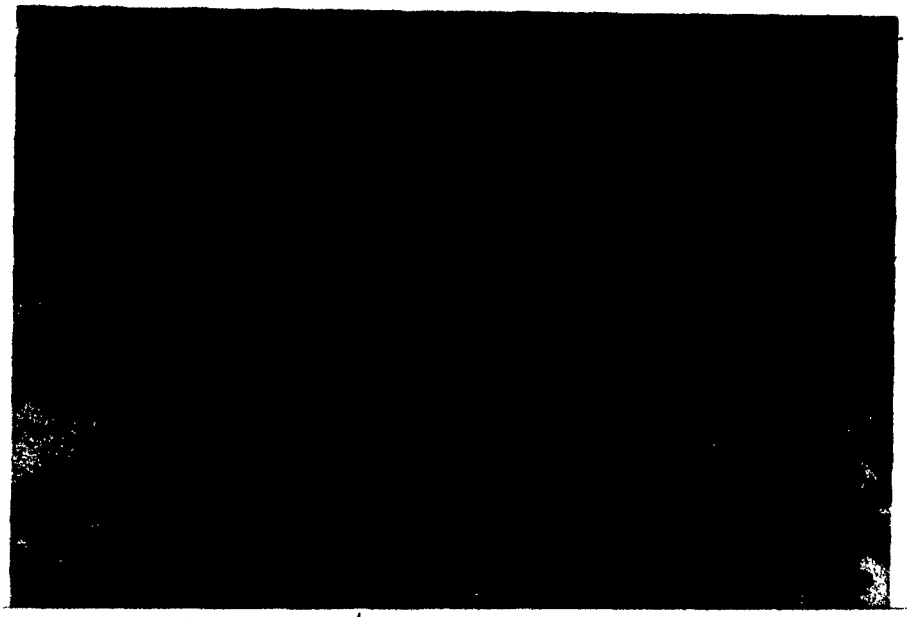


fig. 21

FIG 22(a)

Low Power View



(b)

Lung Abcess HP

H & E

(c)

High Power GM Stain

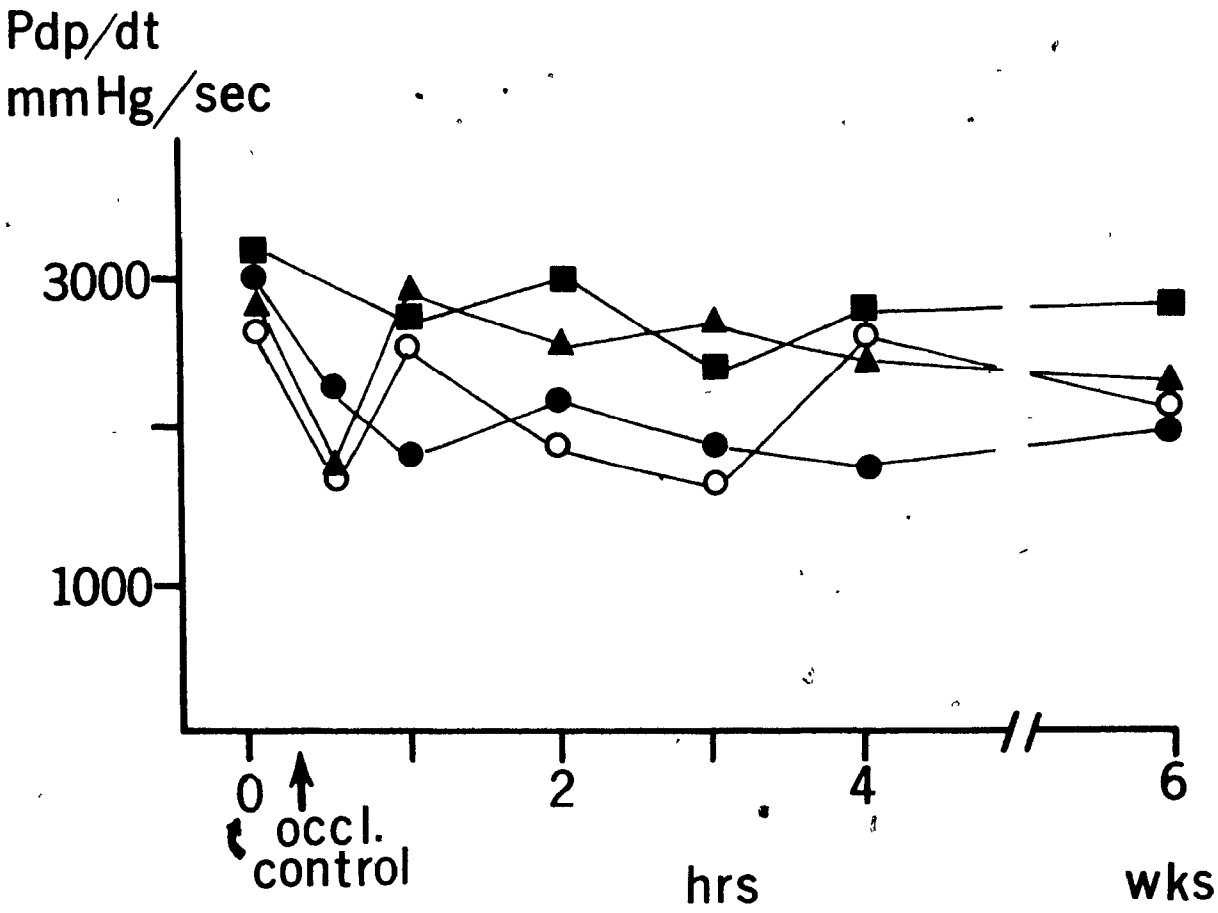


fig. 23 Peak dp/dt course (see text p.54)

■ = SHAM

○ = 2 hr occl.

▲ = 4 hr occl.

● = Perm. occl

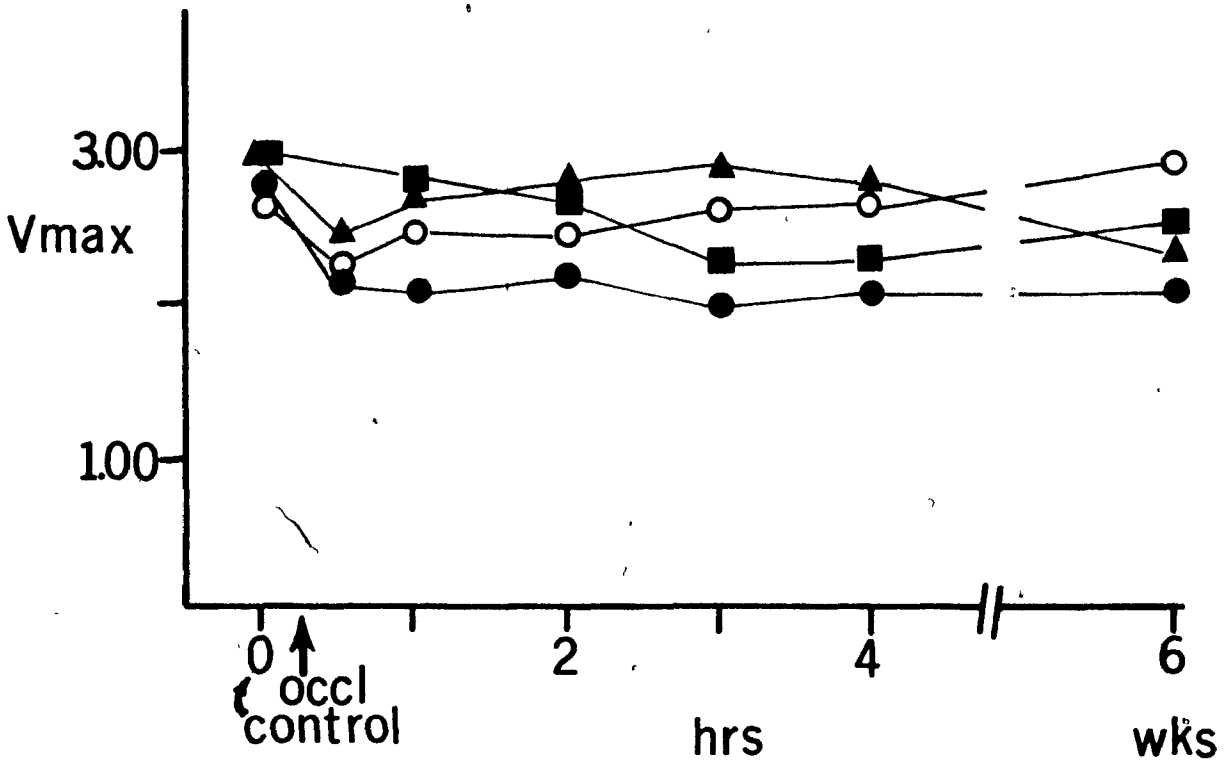


fig. 24 Vmax course (see text p.54)

■ = SHAM operation
○ = 2 hr occl
▲ = 4 hr occl
● = Perm. occl