A. THE EFFECT OF EPICARDECTOMY AND CARDIC NEURECTOMY ON THE VENTRICULAR FIBRILLATION THRESHOLD.

B. STUDIES ON A CORONARY VASODILATOR AGENT.

by

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T A B L E O F C O N T E N T S

I L L U S T R A T I O N S

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SECTION B.

P R E F A C E

The experimental work presented in this thesis is the product of 2 years of research carried out in the Department of Experimental Surgery at McGill University.

The effect of myocardial ischaemia, the immediate and late effects of epicardectomy and neurectomy on the ventricular fibrillation threshold were studied. The effect of a coronary dilator on the ventricular fibrillation threshold and survival of animals with ameroid constriction was evaluated.

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CHAPTER I.

INTRODUCTION

The importance of removing the epicardium for myocardial revascularization was recognized by Beck in 1935.

Beck and Tichy (1935) recommended removal of the epicardium irrespective of the graft or material used, be it talc powder, pericardium, pericardial fat, mediastinal tissue, pleura, etc. Beck believed that the epicardium was a barrier to the development of extra-coronary vessels. Further, he stated that a pressure differential was necessary to promote anastomoses between the cardiac and extra-cardiac vascular beds.

Stanton, Schildt and Beck (1941) studied the effect of surgical removal of the epicardium on

(A) Survival after ligation of the anterior descending artery;

(B) The development of collaterals between the anterior descending and the other two coronary arteries;

(C) The extent of infarction before and after removal of the epicardium.

In 50 control dogs the mortality of ligation of the anterior descending artery was 70%, while in another series of 50 dogs where ligation of the anterior descending artery was done 1-3 weeks after epicardectomy, the mortality was

only 38%.

To study the development of collaterals after ligation of the anterior descending artery he injected the right coronary artery and the circumflex branch of the left coronary artery. In 10 controls there was no filling of the anterior descending artery and subsequently no intercoronary communications in 4, slight filling in 4 and intermediate filling in 2. In those that had an epicardectomy there was good filling of the anterior descending artery in 5, intermediate filling in 1, slight filling in 1 and no filling in 3.

Histological studies indicated that there were less infarctions in the epicardectomized dogs than in the controls, size and incidence wise. These workers concluded that epicardectomy was effective in opening intercoronary communications.

Vineberg and Buller (1957) also recommended removal of the epicardium before application of the pericardial fat pads as a supplement to the internal mammary artery implant (Vineberg 1953).

Harken et al in 1955 using 95% phenol to remove the epicardium reported reduction of the mortality rate from ligation of the anterior descending artery from 70% to 10%. He was able to show blood vessels 40 micra or

larger going to the heart from the thoracic aorta when it was injected 3 months after epicardectomy.

Chari in 1960 used ameroid constrictors on both the anterior descending and circumflex arteries to produce chronic ischaemia. The mortality of these dogs was 80% within 24 days. Twenty percent survived the coronary constriction. In a similar group of dogs epicardectomy was done at the same time as ameroid constriction. The survival rate was 5 out of 9 or more than 59%, and yet only one of these 5 surviving dogs showed an extra-coronary anastomosis.

Pifarre in 1962 using the same technique found that the mortality rate from ameroid constriction was 90% and that after epicardectomy it was only 50%, i.e. there was a 40% improvement after epicardectomy alone.

Beck removed the epicardium to encourage extra-coronary collaterals. Vineberg suggested and has gathered evidence to show that the removal of the epicardium alters the hydrostatics of the myocardial circulation (Vineberg, Becerra and Chari, 1961). They suggested that after removal of the epicardium the entire myocardial fibre network is loosened so that the intrinsic sponge-like character of the myocardium is accentuated. Pre-existing arterio-luminal and myocardial sinusoidal spaces enlarge (Wearn J. T. et al, 1933) . Evaluating the effect of epicardectomy against the

ameroid constriction test they reported an increase of survival rate from 20% without epicardectomy to 59% with epicardectomy. Injection of the left ventricle in the living beating heart with Schlesinger mass showed that the mass was siphoned into the left ventricular wall to fill the coronary arteries in 4 of the surviving dogs. Aortic injections did not show any extra-coronary vessels in 9 out of 10 surviving dogs to account for the protective action of epicardectomy.

Chari (1961) suggested that removal of the epicardium disrupts the afferent sensory pathways which are distributed deep to the thin mesothelial layer of the epicardium.

Manning et al (1939) reported a marked difference in mortality following acute ligation of the anterior descending artery between the anaesthetized and the conscious dog. They suggested that perhaps with the sudden accumulation of metabolites the ischaemic area sets up afferent sympathetic impulses that may, in turn, initiate efferent parasympathetic vasoconstrictor impulses which produce spasm of the medium sized and the smaller coronary arteries. The implication is that anaesthesia abolished this reflex mechanism and thus reduced the mortality rate.

McEachern et al in 1940 ligated the anterior descending artery after bilateral stellate and upper five thoracic ganglia sympathectomy and reported no mortality

within the first 24 hours.

The mortality figures from ligation of the anterior descending artery alone of the above 2 workers are much lower than those reported by others (Stanton 1941, Vineberg 1955, Glover 1957). Using distal occlusion of the anterior descending artery and adrenalin injection to produce ventricular fibrillation (Fauteux M, A. 1946) reported that pericoronary neurectomy helps substantially to prevent ventricular fibrillation following coronary occlusion. Survival from occlusion of the circumflex coronary artery increased from 20% in control series to 60% if the dog had been protected by pericoronary neurectomy sometime before the circumflex coronary artery occlusion (Fauteux, M. B. 1946).

Reports of mortality rate following occlusion of the anterior descending artery from different centres varies from 10 - 100% (Kline 1959) which is probably due to variations of the site of occlusion and normal anatomical variations in the distribution of the coronary arteries.

In this experimental study an attempt has been made to study and try to clarify:

1 - The effect of epicardectomy on the heart.

2 - If epicardectomy has a protective action against coronary occlusion, and is a pressure differential necessary to obtain this protection.

3 - Effect of cardiac denervation or neurectomy.

Reports of mortality rate following occlusion of the anterior descending artery by different investigators vary from 10 - 100%. Because of this and since left ventricular fibrillation is a major cause of death in the experimental animal (Chari, 1961) and human beings (Rosenberg & Malach, 1960) we used quantitative determination of the left ventricular threshold in this study (Wiggers, 1940) to assess improvement or deterioration before and after the surgical procedures.

Also investigated in this study are: -

1 - The effect of a coronary vasodilator agent on the ventricular fibrillation threshold;

2 - The chronic and acute effects of a coronary vasodilator agent on coronary backflow;

3 - The effect of a coronary vasodilator agent on survival of animals with coronary artery ameroid constriction.

CHAPTER II

ANATOMICAL CONSIDERATIONS

The heart is a hollow muscular organ, enclosed in the pericardial sac. It consists of 3 layers: the endocardium, the myocardium and the epicardium. The epicardium is reflected over the great vessels to be continuous with the serous layer of the pericardium.

The heart is held in position within the pericardium by the great vessels and the epicardial reflection over them. Thus the heart has no continuity with the rest of the body except through the great vessels. The heart lies free within the pericardial cavity.

A. THE PERICARDIUM:

The pericardium comprises 2 sacs intimately connected with one another but different in structure.

The outer is the fibrous pericardium and the inner the serous pericardium which lines the fibrous pericardium and is reflected over the myocardium to become continuous with the epicardium or the visceral layer of the serous pericardium.

The fibrous layer of the pericardium consists of a dense network of fibrous tissue.

The serous lining of the pericardial sac consists of a single layer of cells resting on a layer of subserous areolar tissue that blends with the fibrous

pericardium. The pericardial cavity is a potential space. It contains 25 - 30 c.c. of fluid that serves to minimize friction between the visceral and parietal layers of the pericardium.

B. THE EPICARDIUM:

The epicardium consists of a superficial layer of single flattened cells resting on subserous areolar tissue. This areolar tissue is continuous with the interstitial tissue of the myocardium. It is also continuous with the connective tissue forming the serosa of the great vessels of the heart.

C. THE MYOCARDIUM:

The myocardium consists of cardiac muscle and its supporting connective tissue. The fibres of the atrial myocardium are attached to the annuli surrounding the two atrio-ventricular ostia.

The ventricular myocardium consists of interwoven bundles and bands of muscle fibres which are partially separated from each other by fibro-elastic connective tissue and distinguishable by their orientations (Robb & Robb,1942). In general the fibre bands of the layer nearest the endocardium have a course almost at right angles to that of the most superficial fibre bundles of the same area. The intervening fibre bundles exhibit all degrees of intermediate obliquity. All bands of cardiac muscle arise from and

insert into the fibrous framework of the heart, mainly the fibrous base.

Cardiac muscle fibres are invested by a layer of delicate reticular and collagenous fibres which make up the endomysium. Groups of muscle fibres are partially set apart from adjacent bundles by more dense layers of fibro-elastic connective tissue, the perimysium.

The perimysial tissue is continuous with the endomysium and its fibres blend with those of the endocardium and epicardium welding the heart into a coherent unit. It is in the perimysium and the endomysium that the network of blood and lymph capillaries and myocardial sinusoids are present.

D. THE ENDOCARDIUM:

All the cavities of the heart are lined with a simple squamous epithelium, called endothelium. This delicate lining is supported by a layer of fibro-elastic connective tissue. The endothelium and its subjecent connective tissue make up the endocardium. The connective tissue of the endocardium tends to be differentiated into a sub-endothelial layer of deliacte collagenous fibres and a deeper layer with abundant elastic fibres. In it are found a few blood and lymph vessels, and a rudimentary layer of smooth muscle fibres.

E. BLOOD VESSELS OF THE HEART:

a) Coronary Arteries:

The heart is supplied by 2 coronary arteries, the right and the left coronary arteries. The left arises from the left posterior aspect of the aorta. The right arises from the right anterior surface of the aorta (May,1960). The coronary orifices are above the line of reflection of the aortic valve.

An accessory right coronary artery is present in approximately half of the cases (Schlesinger 1949).

The main left coronary artery varies from 5 to 10 mm. in diameter, the wider vessels being the shorter ones. It runs laterally and ventrally between the root of the pulmonary trunk and the left atrium (Gould, 1953). The trunk lies relatively loose in the epicardial fat. Throughout most of its course, the bifurcation and the initial four centimeters of the branches, it is covered by the left atrial appendage which lies directly on it. After a distance of 1 - 3 cm. the main left coronary artery bifurcates into the left anterior descending or anterior interventricular artery and left circumflex or left atrio-ventricular artery (May, 1960).

The left anterior descending artery begins as a direct continuation of the main left coronary artery; the anterior descending branch gently curves around the base of the main pulmonary artery to enter the anterior interventricular sulcus, where it courses to the apex of the heart.

Passing around the apex it turns up into the posterior interventricular sulcus, ascending towards the crux and being met at its distal end by terminal branches of the posterior descending artery. In this region the anterior descending artery which is now posterior and descending supplies branches to the apical portion of the posterior walls of both right and left ventricles.

Anteriorly branches are also supplied to both ventricles, mainly the left. The right ventricular branches begin at approximately the level of the pulmonary valve, where one or more branches curve to meet similar branches arising from the proximal right coronary. Small vessels branch to the anterior surface of the right ventricle throughout the course of the anterior descending artery.

A variable number of large branches leave the anterior descending artery at an acute angle to supply the anterior wall of the left ventricle. These communicate with each other in both their epicardial and sub-endocardial portions.

A major branch from the left anterior descending coronary artery supplies the inter-ventricular septum (James,1961).

The left circumflex coronary artery begins at an angle nearly perpendicular to the main left coronary artery. It lies in the left atrio-ventricular sulcus. Its origin and the first few centimeters lie beneath the left atrial appendage near the margo obtusus where it often terminates

as the left marginal artery by descending a variable distance towards the left ventricular apex.

The ventricular branches of the circumflex artery arise at acute angles from the parent trunk. Their course is towards the margo obtusus and roughly parallel to the primary branches of the anterior descending artery.

The right coronary artery commonly has 2 aortic ostia. The smaller one or second right is the "conus artery" (Schlesinger, 1949) is present in approximately half the cases. The conus artery curves away from the main right coronary artery into a semicircle at the level of the pulmonary valve to join the analogous small branches from the main left or anterior descending coronary artery to form Vieussens ring.

The right coronary artery is situated more deeply in fat in the anterior atrio-ventricular groove than the left circumflex artery. The branches depart perpendicularly. On the anterior ventricular wall, the branches are variable in number, are generally long, extend nearly to the anterior interventricular sulcus, where they may anastomose with branches of the left anterior descending artery (Baroldi, 1956). On the posterior surface of the right ventricle, the ventricular branches are much shorter than those of the anterior

surface. Usually the right coronary artery terminates as the posterior descending artery. The short branches arise perpendicularly and supply a portion of the posterior wall near the atrio-ventricular sulcus. The remaining posterior right ventricle being supplied by the posterior descending artery and branches from the right marginal artery; near the apex there is some supply from the left anterior descending artery (James 1961).

The posterior descending coronary artery is the terminal branch of the right coronary artery. At the crux of the heart, the posterior descending artery begins by penetrating the heart with a deep "U" shaped turn beneath the posterior interventricular vein and emerges into the epicardium again on the other side. From the deepest penetration of this "U" turn arises the atrio-ventricular node artery (James 1961).

The posterior descending artery then courses a variable distance down the posterior interventricular sulcus towards the apex, joining the terminal ascending branches of the left anterior descending artery.

The arteries of the interventricular septum:

The interventricular septal blood supply is predominantly from the anterior descending artery (James 1961). Most often these are 4 to 6 large arteries penetrating the septum from the left anterior descending artery. On penetration these vessels assume a course close to the endocardium on the right side of the septum.

b) Veins of the heart:

The veins of the heart lie parallel to the branches of the coronary arteries. They return the blood to the right atrium through the coronary sinus. This is a wide venous channel situated in the posterior part of the coronary sulcus and covered by muscular fibres of the left atrium. It ends in the right atrium between the opening of the inferior vena cava and the atrio-ventricular valve (Gould 1953).

The veins that end in the coronary sinus are: The great cardiac vein, the middle cardiac vein, the small cardiac vein and the posterior vein of the left ventricle.

The anterior cardiac veins lie on the ventral aspect of the right ventricle and empty directly into the right atrium (Gregg 1947).

The veins of Thebesius, consisting of a number of minute veins which arise in the muscular wall of the heart open into the atria and the ventricles.

F. INNERVATION OF THE HEART:

The sympathetic, parasympathetic and afferent fibres mingle in a superficial and deep cardiac plexus located in relation to the base of the heart.

The superficial plexus lies in the concavity of the arch of the aorta and superficial to the pericardium.

The deep cardiac plexus is situated behind the arch of the aorta and in part between the aorta and pulmonary veins. It consists of 2 lateral parts joined together by

numerous bundles of nerve fibres. It is also connected to the superficial plexus.

Extension of the deep cardiac plexus along the coronary arteries constitutes the right and left coronary plexuses.

The cardiac plexus includes numerous ganglia, all of which are parasympathetic. The pre-ganglionic fibres connecting the ganglia with the central nervous system are components of the vagus nerves.

A single cardiac ganglion, the ganglion of Wrisberg is usually located in the concavity of the aortic arch.

The sympathetic nerves of the heart include the superior, middle and inferior cervical and the thoracic sympathetic cardiac nerves.

The superior cervical sympathetic cardiac nerve regularly arises from the superior cervical sympathetic ganglion, either as a single trunk or by several roots from the ganglion and one or more from the sympathetic trunk.

The middle cardiac nerve arises from the middle cervical ganglion or in the absence of this ganglion directly from the sympathetic branch.

The inferior cervical sympathetic cardiac nerve arises by several roots from the lower cervical portion of the sympathetic trunk and the inferior cervical or stellate ganglion.

The thoracic sympathetic cardiac nerves vary in

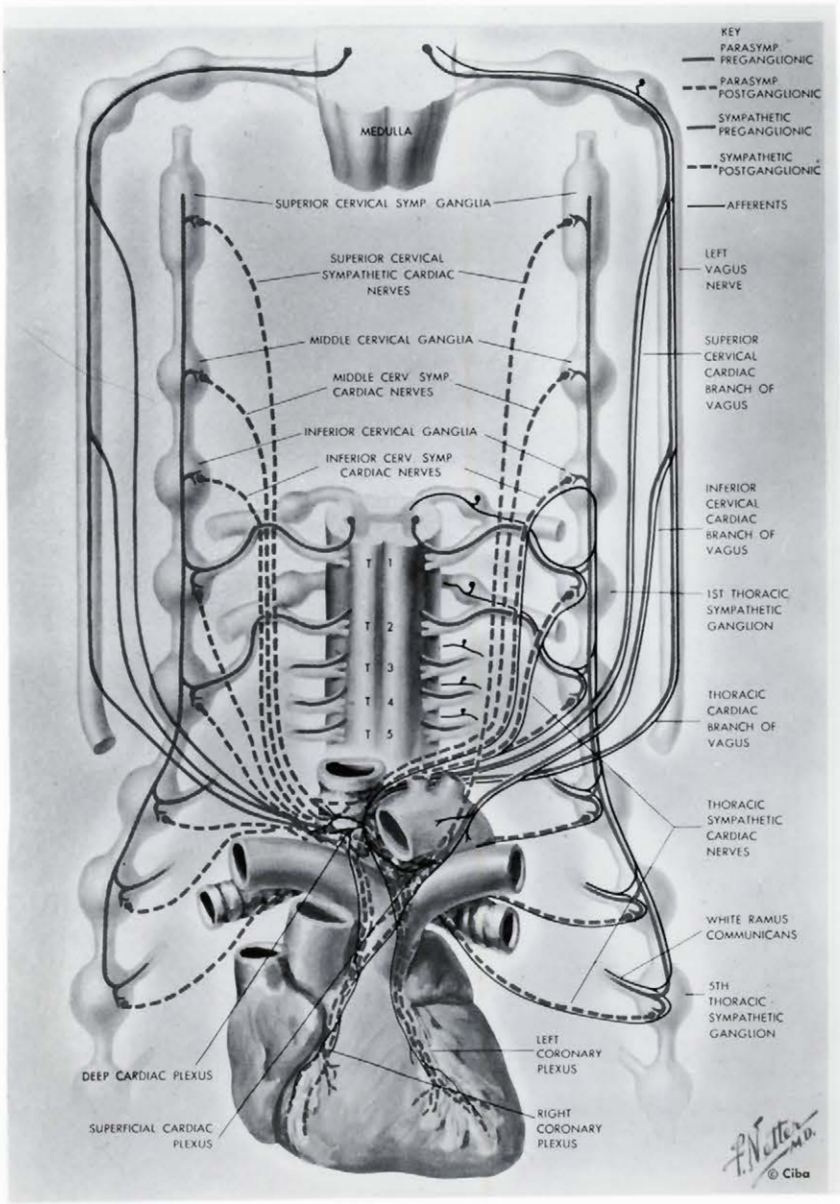

Fig. 1 - Diagram of the nerves supplying the heart and their origin. (From the Ciba Collection of Medical Illustrations, Vol. 1)

number. They arise usually from the upper 4 or 5 thoracic segments of the sympathetic trunk. Occasionally a ramus arising from the 6th segment of the sympathetic trunk joins the cardiac plexus.

The left superior cervical cardiac nerve joins the superficial cardiac plexus, while all other sympathetic cardiac nerves join the deep plexus.

The efferent nerve fibres extending from the sympathetic trunk into the cardiac plexus all arise in sympathetic trunk ganglia.

The sympathetic cardiac nerves except the superior and the middle cervical are accompanied by afferent spinal nerve components which conduct sensory impulses from the heart and the coronary blood vessels.

The parasympathetic innervation of the heart involves 3 branches of the vagus on either side.

The superficial cervical cardiac branch arises from the vagus trunk just distal to the origin of the superior laryngeal nerve.

The inferior cervical cardiac branch usually arises from the recurrent nerve.

The 3rd or thoracic cardiac branch arises from the vagus nerve within the thorax.

On the left side the inferior cervical cardiac branch of the vagus joins the superficial cardiac plexus. All other cardiac branches of the vagi join the deep cardiac plexus.

The so-called depressor nerves consist of afferent vagus components which are connected with the receptors of the proximal parts of the aorta and adjacent cardiac wall (Ciba 1958).

C H A P T E R III.

ANATOMICAL PATHOLOGICAL CONSIDERATIONS

The presence of physiologically functional inter arterial coronary anastomosis has been the subject of controversy. Schlesinger (1938) in an injection and dissection study of human hearts felt that the coronary arteries are true "Cohnheim end arteries". Later he modified this opinion. Inter arterial anastomosis could be present in normal human hearts, they are less than 40 micra in diameter, could be demonstrated by watery solutions and are of no functional significance.

Blumgart et al (1940) in a study of 125 human autopsies reported that intercoronary anastomosis larger than 40 micra in diameter are not found in normal hearts. Anastomotic communications between 40 and 200 micra in diameter develop as a result of arteriosclerotic narrowing or occlusion. These could be demonstrated by Schlesinger mass injections. Age per se in absence of arteriosclerotic narrowing is not a stimulus for functional intercoronary anastomosis.

Zoll in 1951 analysing the results of studying 1050 human hearts came to the conclusion that intercoronary anastomosis measuring 40 micra in diameter are present in 9% of normal human hearts. Slight or even moderate arteriosclerotic narrowing of the coronary arteries did not increase the incidence of intercoronary anastomosis. With 75% narrowing

of the diameter of the artery the incidence of intercoronary anastomosis was 58%. If the coronary artery narrowing becomes acute occlusion the incidence of intercoronary anastomosis was 89%, and this became 100% with complete and chronic occlusion of the artery.

In hearts with no arteriosclerosis, anaemia, hypertrophy or valvular disease increased the incidence of intercoronaries from 9% to between 26% - 39%.

On the other hand, Prinzmetal et al (1947) using radioactive microspheres reported that there are intercoronary arterial anastomosis present in the normal human hearts varying between 70 and 180 micra, that there are arterio-luminal vessels between 70 and 220 micra and arterio-venous anastomosis between 70 and 170 micra.

Baroldi et al (1956) found that normal human hearts have arterial anastomosis ranging between 20 and 350 micra. They felt that coronary collateral circulation found in arteriosclerotic patients can be interpreted as a result of a hypertrophic evolution of the collateral vessels existing in every normal heart.

Bellman and Frank (1958) reported arterial anastomosis up to 200 micra in 8 patients without coronary disease.

May (1960) in a study of 200 human hearts stated that whenever atherosclerosis occurred one type or another of collaterals appeared. In those hearts devoid of atheromatous lesions no collateral vessels were noted. May classified

collateral vessels in 4 types:

1) By-pass collaterals. These arise from the coronary arteries from above atheromatous lesions to divert the blood below the site of occlusion.

2) Inter-arterial collaterals (homo-coronaries). These connect branches of the same coronary artery.

3) Trans-arterial collaterals (inter-coronary). These anastomose branches of different coronary arteries together.

4) Scar collaterals. These are newly developed vessels from adjacent coronary branches near the infarct area in response to necrobiosis. These vessels were coursing through the scarred area.

The one area where no collateral circulation was evident was in the first few centimeters of the main stem coronary vessels.

Coronary artery occlusions are mainly limited to the proximal parts of the 3 main coronary arteries and their branches in their epicardial portions (Schlesinger & Zoll, 1941). The degree of atherosclerosis decreased progressively from the proximal to the distal parts of the

coronary arteries in any decade from 30 to 90 years (White,1956). As a result of this occlusive process the myocardial circulation is reduced to a variable degree. The outcome will depend on the nature and the extent of the occlusive process and whether intercoronary collaterals are present or not.

Crafoord (1961) estimated that cardiovascular disease is responsible for more than half of the total deaths and coronary artery disease is responsible for 20% of deaths in the cardiovascular group.

Twenty-five percent of those with a myocardial infarction die in the first attack.

Factors related to coronary artery disease deaths:

Beck (1958) analysing his experimental and clinical experience during 25 years felt that there are 3 dominant causes of death:

1) The production of an unstable electrical condition in the heart, resulting in ventricular fibrillation.
2) Reduction of total coronary inflow.
3) Destruction of muscle.

Sudden localized occlusion of a coronary artery in a heart that did not have a chance to develop intercoronary collaterals will result in an uneven distribution of oxygen and this is accompanied by electrical instability of the heart. When "pink and blue" areas of the myocardium are in juxtaposition, the ST segment is elevated over the cyanosed muscle and depressed over the well-oxygenated muscle. Beck stated

that these patterns indicate the production of electricity between the pink and the blue muscle and they are not currents of injury but are currents of oxygen differential. When they become strong enough they produce ventricular fibrillation and death. This is an interesting theory but still debatable.

Yater (1951) in a study of 950 autopsies reported that the hearts of one-third of all persons who died of coronary artery disease showed no myocardial infarcts.

Stround (1948) in a review of 80 cases of sudden death due to heart disease found that 31 patients or 39% died of ventricular fibrillation.

Miller (1939) analyzed 37 cases of sudden death from coronary artery disease. There was rupture of the left ventricle in three. With the exception of these three cases "autopsy observations failed to explain the sudden death, in fact the hearts appeared compatible with the continuance of a fairly efficient circulation".

Coronary sclerosis was present from moderate to a marked degree in all cases. This,in the light of Zoll's findings (1951), would mean that there was very little intercoronary anastomosis in these hearts.

Woods (1942) in a study of 128 unselected patients with acute coronary occlusion, reported that 60 of these patients died within 6 weeks of the onset of the acute attack. Ventricular fibrillation was the probable cause of death in 32 of these cases, more than 50% of those dying suddenly from an

acute coronary occlusion.

Rosenberg and Malach (1960) in another review of 64 patients with acute myocardial infarction, found that ventricular fibrillation was reported as the cause of death in 54% of 60 patients with fatal acute coronary occlusion within 6 weeks after the acute episode and within 4 weeks in 26% of another 281 patients with myocardial infarction who came to autopsy.

Moritz (1935) in a study of 94 human hearts who sustained major trunk occlusion noted that despite the fact that the incidence of bilateral coronary occlusion increased with age, the incidence of sudden unexpected death from coronary occlusion decreased with age.

In an experimental study Blumgart (1955) found that although evidence of early development of collaterals may be present within 2 days, 12 or more days are necessary for their development and certainly this continues for several months.

In spite of the divergent opinions, it seems that there are still certain points of agreement:

1) Coronary artery narrowing or occlusion is the best stimulant for the development of intercoronary collaterals.

2) Intercoronary anastomosis less than 40 micra in diameter are present in normal human hearts irrespective of age. These communications could be demonstrated by watery injections but not by larger-sized particle injection media and they are most probably of no functional significance.

CHAPTER IV

A REVIEW OF THE FACTORS AFFECTING THE SUSCEPTIBILITY OF THE VENTRICLES TO FIBRILLATION

TEMPERATURE:

Phibbs et al (1959) determined the fibrillation threshold of the anterior surface of the dog's left ventricle using the Shumway technique. The oesophageal temperature was monitored and kept constant for every determination. At 37°C temperature, the mean threshold was 20.9 m. amperes. When the dogs were cooled to 33° this was 14.1 and at 29°C it was 9.7 m. amperes. Raising the temperature from 37°C to 40°C raised the threshold from 20.4 to 35.6.

At 37°C the ventricular fibrillation threshold after occlusion of the anterior descending artery was 4.9 m. amperes. This same threshold came up to 22 m. amperes with raising the oesophageal temperature to 40°.

Using rabbits' hearts, Covino (1958) was able to arrest ventricular fibrillation by cooling to 25°C. Raising the temperature to 38°C again resulted in ventricular fibrillation. Covino's results are in agreement with Burn's and Goodford's (1957), and Beaulinese's and Day's (1957). Milton (1959) also reported a decrease in the proportion of fibrillating rabbits' ventricles on cooling from 37° to 32°, at 27° none of the hearts fibrillated.

Although the techniques used are different, it

appears that there is a species difference, in the dog a rise of temperature afforded protection from ventricular fibrillation while in the rabbit cooling arrested fibrillation.

OXYGEN:

Harris (1948) produced anoxia by rebreathing in a large respirometer tank with an external circuit including soda lime cartridge. This technique reduced the O_2 content slowly and gradually in several hours to 5%. In 10 dogs there was pacemaker failure in 6 and conduction failure in 4. Whenever conduction failed due to anoxia the pacemakers failed and vice versa. In no instance was there ventricular fibrillation. Occlusion of the anterior descending artery resulted in ventricular fibrillation in 50% of the trials.

Brofman (1956) arrived at essentially the same results.

Badeer (1959) obtained 100% ventricular asystole by giving 100% nitrogen or carbon monoxide and surprisingly when he tied both right and left coronary arteries simultaneously 90% of the dogs developed ventricular fibrillation and only 10% went into asystole.

The same author (1962) compared in 2 series of dogs, the effect of ligation of the anterior descending artery while the dogs breathed room air and 100% O_2. The results were essentially the same. Within an hour 20% of

those breathing room air and 28% of those breathing 100% O_2 fibrillated. He considered this a proof against the theory of "current of O_2 differential" while in fact the results were inconclusive.

More recently W.D. Warren (1962) determined tissue O_2 with the use of bare platinum microelectrode and simultaneously recorded epicardial electrocardiograms from the same area in ischaemic myocardium due to coronary occlusion, in diffusely hypoxic myocardium and in diffuse hypoxia plus coronary artery occlusion. In diffuse hypoxia plus coronary occlusion, there was severe diffuse hypoxia which precluded any oxygen differential between ischaemic and non-ischaemic myocardium. In spite of that the current of injury appeared.

These workers concluded that although there were marked differences in oxygen tension between ischaemic and non-ischaemic areas of the myocardium, this was but one of the differences and it is not the factor leading to current of injury and ventricular fibrillation.

Coffman & Gregg (1960) clamped the endotracheal tube in 33 animals. Ventricular fibrillation occurred in 33% of them and cardiac asystole in 66%. In all but 10 dogs there was an early phase of complete heart block. If the vagi were cut during this stage immediately normal sinus rhythm was restored, then heart block reappeared probably

on the basis of myocardial anoxia.

Burn (1960) found that ventricular fibrillation was more readily produced in isolated rabbits' hearts by electrical stimulation when the O_2 supply to the heart was reduced.

Danese (1962) ligated the circumflex artery and perfused the distal end with homologus serum for one hour. In no instance was there ventricular fibrillation. In his control series 60% developed ventricular fibrillation after acute ligation within the hour.

GLUCOSE:

Burn (1960 & 1961) has shown that in rabbits' hearts perfused with glucose-free solution for 2½ hours, fibrillation occurred spontaneously. This fibrillation was arrested if the perfusing medium was changed to a glucose-containing one.

Lack of glucose always caused fibrillation in the rabbit's heart after stimulation (Goodford 1958). Addition of insulin to a heart perfused with low glucose and in fibrillation arrested fibrillation. It appears that lack of glucose shortens the refractory period and enhances ventricular fibrillation.

QUINIDINE:

Lewis (1926) demonstrated that the relative refractory period was lengthened by quinidine, but Wedd & Blair (1942) were unable to change the length of the

absolute or relative refractory period of the turtle's heart. However, after quinidine, the electrical resistance to stimulation was increased during the relative refractory period.

DiPalma (1949) stated that quinidine lengthens the relative refractory period in man as evidenced by an increased QT interval (Sagall, 1943).

Wegria and Nickerson (1942) reported that quinidine reduced the susceptibility of the heart to ventricular fibrillation if the dose were not too large or given too rapidly. Scott et al (1945) also reported on the protective action of quinidine in raising the fibrillation threshold against the production of ventricular fibrillation following electrical stimulation in animals.

Stephenson (1960) reported that quinidine 15 mgm/kg body weight reduced the incidence of ventricular fibrillation after occlusion and after release of the anterior descending artery. Nelson (1960) also felt that quinidine has a protective action against coronary occlusion.

Berman (1958) reported that in hypothermic arrest with Acetylcholine, quinidine offered protection against ventricular fibrillation when it was given before cooling started.

Williams (1958) reported that quinidine did increase the incidence of ventricular fibrillation following

occlusion of the anterior descending artery although the total mortality was essentially the same as in the control group.

Laadt (1950) reported that quinidine offered no protection whatsoever from occlusion of the circumflex coronary artery. On the contrary, it increased the mortality from 80% within the first 24 hours in the controls to 100% immediately after quinidine was given, 80% died in ventricular fibrillation. He concluded that quinidine in the presence of coronary artery occlusion suggested a harmful effect.

Goott's work (1959) showed that quinidine was of little value in prevention of post-hypercapnic ventricular fibrillation in dogs.

EPINEPHRINE:

Wegria and Nickerson found that epinephrine raised the ventricular fibrillation threshold in dogs as much as quinidine. This occurred during the hypertensive period of the epinephrine effect. More recently, however, Hoffman, Siebens et al (1955) demonstrated that both epinephrine and nor-epinephrine increased the vulnerability of the dog's ventricles to fibrillation. These drugs produced a brief lowering of the ventricular fibrillation threshold lasting for 1 - 2 minutes. These effects were dose related and coincide with changes of similar direction in the level of resting excitability.

DiPalma (1950) stated that epinephrine per se is not a dibrillatory drug in the normal heart, but in hearts where local block already exists as after chloroform or coronary occlusion epinephrine increases the irritability of the heart and thus acts to increase the degree of local block and increases the susceptibility to fibrillation.

MAGNESIUM:(Mg)

Carden (1957) investigating the role of Mg in the production or prevention of ventricular fibrillation cannulated the circumflex coronary artery after occluding its proximal end, and perfused the distal end with different solutions. Perfusion with normal saline resulted in 60% ventricular fibrillation and Ringer's solution in 80%. A solution of 2 m. equivalents of Mg in normal saline offered the best protection resulting in 8% ventricular fibrillation.

Goott also reported maximal protection against hypercapnia-produced ventricular fibrillation by the use of magnesium sulphate.

Karki (1957) perfused rabbit's hearts with different solutions and used electric stimulation to produce fibrillation. In the presence of normal Ca and K, electrically induced fibrillation was arrested in every instance by adding a 30 m.M. solution of Mg. If fibrillation was induced electrically and the concentration of Ca doubled,

adding the same high Mg concentration failed to arrest fibrillation in 3 out of 3 cases, showing that the defibrillating action of Mg depended on an antagonism with Ca.

Mg also prevented fibrillation from occurring when the ventricles were being stimulated electrically, while with no Mg in the perfusing solution, electric stimulation would have resulted in fibrillation.

Magnesium sulphate has also been known to have a protective effect against ventricular fibrillation produced by toxic doses of mercurial diuretics (Carver, B.N. 1950).

EFFECT OF POTASSIUM, CALCIUM & SODIUM:

A. Armitage (1957) perfused rabbits' hearts and applied electric shocks to produce ventricular fibrillation. The solution contained K 5.6 m.K/L, Ca 2.2 m.M/L and Na 163 m.M/L. In the control series 39% fibrillated with the electric shock. If the K was reduced to 4.2 (75% of the normal) 77% of the hearts fibrillated and with a further reduction of K to 1.4 m.M/L 100% fibrillated. On the other hand if K was doubled to 11.2 the electric shocks failed to produce fibrillation at all. These results are in agreement with Milton's results.

B. In experiments with Ca in the standard concentration of 2.2 m.M. 25% fibrillated while at 8.8 m.M. 83%

fibrillated. If the Ca was reduced to 1.1 m.M. only 16% of the hearts did fibrillate (Milton 1959).

Armitage's results showed the same trend, that with increase of Ca concentration the incidence of fibrillation increased and with a reduction it decreased.

Calcium has been reported to have a protective action against ventricular fibrillation produced by hypercapnia. Following prolonged hypercapnia the arterial pH was rapidly raised to normal by ventilation with room air. This resulted in ventricular fibrillation in 14 out of 15 dogs. When Ca gluconate was given during the period of hypercapnia and immediately after, no fibrillation occurred in 12 dogs. Arrhythmias in the post hypercapnia period was minimal and was even suppressed by accelerating the calcium infusion.

C. Reduction of Na concentration to half that of the original solution resulted in raising the incidence of fibrillation from 25% to 67% (Mioton). Karki's experiment showed the same trend. On the other hand Grumbach (1957) reported a reversion of fibrillating hearts to normal sinus rhythm with reduction of the Na concentration in the perfusing fluid.

Burn (1950) suggested that the increased east with which fibrillation is produced by stimulation when the heart is perfused with a solution low in Na may perhaps

be explained by the effect of Na concentration on the active transport of K resulting in a decrease in this active transport.

ACIDOSIS AND ALKALOSIS:

Williams (1958) found that although acidosis did not increase the mortality from occlusion of the anterior descending artery, it did increase the incidence of ventricular fibrillation from 20% in the control to 40%. Alkalosis increased ventricular fibrillation to 60%.

Brown (1956) reduced the pH from 7.36 to 6.67 by rebreathing the dogs 30% CO_2 for 2 hours and 40% for another 2 hours. At the end of the experiment the animals were given room air. All dogs developed arrythmia and 70% developed ventricular fibrillation. These results are also in agreement with those of Gordon et al (1957).

SYMPATHECTOMY AND CARDIAC DENERVATION:

A. S. Harris and associates (1951) reported that sympathectomy reduced the incidence of ventricular fibrillation occurring immediately after occlusion of the anterior descending artery. The frequency of ectopic beats in those that did not fibrillate was also lower after sympathectomy.

Four and a half to 8 hours after occlusion, when there were as many as 50 ectopic beats/minute among the controls there were no ectopic beats at all in those with bilateral upper thoracic sympathectomy.

The duration of the time during which delayed ectopic activity usually occurrs, Harris's 3rd stage was shortened by cardiac sympathectomy.

McEachern's (1940) work showed that ablation of the cardiac sensory pathways reduced the incidence of ventricular fibrillation but the size of infarctions was not changed following coronary occlusion. Shumacker et al (1956) work showed that upper dorsal sympathectomy protected the ventricles from fibrillation produced by hypothermia.

Carver (1956) reported reduction of ventricular fibrillation due to occlusion of the anterior descending artery from 75% to 20% if the dogs were previously protected by basilar cardiac denervation.

On the other hand, Goott reported no change in the ventricular fibrillation threshold after sympathectomy.

CONDUCTION DEFECTS:

Infiltration of the A-V node by procaine prevented the occurrence of ventricular fibrillation after ligation of the main left coronary artery. Either idioventricular rhythm or slowing of the heart and asystole developed in the majority of instances (Webb 1958).

Riberi (1956) also reported that S-A node infiltration with procaine afforded the ventricles protection against ventricular fibrillation in the hypothermic state.

C H A P T E R V.

ATTEMPTS AT QUANTITATIVE MEASUREMENTS OF THE V.F.T.

In reviewing the literature probably as many methods were used to assess the susceptibility of the ventricles to fibrillation as there are workers. Most of these methods fall in the following groups:

I. Bio-assay Methods:

(a) Meek (1937) used test doses of adrenaline which in the normal animal caused "reflex vagal inhibition of the pacemaker with or without escape of the A-V node, bundle or ventricle, but never tachycardia or fibrillation". After administration of different anaesthetic agents the same test dose of adrenaline was given and the onset of cardiac irregularities and ventricular fibrillation were noted and compared with the controls.

(b) Shen and Simon (1938) used "Chloroform adrenalin" fibrillation to evaluate the protective action of novocaine against ventricular fibrillation. They allowed the animals to breathe chloroform air mixture for 5 minutes at the end of which time 0.02 mgm adrenalin/kgm was injected intravenously, and the incidence of ventricular fibrillation was recorded. If ventricular fibrillation did not occur the same procedure was repeated. This served as the control series. In another series they gave a dose of novocaine with the

adrenalin after the chloroform inhalation and recorded the difference in the incidence of ventricular fibrillation.

(c) Similarly Shen (1939) used "Benzol-Adrenalin" fibrillation. He showed that whereas 8 dogs died of Benzol-Adrenalin, in another group of 7 dogs protected by 8-10 mgm/kgm procaine, fibrillation never developed. Smaller doses of procaine administered to a third group of 5 dogs failed to protect them.

(d) Burstein and Marangoni (1940) used adrenalin and cyclopropaine to produce ventricular fibrillation in normal dogs and in those previously protected by procaine.

(e) Fauteux (1946) used a combination of adrenalin injection and ligation of the A.D.A. or circumflex artery at a level which would not produce ventricular fibrillation by itself within one hour, to produce ventricular fibrillation. He then assessed the protective action of pericoronary neurectomy and ligation of the great cardiac vein in a similarly treated group of dogs.

(f) Malinow (1953) used Calcium Chloride intravenously to produce ventricular fibrillation in rats. He considered short or long runs of ventricular flutter and fibrillation as ventricular fibrillation and used this calcium chloride-induced arrythmia to assess the protective action of different drugs and surgical procedures.

(g) Berman (1958) compared the incidence of ventricular

fibrillation from acetylcholine and hypothermia alone with that of acetylcholine, hypothermia and magnesium sulphate, quinidine or histadyl.

(h) Carver (1950) studied the effect of vagotomy and different drugs on the incidence of ventricular fibrillation produced by large doses of mercurial dieuretics.

It is obvious that so many factors influence the production of ventricular fibrillation by combination of drugs, or drugs and hypothermia or ischaemia that these techniques could not be used as an accurate quantitative measure of ventricular fibrillation.

II. Methods based on determination of the strength or duration of currents which are just sufficient to induce ventricular fibrillation:

(a) Hoff and Nahum (1934) applied 60 cycle alternating currents through the limb of cats keeping the strength constant but varying the duration. They reported that A.C. shocks of shorter duration induce fibrillation following the use of epinephrine but shocks of longer duration were required after subcutaneous administration of acetyl choline.

(b) Moisset deEspane (1937) found that stronger tetanizing currents were necessary to induce ventricular fibrillation in dogs after administration of quinidine.

The nature of such thresholds is extremely doubtful since Wiggers has shown that a very brief unitary stimulus

applied during the vulnerable period of a single systole can induce fibrillation. He also showed that oscillating currents give erratic response even if the amplitude and frequency were kept constant.

III. Determining the duration of fibrillation or the number of times of spontaneous recovery from fibrillation in cats:

(a) Smith and Mulder (1936) used the duration of fibrillation after a 2 seconds tetanizing current as a quantitative measure in studying the effect of stimulation of the accelerator nerve.

(b) Van Dongen (1936) similarly used the number of times that spontaneous recovery from fibrillation, due to the electric current, takes place after denervating the heart and the use of different drugs.

Ettinger (1935) however, found that there was no relation between the strength of current and duration of fibrillation in 40 normal cats. The same effective current applied at different times to the same animal induced fibrillation verying greatly in duration. Wiggers (1940) also reported that in one cat the duration in 8 consecutive tests varied from 2 - 92 seconds.

IV. Comparing threshold shocks which, when applied during diastole, will induce a premature beat:

This was used by McCord (1913) who reported that V.F.T. was reduced by the intravenous use of potassium chloride.

V. Beck and Mautz (1937) utilized the reduction of the number of counter-shocks that are necessary to defibrillate the heart as another quantitative measurement in studying V.F.T.

VI. Bluementhal and Oppenheimer (1939) suggested using the amount of Barium chloride which is just sufficient to fibrillate the heart. This technique allows only one determination on one animal.

VII. Hypothermia and venous inflow occlusion was used by Shumacker (1956), to study the effect of sympathetic paralysis, vagal paralysis, vagal stimulation and ganglion blocking agents on ventricular fibrillation.

VIII. Coronary artery occlusion as a way of assessing the susceptibility to ventricular fibrillation was used by Badeer (1962), Stephenson (1960).

Since mortality after occlusion of the A.D.A. varies widely from center to center, it is to be expected that the incidence of ventricular fibrillation will also vary.

IX. Wiggers, C.J. and Wegria, R., in a series of

experiments (1938, 1939, 1940) studied the effects of different types of electric shocks and their relation to cardiac systole in the production of ventricular fibrillation.

They recommended that the intensity of a brief, single shock, applied during the vulnerable period of systole to produce ventricular fibrillation, be used as a quantitative measure to study ventricular fibrillation. The duration of the current to be kept constant. They also found that rectilinear shocks of 10 - 30 m. seconds duration were most convenient since they fell entirely during the vulnerable period and that bipolar stimulation is preferable to unipolar. These workers were also aware of the variations of ventricular fibrillation threshold due to change in temperature or site of electrodes. The instrumentation used was somewhat complicated.

Shumway, Johnson and Stish (1957) utilizing the facts pointed out by Wiggers, described a technique and instrumentation by which V.F.T. could be accurately determined. They also established certain criteria that should be satisfied before any group of shocks producing fibrillation could be comparable. These are:

1. The current must be measured;
2. Duration of the current must be the same for all shocks;
3. It should always be a single shock;
4. This shock should be delivered during the vulnerable period.

This technique has been repeatedly used since then and found very satisfactory. It is essentially the one used for this study.

CHAPTER VI.

A. Instrumentation

This is essentially the same as that used by Shumway , Johnson and Stich (1957). Instead of using a separate stimulator, a trigger box and two oscilloscopes, a single unit Cardiostimuloscope* was specifically developed for this study. The unit consists of a conventional Electrocardioscope circuit, a triggered time base driven by the R wave which shows one cycle only, at any heart rate. A time delay variable starting from front of the R wave to the end of the T Wave. The delayed pulse is used to trigger a thyratron which allows one pulse only to pass through at the time of the stimulation.

The pulse coming from the thyratron triggers a 10 m. second pulse of over 100 V. from a Schmidt trigger and a D.C. amplifier composed of a cathode follower which delivers the pulse to the output circuit through a series variable resistance. This permits adjustment of the current applied to the electrodes.

The current is measured through a large capacitor in series with the electrodes, with a high resistance voltmeter calibrated in m. Amperes. across the capacitor.

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* Designed and built by Mr. C. Haefelfinger of A.Tech Company, 146 Pacific Ave., Laval des Rapides, P.Q.

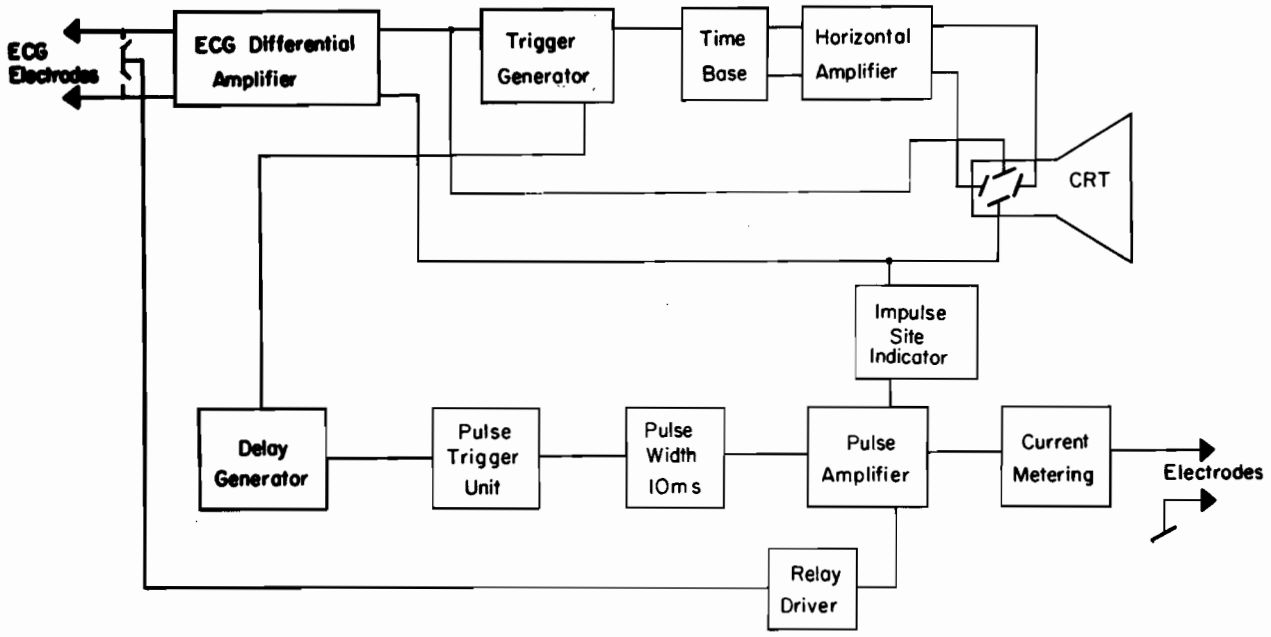

Fig. II. Block Diagram of the circuit of the Cardiostimuloscope.

The pulse current applied to the heart develops a large signal displayed on the cardioscope at time of stimulation. To avoid amplifier and recorder overload a relay shorts the input at time of the stimulus.

The time delay, which indicates the site of the impulse, is continuously monitored on the scope and is seen as a small bright dot superimposed on the E.C.G. tracing. The apparatus could be connected to a recording unit to obtain permanent records.

By adjusting the output and delay settings, a single square-wave electric shock from 1.5 to 65 m. Amperes could be delivered to the heart at any spot in the cardiac cycle from front of the R wave to the end of the T upon release of the triggering button.

The duration of the impulse was fixed at 10. m. seconds for all the times. It could not be changed.

For E.C.G. electrodes, needles were found more convenient. Two needles from the right arm and left leg were used. Two very fine needles were used to stimulate the heart.

Fig. III. A photograph of the instruments used. The numbers on the Cardiostimuloscope represent:

1 - E.C.G. inlet

2 - Cardioscope screen

3 - Gain control

4 - Triggering sensitivity

5 - Tracing Speed

6 - Triggering button

7 - Delay range

8 - Output control

9 - Output range

10 - Output of stimulating electrodes

11 - Stimulus positioning

B. Methods

Adult mongrel dogs varying in weight between 40 and 50 lbs were used. Sodium pentobarbital 30 mg per kg body weight intravenously was used for anaesthesia. This dose was adequate for most of the experiments; 30 to 60 mgm supplements were sometimes given 2 to 3 hours after the initial dose if more was required.

The animals were intubated with a cuffed endotracheal tube and ventilated with a mixture of 40% O_2 and air using the Bird respirator.

The dogs were shaved and the skin prepared and draped in the usual way. Sterile technique was used when survival of the animal was planned. A left fifth intercostal space thoracotomy was made, the left lung was retracted posteriorly and the pericardium opened longitudinally anterior and parallel to the phrenic nerve. The edges of the pericardium were sutured to the edges of the wound, making a cradle out of the pericardial sac. The temperature of the dog was measured in the oesophagus by a telethermometer electrode and monitored continuously. This was kept constant within 1 degree Centigrade for any one dog (Phibbs 1959). All thresholds were determined on the anterior surface of the left ventricle in the area of distribution of

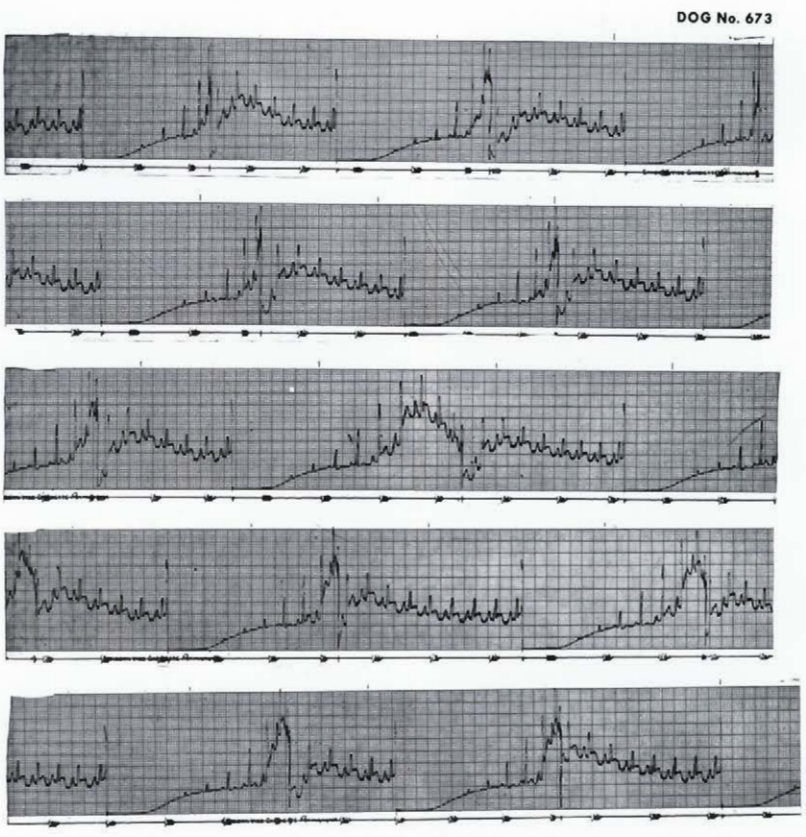

Fig. IV. E.C.G. recording of a typical scanning of the cardiac cycle.

A. Scanning started in front of the R wave and advanced by 5-10 m.seconds.

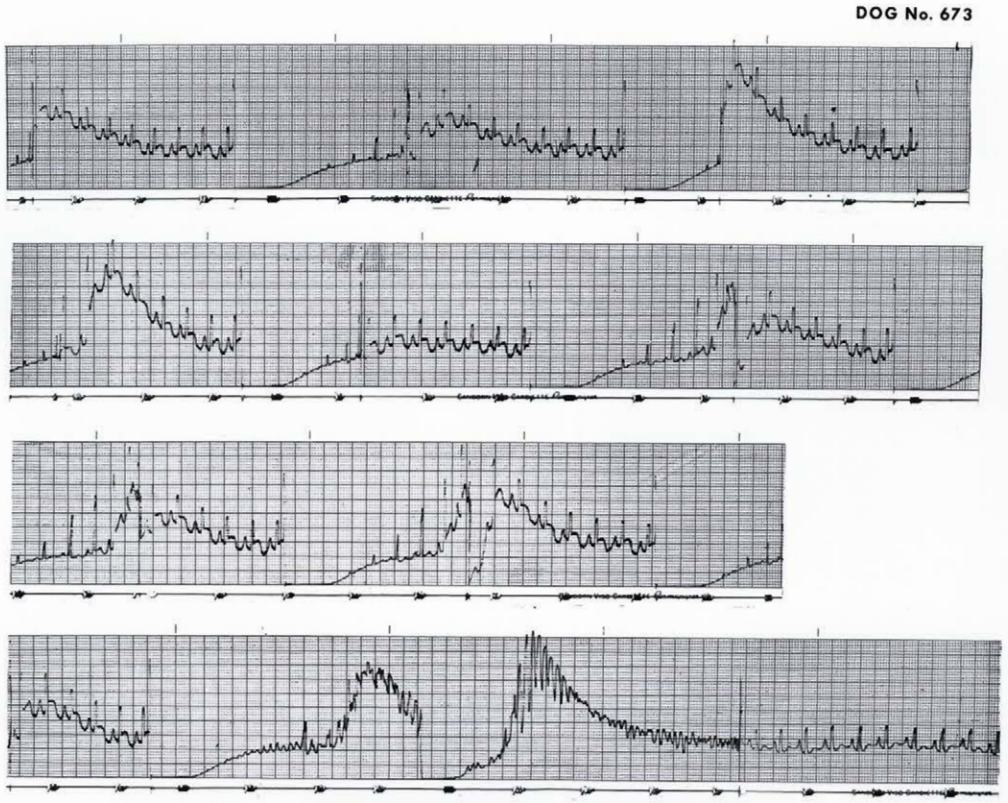

Fig. IV. B. Continuation of the same tracing of Fig. IV. A. Stimulation resulted in ventricular fibrillation after the 22nd schock. The heart was immediately defibrillated.

the anterior descending artery. The site of the electrode was always kept the same. The inter-electrode distance varied between 15 and 25 m.m. but was kept constant for each dog.

The heart electrodes were L shaped and the horizontal limb of the L was placed about 3 m.m. deep in the myocardium. The needles were left in the heart all during the time of stimulation, but were taken out to defibrillate the heart. The animal was placed on a wooden table and no grounds were ever used in order to keep the dog completely insulated.

A single stimulus of 10 milliseconds duration was delivered to the heart beginning with the Q.R.S. complex and was repeated in subsequent cardiac cycles, each time increasing the delay by 5 milliseconds. This was the absolute maximum of the delay increase between stimuli. About 15 beats were allowed between each stimulus. This was repeated throughout the cardiac cycle. Since the duration of the impulse was 10 milliseconds and the delay from the R wave was increased by 5 milliseconds, we could deliver stimuli to the heart before, during and following the entire vulnerable period, the last 30 - 90 milliseconds of cardiac systole.

After sweeping the whole cardiac cycle at one

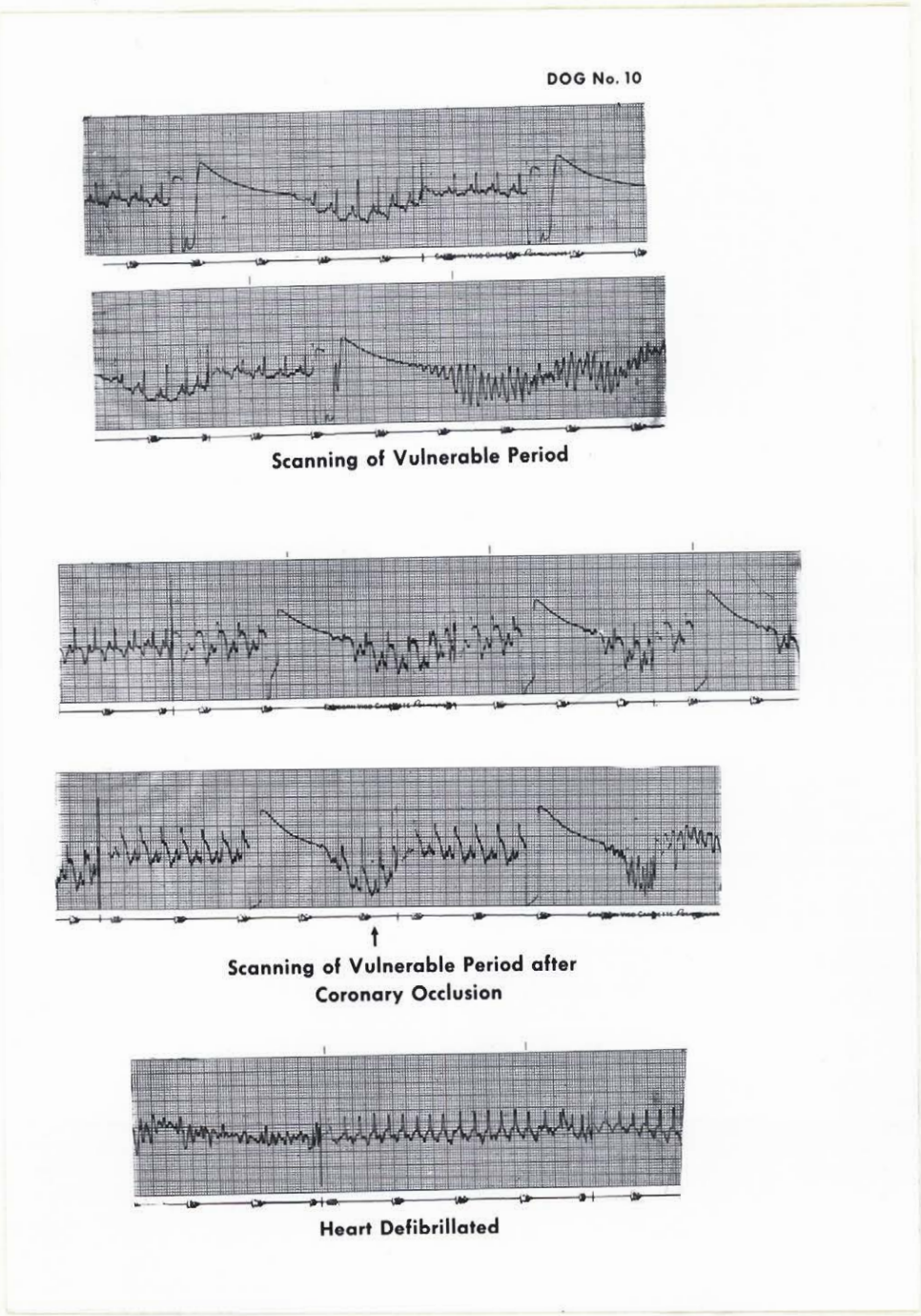

Fig. V. E.C.G. tracings showing scanning of the vulnerable period of a normal heart resulting in V.F. The lower tracings are of the same procedure in presence of coronary occlusion in the same dog.

sub-threshold strength, the procedure was completely repeated using a stimulus 1 - 2 m. Amperes higher than the preceding one.

Since the majority of the normal ventricular fibrillation threshold are in the twenties, it was felt that 10 or 12 m. Amperes is a safe sub-threshold level at which to start scanning. This was repeated until persistent ventricular fibrillation occurred at which time the heart was defibrillated quickly.

Defibrillation:

For defibrillation a Medtronic internal defibrillator was used. Large 8 x 12 cm. heart-shaped paddles were used to avoid thermal injury to the heart. Single shocks of 100 Volts and 0.15 second duration were used and one shock was usually effective. If the ventricular fibrillation threshold was determined in the presence of ischaemia a second shock was sometimes required.

No drugs were ever used in this study to resuscitate the heart. Defibrillation by counter-shock technique produced no significant changes in either excitability or vulnerability. This is in agreement with the findings of Hoffman, Suckling and Brooks (1955).

At least 20 minutes were allowed before a

second determination was attempted. After performing the operation and determining all desired V.F.T's the pericardium was closed. The lung was expanded, a chest tube placed in a suitable position and connected to an underwater seal. The chest was then closed. Suction on the chest bottle was then applied for a few minutes to expand the lungs and the tube was then withdrawn.

C. Operations

i). Coronary occlusion.

The anterior descending branch of the left coronary artery was exposed 1 cm. from its origin. A small incision in the epicardium overlying the vessel was made and using a right angle forceps the artery was gently exposed and completely freed from surrounding tissues, all around, for a length of about 4 m.m.

A suture was passed underneath the artery for traction purposes. To determine the V.F.T. in the presence of ischaemia, the heart electrodes were placed and the output of the Cardiostimuloscope was adjusted to 3 m. Amperes. The artery was then occluded using a small non-crushing vascular clamp. A full minute was allowed to elapse before stimulation was started to allow for stabilization of the heart (Phibbs 1959). Scanning was carried out for 3-4 minutes at a time, then the occluding clamp was removed slowly. After 2 - 3 minutes the same

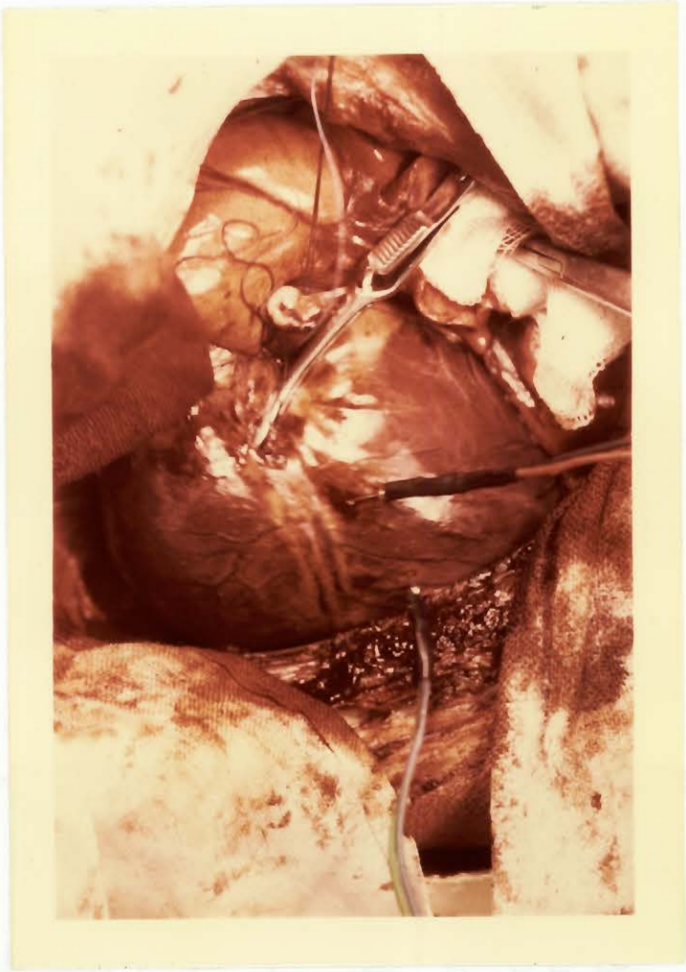

Fig. VI. Photograph of the heart showing the stimulating electrodes in position while the A.D.A. is occluded.

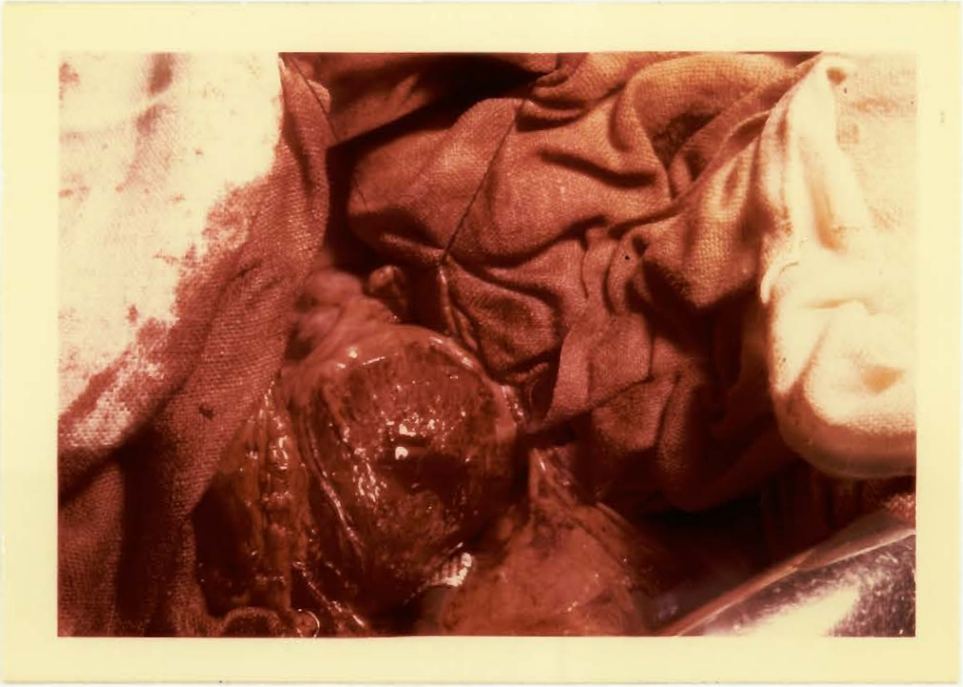

Fig. VII. Epicardectomy. Photograph of the heart after the epicardium of the left ventricle has been removed.

process was repeated. Only the artery was occluded. The veins were intact. Determination of the V.F.T. in the presence of ischaemia was performed routinely in all dogs before any other procedure was done.

ii) Epicardectomy.

The epicardium was removed from both ventricles, anterior and posterior surfaces, as much epicardium was removed as possible until small punctate bleeding points were seen on the surface of the myocardium. Care was taken not to injure the coronary vessels. Small coronary veins that were inadvertently injured were sutured using #5-0 silk. The Beck scraper was mainly used. To remove the epicardium in between the coronary vessels the scraper developed by Pifarre (1962) was useful.

After epicardectomy, it was noted that the size of the heart was larger and closing the pericardial sac was difficult. In one case by forcing the pericardium together the ventricles fibrillated spontaneously, so the pericardium was left open after all epicardectomy procedures.

iii) Neurectomy:

The pericardium was opened as high as possible. The thymus gland was dissected off the upper end of the pericardium in order to open it. This exposed the

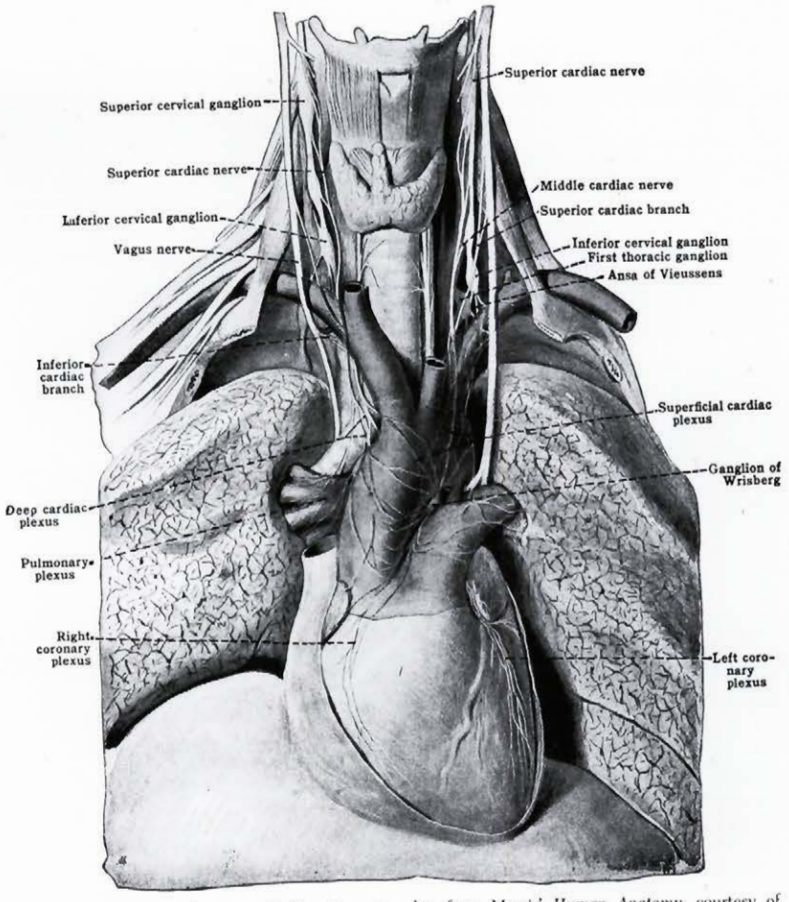

Figure III-28. Ventral view of dissection to show the nerve supply to the heart. (After Tandler, from Morris' *Human Anatomy*, courtesy of Julius Springer and The Blakiston Company.)

Fig. VIII. Photograph of a dissection of the nerves supplying the heart.

pulmonary artery to its bifurcation and the ascending aorta underneath. The left atrial appendage was retracted posteriorly.

The adventitia of the pulmonary artery was incised longitudinally from above the pulmonary valve by about 0.5 cm. to the bifurcation, a distance of 3 - 4 cm. Using the forceps and fine dissecting scissors, dissection was carried along the whole length of the artery, forward, towards the aorta raising a wide flap of adventitia. This is continued over the aorta, left side, anteriorly and then the right side. Dissection is carried as far to the right as possible. Since this is done from the left side, the aorta was retracted upwards and to the left in order to remove the adventitia of the right side. The adventitial flap including the aortic fat bodies (Davis, 1927) is then excised. This exposed well the space between the pulmonary artery and the root of the aorta.

Using the left thumb and index finger, the aorta was retracted away from the pulmonary artery. This exposed the deep cardiac plexus and the ganglion of Wrisberg; using the scissors these nerve fibres and ganglion were excised.

The adventitia over the posterior surface of

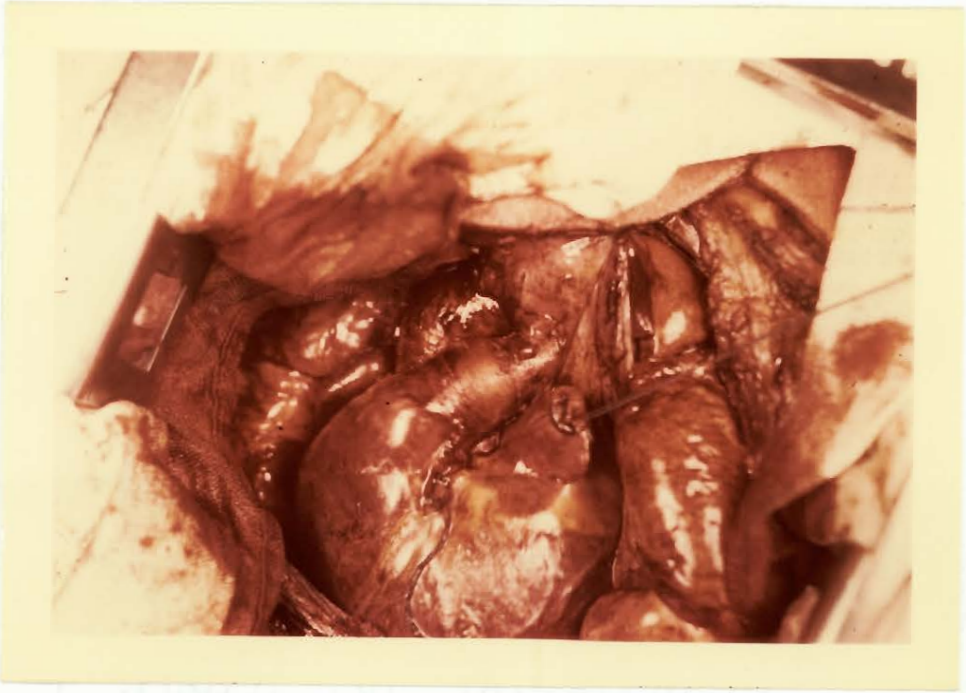

Fig. IX. Neurectomy. Photograph of the heart after excision of the periaortic, peripulmonary and pericoronary cardiac nerves.

the pulmonary artery was then removed. The epicardium and epicardial fat overlying the left coronary artery were incised. The artery was exposed and its adventitia together with the overlying tissues were removed. This was done over the main left coronary artery and for about 2 cm. over the circumflex and anterior descending artery.

In carrying the dissection over the root of the aorta, care should be taken not to injure the right coronary artery or its branches.

CHAPTER VII

EXPERIMENTAL PLAN

In order to study the immediate and late effects of epicardectomy and neurectomy of the heart on the V.F.T. the following groups of experiments were performed:

I. Control of the Technique:

Repeated determination of the normal V.F.T. on the same dog at hourly intervals to ascertain the accuracy and reproducibility of the results.

II. Determination of V.F.T. after occlusion of the A.D.A.

In this group repeated determination of the V.F.T. in the presence of A.D.A. occlusion was performed. After determination of the normal V.F.T., the A.D.A. was occluded and the V.F.T. determined in presence of the occlusion. The coronary occlusion was released and the heart defibrillated. This procedure was repeated 4 - 5 times in the same dog at hourly intervals to study the effect of coronary ischaemia on subsequent determinations of V.F.T.

III. Immediate effect of epicardectomy on V.F.T. in the presence of A.D.A. occlusion:

In this group the normal V.F.T. was determined, the heart defibrillated. The A.D.A. was occluded, the V.F.T.

redetermined and the heart defibrillated. Epicardectomy was performed, the A.D.A. occluded in exactly the same spot as before, the V.F.T. determined again and the heart defibrillated. The chest was closed and the animals allowed to survive.

IV. Late effect of epicardectomy on V.F.T. in the presence of A.D.A. occlusion:

Animals of group III which had epicardectomy were re-examined about 3 weeks post-epicardectomy. The chest was reopened and the heart exposed. The V.F.T. was determined in approximately the same area as in the first operation and the heart defibrillated. The A.D.A. was occluded at precisely the same level of the previous operation. This spot was marked in the first operation by leaving a loop of suture material around the artery, and the V.F.T. determined.

V. Immediate effect of Cardiac Neurectomy on V.F.T. in the presence of A.D.A. occlusion:

In this group the V.F.T. was determined in the normal heart and after occlusion of the A.D.A. Cardiac neurectomy was performed, the A.D.A. occluded, the V.F.T. determined and the heart defibrillated. The chest was closed and the animals allowed to survive.

VI. Late effect of Cardiac Neurectomy on V.F.T. in the presence of coronary occlusion:

Animals of group V were re-examined one week post neurectomy. The chest and pericardium reopened and the heart exposed. The V.F.T. was determined before and after occlusion of the A.D.A. as in the other groups.

CHAPTER VIII

RESULTS

Group 1. (Repeated determination of V.F.T. in normal dogs)

Experiment 1:

This dog was operated upon on October 11, 1962. The oesophageal temperature was 38°C. The cardiac cycle was scanned at 12 m.A.; this did not result in fibrillation. The strength of the stimulus was increased to 14, 15, 16, 17.5, 19, 20 and 21 m.A. Ventricular fibrillation occurred at 21 m.A. which was considered the V.F.T. The heart defibrillated, and one hour later the whole process was repeated, starting from 18 m.A., then 20 and 21, which resulted in ventricular fibrillation. One hour after defibrillation a third determination of the V.F.T. was 22 m.A.

Experiment 2:

This dog was operated upon on October 16, 1962. The oesophageal temperature was 37.5°C. The first determination of the V.F.T. was 24 m.A., that was the same for the second determination. On the third determination the V.F.T. was 23 m.A. and on the fourth it was again 24 m.A.

Experiment 3:

This dog was operated upon on October 17, 1962. Oesophageal temperature was 38.5°C. The V.F.T. was 20 m.A. on the first and second determinations. The same current

failed to fibrillate the heart on the third trial and the current was increased to 21 m.A. which resulted in fibrillation. On the fourth determination, the V.F.T. was 20 m.A.

Experiment 4:

This dog was operated upon on November 7. The oesophageal temperature was 38°C. The V.F.T. was 27 m.A. on the first determination, 29 on the second and 27 on the third and fourth determinations.

Experiment 5:

This dog was operated upon on November 7. The temperature was 37.5°C. The V.F.T. was 27 m.A. on 4 consecutive determinations.

The results of this group are graphically represented in Fig.X.

Group II (Repeated determination of V.F.T. in presence of ischaemia)

Experiment 6:

This dog was operated upon on November 6, 1962. The temperature was 37.5°C. The normal V.F.T. was 27 m.A. on 3 determinations. After occlusion of the A.D.A., the V.F.T. dropped to 5 m.A., and was the same in 5 determinations.

Experiment 7:

This dog was operated upon on November 12, the temperature was 38°C and the normal V.F.T. was 27 m.A. on

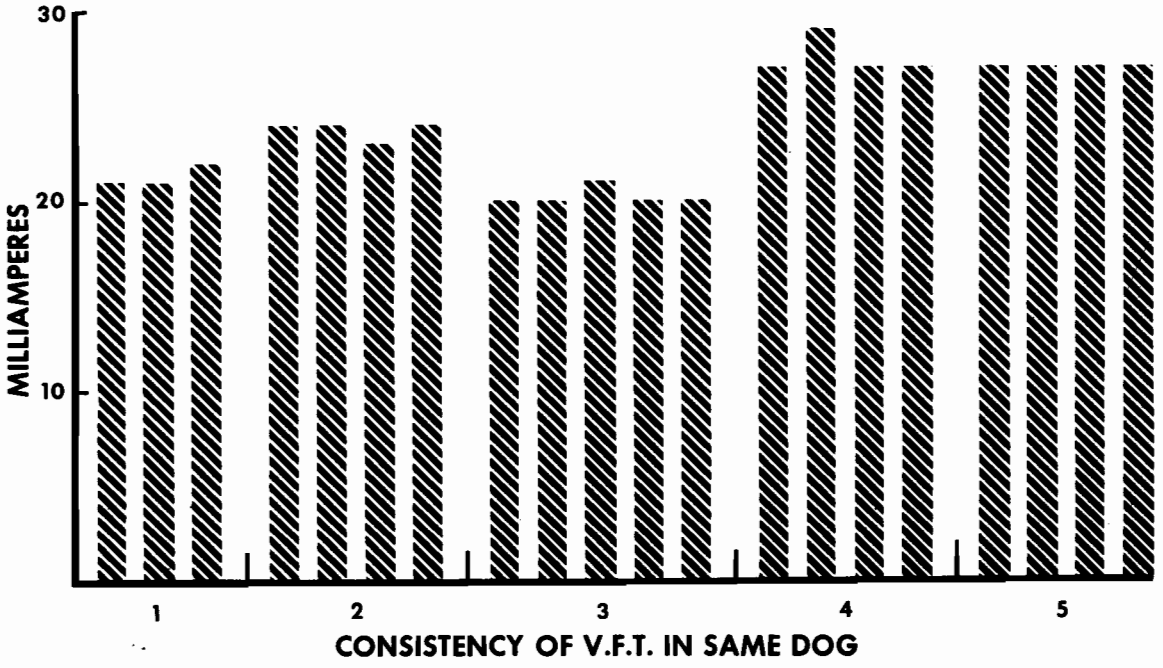

Fig. X. Diagram illustrating the consistency of the normal V.F.T. in the same dog.

2 determinations and after occlusion of the A.D.A. it dropped to 5 m.A. On the second determination after occlusion the V.F.T. was 6 m.A., while on the third and fourth determinations the V.F.T. was 5 m.A.

Experiment 8:

This was done on November 13, the temperature was 37°C. The normal V.F.T. was 16 m.A. on 2 consecutive determinations and after occlusion of the A.D.A. it dropped to 4 m.A. on 4 determinations.

Experiment 9:

This was done on November 14, the temperature was 37°C. The normal V.F.T. was 25 m.A. and after occlusion it dropped to 5 m.A. which was consistent in 3 determinations.

Experiment 10:

This was done on November 19. The oesophageal temperature was 37°C. The normal V.F.T. was 19 m.A. on 2 determinations and after occlusion of the A.D.A. it dropped to 4 m.A. That was constant during 5 determinations.

The results of this group are graphically represented in Fig. XI.

Group III (Immediate effect of epicardectomy)

Dog No. 629:

This dog was operated upon on December 12. The oesophageal temperature was 37°C. The normal V.F.T. was

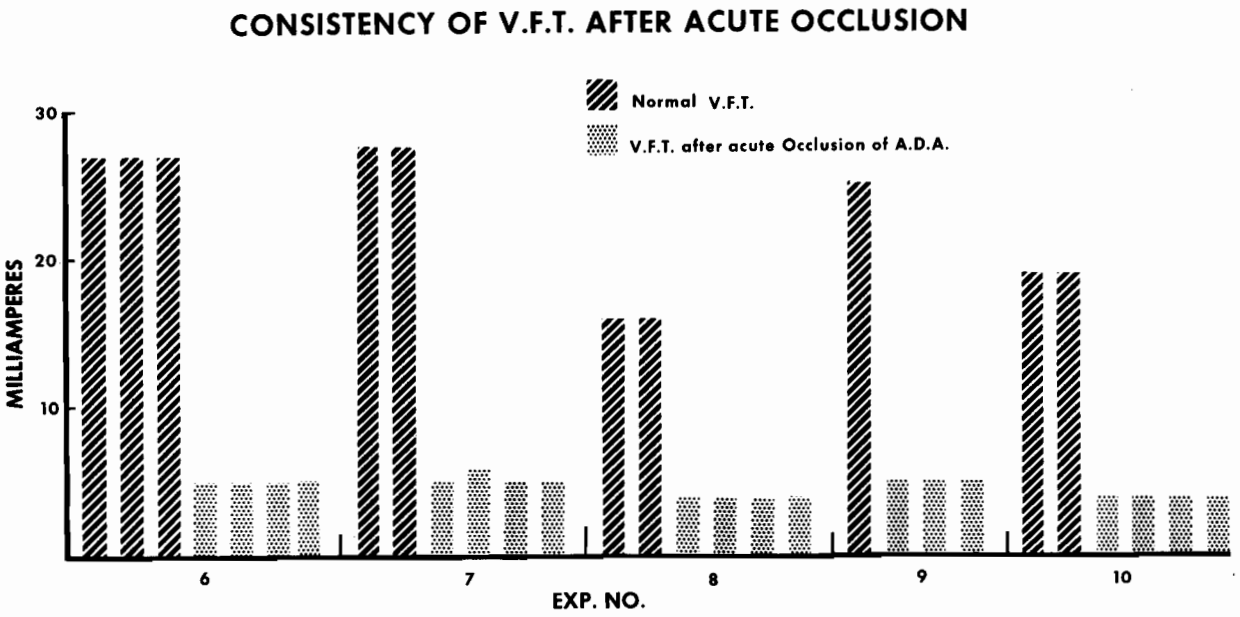

Fig. XI. Diagram illustrating the consistency of the V.F.T. in presence of coronary occlusion.

12.5 m.A.; after occlusion of the A.D.A. this dropped to 5 m.A. and immediately after epicardectomy, in the presence of A.D.A. occlusion, the V.F.T. was 6 m.A.

Dog No. 166:

This dog was operated upon on November 22. The temperature was 38.5°C. The normal V.F.T. was 25 m.A. and after occlusion of the A.D.A. this dropped to 5 m.A. Immediately after epicardectomy, in the presenceof A.D.A. occlusion, the V.F.T. was 7 m.A.

Dog No. 10:

This dog was operated upon on November 28. The temperature was 38°C. The normal V.F.T. was 30 m.A. which dropped to 5 m.A. after occlusion of the A.D.A. Immediately after epicardectomy, the V.F.T. was 10 m.A. in the presence of A.D.A. occlusion.

Dog No. 649:

This dog was operated upon on November 29, the temperature was 37°C. The normal V.F.T. was 14 m.A; after occlusion of the A.D.A. the V.F.T. dropped to 6 m.A. and immediately after epicardectomy the V.F.T. did not show any change.

Dog No. 686:

This dog was operated upon on November 30. The temperature was 37.5°C. The normal V.F.T. was 30 m.A. After occlusion of the A.D.A., the V.F.T. was 4 and

immediately after epicardectomy, in the presence of A.D.A. occlusion, the V.F.T. was 9 m.A.

Dog No. 125:

This dog was operated upon on December 3, 1962. The temperature was 37°C. The normal V.F.T. was 24 m.A. and after occlusion of the A.D.A, it dropped to 3 m.A.; immediately after epicardectomy the V.F.T. was 5 m.A.

Dog No. 687:

This dog was operated upon on December 4, 1962. The temperature was 37.5°C. The normal V.F.T. was 24 m.A. After occlusion of the A.D.A., the V.F.T. dropped to 11 m.A. and immediately after epicardectomy, the V.F.T. became 18 m.A.

Dog No. 695:

This dog was operated upon on December 5. The temperature was 39°C. The normal V.F.T. was 19 m.A. After occlusion of the A.D.A. it dropped to 6 m.A. and immediately after epicardectomy, the V.F.T. was the same.

Dog No. 673:

This dog was operated upon on December 6. The temperature was 38.5°C. The normal V.F.T. was 27 m.A. and after occlusion of the A.D.A. it dropped to 7 m.A. Immediately after epicardectomy the V.F.T. was 10 m.A.

Dog No. 667:

This dog was operated upon on December 7. The

temperature was 37°C. The normal V.F.T. was 22 m.A. and after occlusion of the A.D.A., it dropped to 5 m.A. Immediately after epicardectomy the V.F.T. was 7 m.A.

Dog No. 145:

This dog was operated upon on December 11, 1962. The temperature was 38°C. The normal V.F.T. was 24 m.A. After occlusion of the A.D.A., the V.F.T. was 6 m.A. and unchanged after epicardectomy.

Dog No. 624:

This dog was operated upon on December 13, 1962. The temperature was 37.5°C. The normal V.F.T. was 21 m.A. After occlusion of the A.D.A., the V.F.T. dropped to 6 m.A. and was unchanged after epicardectomy.

The results of this group are tabulated in Table 1.

Group IV. (Late effect of epicardectomy on V.F.T.)

Dog No. 629:

This dog had an epicardectomy on November 21, and was re-operated upon 22 days later on December 12, 1962. The temperature was 37.5°C. During this second operation the V.F.T. was 24 m.A. and after occlusion of the A.D.A., it dropped to 7 m.A.

This dog did not show any protection from ischaemia after epicardectomy.

Dog No. 10:

This dog was operated upon 21 days post epicardectomy.

IMMEDIATE EFFECT OF EPICARDECTOMY ON V.F.T.

DOG No.	Normal V.F.T.	V.F.T. after Acute Ischemia	V.F.T. & Acute Ischemia & Epicardectomy
629	12.5	5	6
166	25	5	7
10	30	5	10
649	14	6	6
686	30	4	9
125	24	3	5
687	24	11	18
695	19	6	6
673	27	7	10
667	22	5	7
145	24	6	6
624	21	6	6
Mean	22.7	5.75	8

Table I. Individual values of group III. dogs.

The probability that 8 dogs will have an increase in the VFT after epicardectomy and 4 will have no change is equal to 0.002.

The temperature was 38°C. The V.F.T. was 30 m.A.; after occlusion of the A.D.A., the V.F.T. was 19 m.A. On injecting the left coronary artery while the A.D.A. was ligated, the A.D.A. was filled from the circumflex branch.

Dog No. 686:

This dog was operated upon on December 19, 20 days post epicardectomy. The temperature was 37.5 and the V.F.T. was 29 m.A. After ligation of the A.D.A. the V.F.T. dropped to 19 m.A.

Injection of the main left coronary artery showed retrograde filling of branches of the A.D.A. in spite of the occlusion.

Dog No. 687:

This dog was operated upon on December 20, 1962, 17 days post epicardectomy. The temperature was 38°C, and the V.F.T. was 24 m.A. ; after occlusion of the A.D.A. it dropped to 18 m.A. Injection of the left coronary artery failed to fill branches of the A.D.A. The X-ray of this injection is reproduced in Fig. XII.

Dog No. 695:

This dog was re-operated upon on December 27, 22 days post epicardectomy. The temperature was 38°C and the V.F.T. was 28 m.A.; after occlusion of the A.D.A. it dropped to 14 m.A. Injection of the left coronary artery filled the A.D.A. retrograde.

Dog No. 673:

This dog was re-operated upon on December 28, 22 days post epicardectomy. The temperature was 38°C and the V.F.T. was 31 m.A.; after occlusion of the A.D.A. it dropped to 14 m.A. Injection of the left coronary artery filled the A.D.A. branches retrograde.

Dog No. 624:

This dog was operated upon on January 2, 1962, 20 days post epicardectomy. The temperature was 37°C, and the V.F.T. was 36; after occlusion of the A.D.A. it dropped to 14. Injection of the left coronary artery filled completely the A.D.A. retrograde. The X-ray of this dog is reproduced in Fig. XIV.

The data from this group are shown in Table II.

Group V. (Immediate effect of cardiac Neurectomy)

Individual Summary

Dog No. 109:

This dog was operated upon on January 3, 1963. The oesophageal temperature was 38°C. The normal V.F.T. was 29 m.A., which dropped to 4 m.A. after occlusion of the A.D.A. Immediately after neurectomy the V.F.T. was 9 m.A.

Dog No. 676:

This dog was operated upon on January 4, the temperature was 37°C. The normal V.F.T. was 24 m.A.

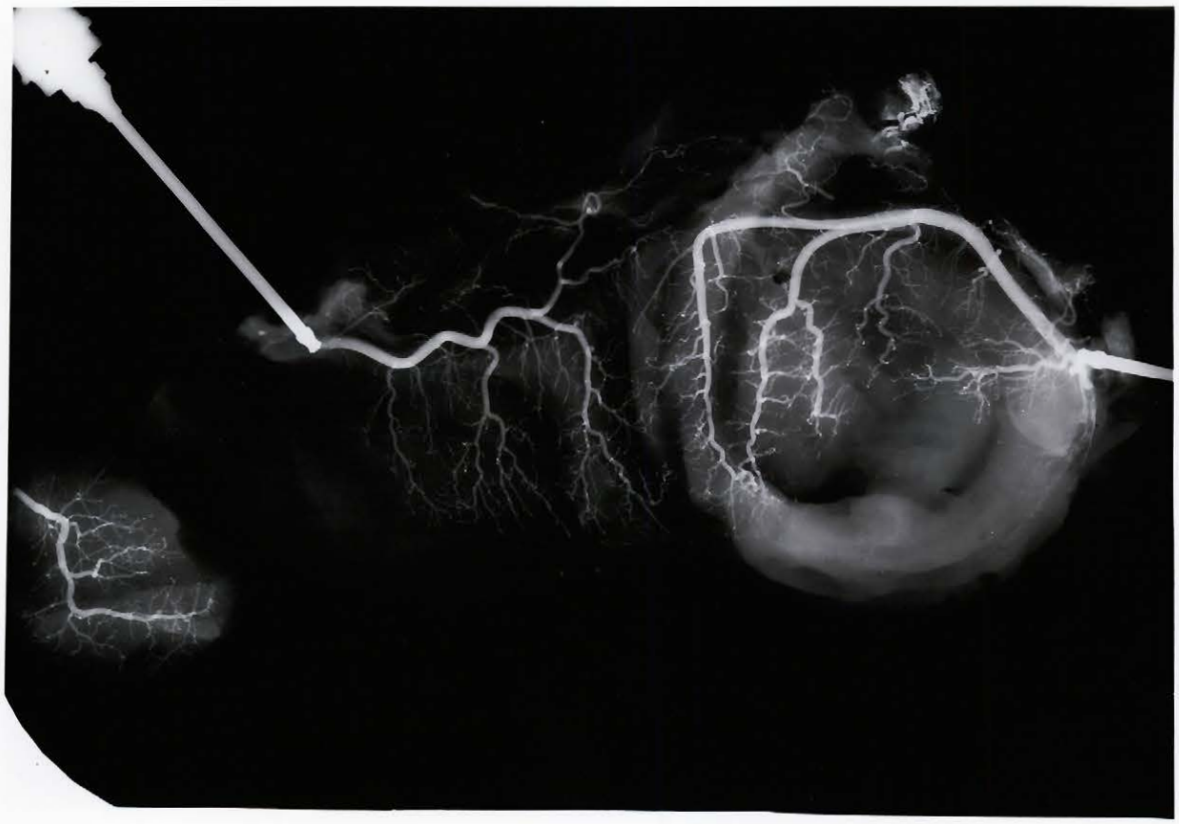

Fig. XII. Reproduction of radiograph of Dog No.687, showing non-filling of the A.D.A. after injection of the right and left coronary arteries. The A.D.A. has been ligated one cm. from its origin.

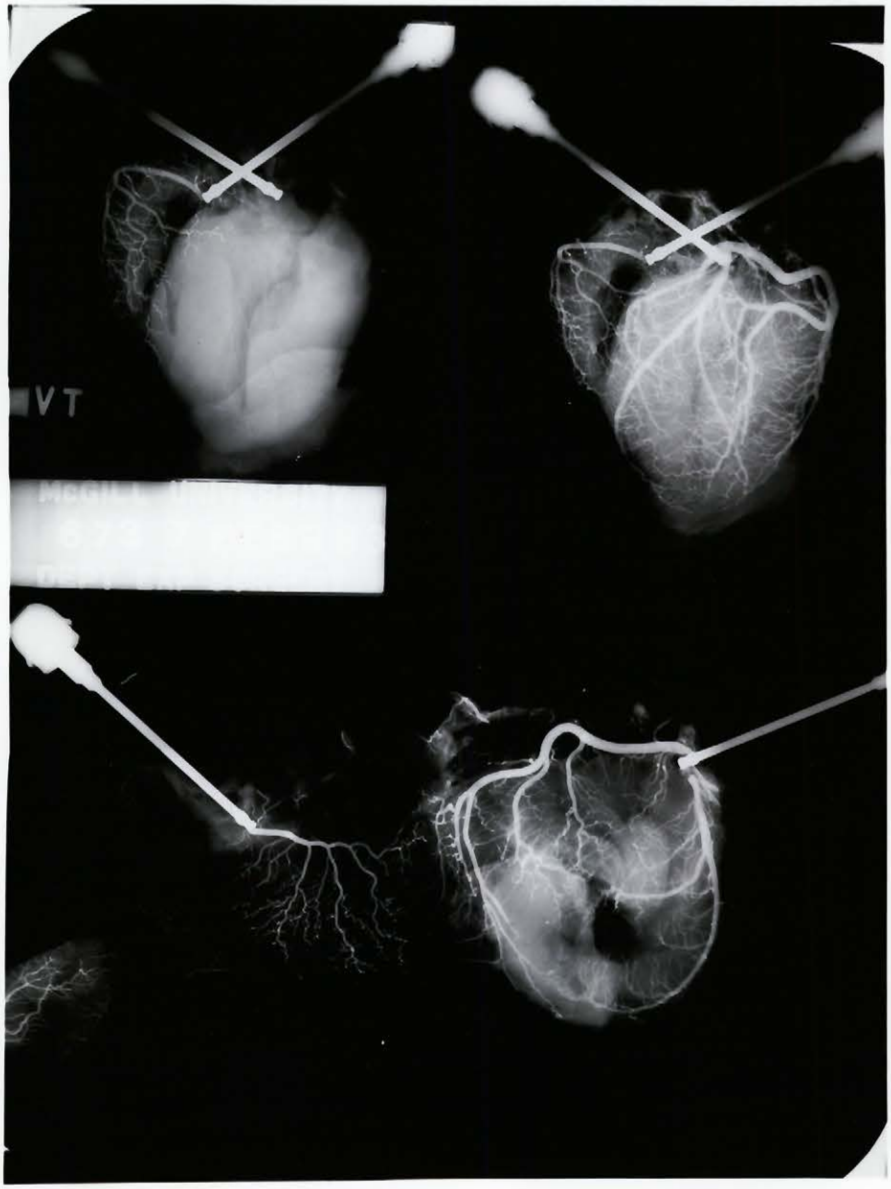

Fig. XIII. Reproduction of radiograph of dog no. 673 showing retrograde filling of the A.D.A. after injection of the left coronary artery inspite of proximal ligation of the A.D.A. The site of ligation is seen in the unrolled heart.

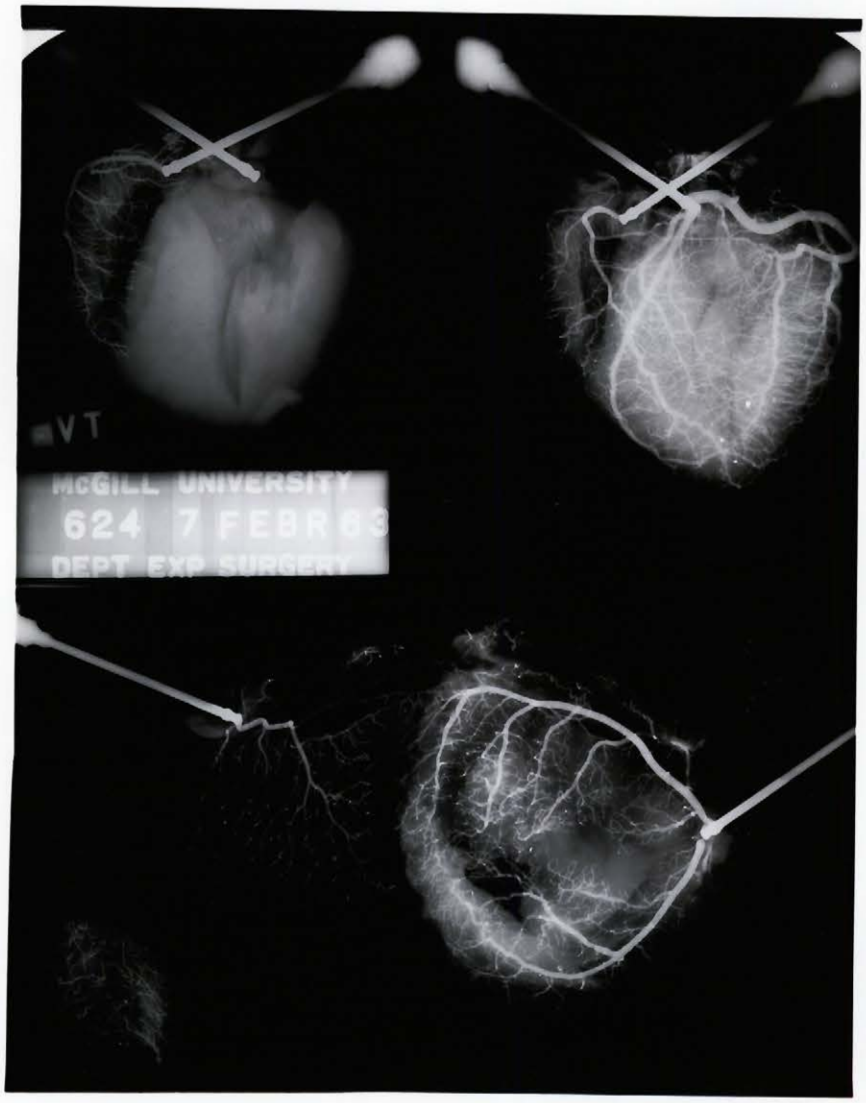

Fig. XIV.A. Reproduction of radiograph of dog no.624 showing retrograde filling of the A.D.A. The site of ligation is seen in the unrolled heart.

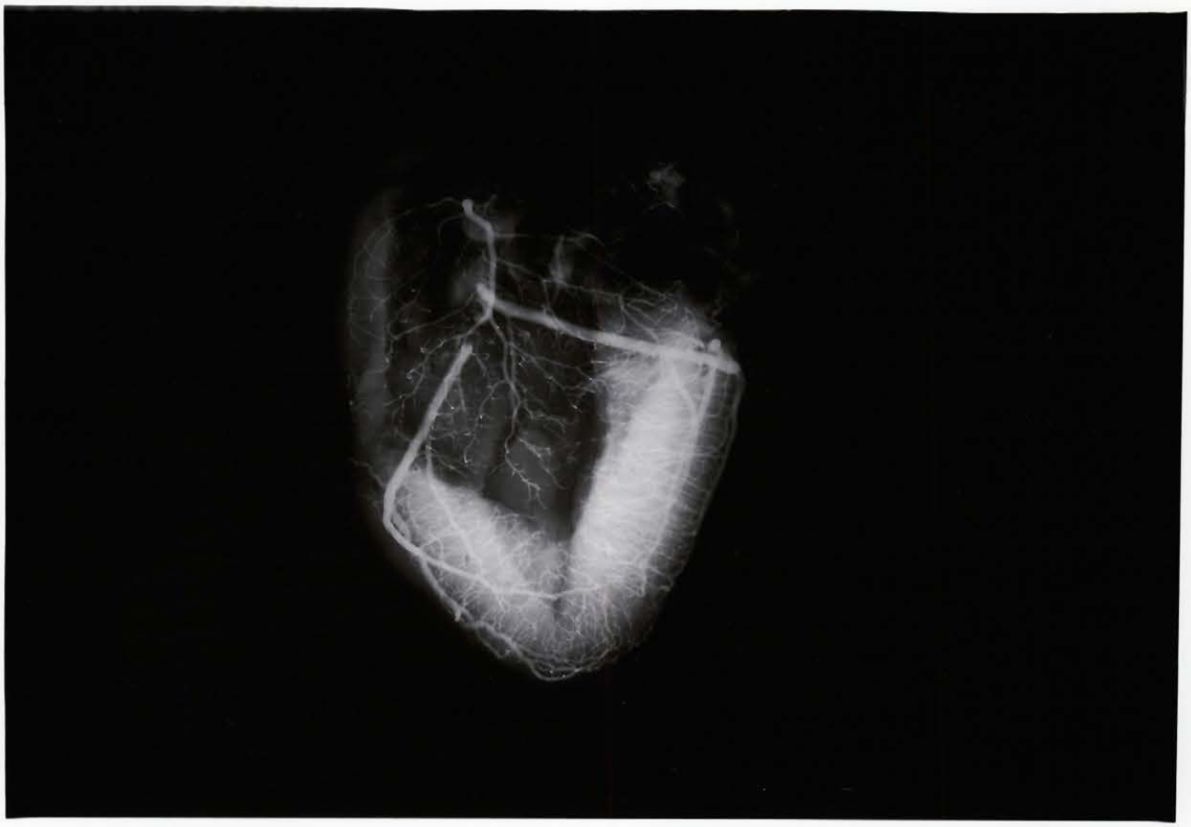

Fig. XIV.B. Reproduction of a lateral radiograph of dog no. 624 demonstrating more clearly the site of ligation of the A.D.A.

DOG No.	V.F.T.	V.F.T. & Acute Ischemia	V.F.T. & Epicardectomy Acute Ischemia	V.F.T. 16-22 days Post Epicardectomy No Ischemia	V.F.T. 16-22 days Post Epica. & Acute Ischemia
629	12.5	5	6	24	7
10	30	5	10	29.30	19
686	30	4	9	29	19
687	24	11	18	24	18
695	19	6	6	28	14
673	27	7	10	31	14
624	21	6	5.6	36	14
Mean	23.3	6.35	9.2	27.8	15

Table II. The individual values of group IV. dogs.

The probability that the 7 dogs will have an increase in the VFT 16-22 days after epicardectomy is equal to 0.004.

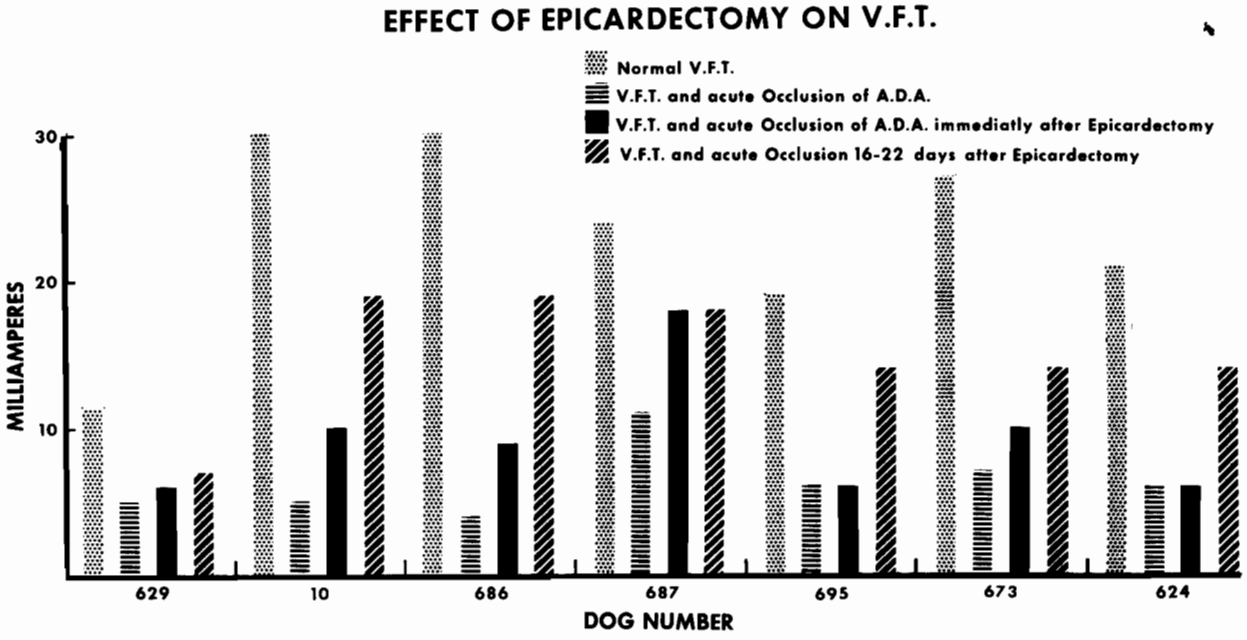

Fig. XV. Illustrates the effects of coronary occlusion, epicardectomy immediate and late on the V.F.T.

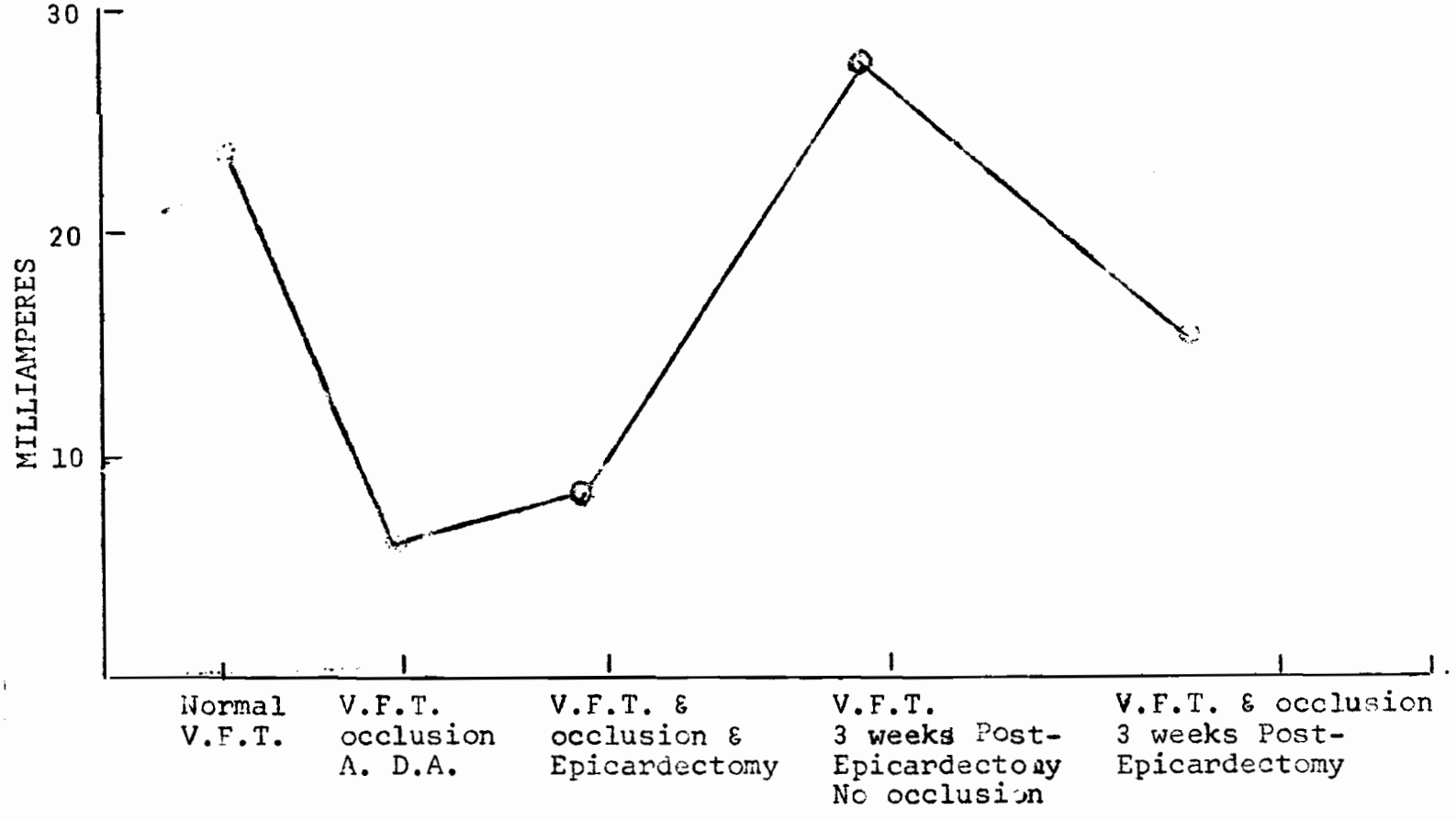

Fig. XVI. Graphic representation of the effects of coronary occlusion, epicardectomy immediate and late on the V. F. T.

and after occlusion of the A.D.A. it dropped to 6. Immediately after neurectomy the V.F.T. did not show any change.

Dog No. 24:

This dog was operated upon on January 7. The temperature was 38°C. The normal V.F.T. was 25 m.A. and after occlusion of the A.D.A. it dropped to 7 m.A. Immediately after neurectomy it was 10 m.A.

Dog No. 641:

This dog was operated upon on January 8. The dog's temperature was 37°C, and the normal V.F.T. was 22 m.A. After occlusion of the A.D.A., it dropped to 3 m.A. and immediately after neurectomy it was 8 m.A.

Dog No. 667:

This dog was operated upon on January 9, 1963. The temperature was 38°C and the V.F.T. was 40 m.A. This is the highest V.F.T. recorded in this project and was repeatedly checked. After occlusion of the A.D.A. it dropped to 6 m.A. Immediately after neurectomy it was 8 m.A.

Dog No. 653:

This dog was operated upon on January 10. The temperature was 37°C and the normal V.F.T. was 25 m.A. After occlusion of the A.D.A. it dropped to 4 m.A. and immediately after neurectomy it was 5 m.A.

Dog No. 888:

This dog was operated upon on February 27. The

temperature was 38°C. and the normal V.F.T. was 26 m.A. After occlusion of the A.D.A. it was 4 m.A. and immediately after neurectomy it was 6 m.A.

Group VI. (Late effect of Neurectomy)

Dog No. 109:

This dog was re-operated upon on January 14, 12 days post neurectomy. The temperature was 38°C. The V.F.T. was 34 m.A. and after occlusion of the A.D.A. it dropped to 10 m.A. Injection of the left coronary failed to fill the A.D.A. in presence of occlusion.

Dog No. 676:

This dog was re-operated upon on January 15, 12 days post neurectomy. The temperature was 37.5°C and the V.F.T. was 34 m.A.; after A.D.A. occlusion, it dropped to 18 m.A. The A.D.A. also failed to show retrograde filling.

Dog No. 24:

This dog was sacrificed on January 15, 8 days post neurectomy. The temperature was 37°C and the V.F.T. was 34 m.A. After A.D.A. occlusion it dropped to 17.5 m.A. The A.D.A. failed to show any retrograde filling.

Dog No. 667:

This dog was sacrificed on January 18, 9 days post neurectomy. The temperature was 38°C and the V.F.T. was 40 m.A.; after occlusion of the A.D.A. the V.F.T. was 7 m.A.

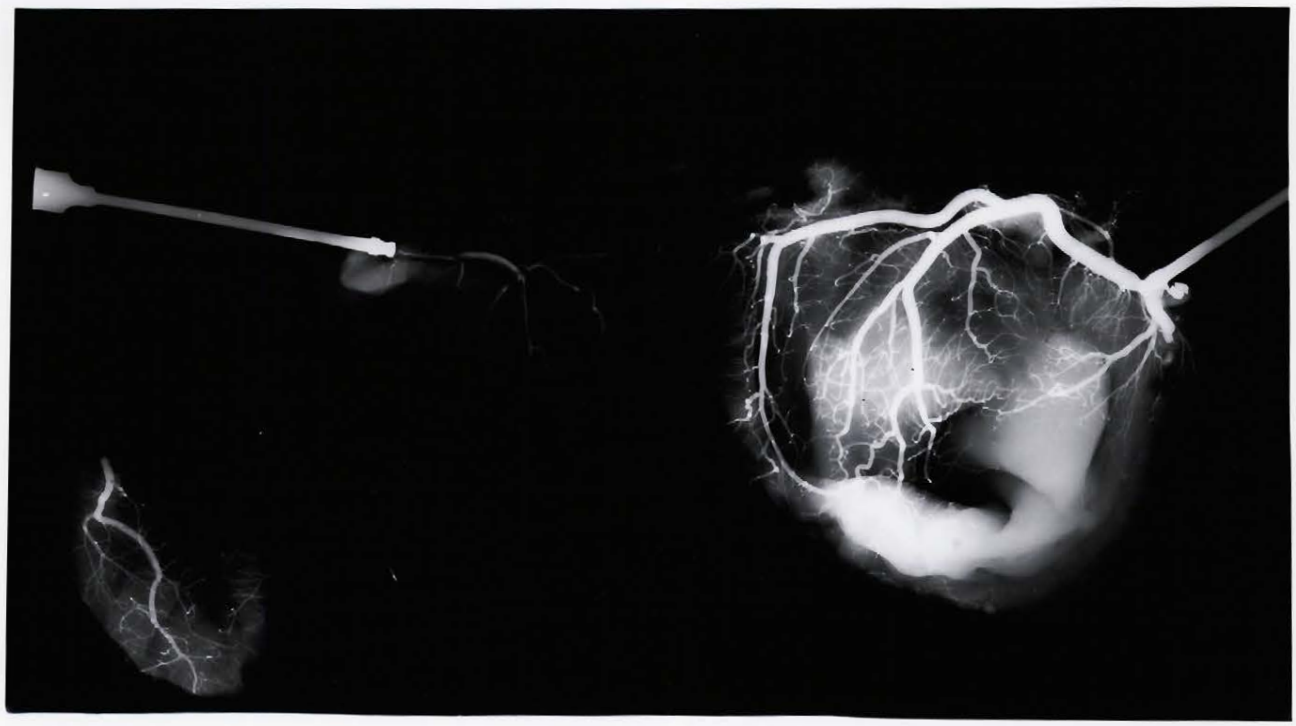

Fig. XVII. Reproduction of radiograph of Dog No.109 showing no retrograde filling of the A.D.A. in the presence of proximal ligation.

Dog No. 888:

This dog was sacrificed on March 6, 7 days post neurectomy. The V.F.T. was 26 m.A. and after occlusion of the A.D.A. was 12 m.A. The A.D.A. did not show retrograde filling.

The results of Groups V and VI are shown in Tables III and IV.

EFFECT OF NEURECTOMY ON V. F. T.

DOG NO.	NORMAL V. F. T.	V.F.T. + A.D.A. occl.	V.F.T.+ Neurectomy + A.D.A.occl.	One week post neurectomy V.F.T.	One week post neurectomy V.F.T.+ A.D.A.occlusion
109	29	4	9	34	10
676	24	6	6	34	18
24	25	7	10	34	17.5
641	22	3	8		
667	40	6	8	40	7
653	25	4	5		
888	26	4	6	26	12
Mean	27.2	4.9	7.2	33.6	12.9

Table III. The individual values of group V. dogs.

The probability that 4 out of 5 dogs will have a higher threshold one week post-neurectomy in presence of coronary artery occlusion is equal to .094.

C H A P T E R IX.

CONCLUSIONS AND DISCUSSION.

In 29 normal dogs studied in these series those of groups I, II, III, and V the V.F.T. varied from 12.5 m.A. to 40 m.A. In 13 or 44% of these dogs the thresholds were between 21 and 25 m.A. and in 9 or 32% the thresholds varied from 26 to 30 m.A., i.e. 76% of the thresholds vary between 21 and 30 m.A. Only 1 normal V.F.T. was above 30 m.A.

The mean value of the normal thresholds in the whole group was 24 m.A.

After occlusion of the A.D.A. there was a marked drop in the V.F.T. The thresholds of 24 dogs, those of groups II, III and V varied from 3 to 11 m.A. In 19 of these dogs or 79% the thresholds varied from 4 to 6 m.A. while 2 or 8% were below 4 m.A. and the threshold in another 2 dogs was 7 m.A. In one case only was the threshold above 7 m.A. The mean value was 5 m.A.

In the epicardectomy group the normal V.F.T. varied between 30 and 12.5 m.A. with a mean of 22.7 m.A. for the whole group. After occlusion of the A.D.A. the thresholds varied from 3 to 11 m.A. with a mean of 5.7 m.A.,

a drop of 74.9% from the normal. Immediately after epicardectomy the thresholds varied from 5 to 18 with a mean of 8 m.A.

Three weeks post epicardectomy the thresholds in absence of ischaemia varied from 24 to 36 m.A. The mean for the 7 dogs of the group was 28.8 m.A. The normal mean of this same group at the first operation was 23.3 m.A., immediately after acute ischaemia this dropped to 6.35 m.A. or 73%. Immediately after epicardectomy and in presence of acute eschaemia the mean V.F.T. was 9.2 m.A. representing a drop of 61%.

In comparing the normal V.F.T., and the V.F.T. 16-22 days post epicardectomy, in absence of ischaemia, it is found that there is an increase from 23.3 m.A. to 28.8 m.A. or 19%.

After occlusion of the A.D.A., 16-22 days post epicardectomy the V.F.T. varied from 7-19 m.A. with a mean of 15 m.A. This 15 m.A. represents 64% of the initial normal V.F.T. and 52% of the threshold obtained before ischaemia during the same second operation. A drop of only 36% of the initial V.F.T. and 48% from the threshold 16-22 days post epicardectomy, compared to a drop of 73% before epicardectomy.

In the neurectomy group the normal V.F.T. varied from 22 to 40 m.A. with a mean of 27.2 m.A. In presence

of ischaemia the thresholds varied from 3 to 7 m.A. with a mean of 4.9 m.A. representing 18.0% of the normal.

Immediately after neurectomy the V.F.T. in presence of ischaemia varied from 5 to 10 m.A. with a mean of 7.2 m.A. One week post neurectomy in a group of 5 dogs the V.F.T. varied from 26-40 m.A. with a mean of 33.6 m.A. The normal mean of these 5 dogs during the first operation was 28.8 m.A. Thus there is a 16.6% increase in the pre-ischaemia thresholds one week post neurectomy.

The pre-neurectomy mean threshold for these 5 dogs after ischaemia was 5.4 m.A. representing 18% of the normal mean.

After occlusion of the A.D.A., one week post neurectomy the thresholds varied from 7-18 m.A. with a mean of 12.9 m.A. which represents 44.9% of the normal pre-neurectomy mean and 38.3% of the one week post neurectomy mean threshold.

This is more than double the mean of the same 5 dogs in presence of ischaemia before neurectomy.

The hearts of Group IV and VI were injected with Schlesinger mass after tying the A.D.A. at the same spot where it was occluded during the V.F.T. determination. In 4 out of 5 satisfactory injections of the post epicardectomy group, the A.D.A. artery was filled by injecting the main left coronary artery, while in 5 similar injections of the

post neurectomy hearts there was no filling what so ever of the A.D.A. or its branches after injecting the left coronary artery.

The protective action of epicardectomy against ventricular fibrillation that is demonstrated by this study might be due to an increased homo-coronary anastomosis as is also shown here and in agreement with earlier works by Stanton & Beck, Harken, and Vineberg. This increase in homo-coronary anastomoses will provide the necessary oxygenated blood to the area of myocardium that is supplied by the occluded artery and thus raise the V.F.T. But the works of Danese (1962), Warren (1962) and Ebert (1962) would suggest that a normal co-ordinated heart action is dependent on other factors besides its dependence on the presence of O_2. It has also been shown that the V.F.T. did not change significantly from its low level 6 months after the onset of chronic ischaemia (VanTyn, 1960) while in a different study the blood supply improved markedly several months after the onset of ischaemia (MacLean, 1962). This would suggest that the improvement in the V.F.T. is dependent on other factors besides increased homo-coronary anastomoses.

Chari (1961) suggested that epicardectomy removes the nerve fibres that are present in the deep layer of the epicardium, thus disrupting the afferent sensory

pathway of impulses that may arise from localized areas of ischaemia in a way acting as a ganglion blocking agent or even a cardiac neurectomy. The work of Guzman (1962) suggested the presence of an intercoronary reflex. It is conceivable that this intercoronary reflex is abolished by epicardectomy.

While neurectomy did not promote homo-coronary anastomoses it still increased the V.F.T. This suggests that it might have abolished intercoronary reflexes, preventing a further diminution in the blood supply of the myocardium adjacent to the area supplied by the occluded coronary artery or that neurectomy interrupted the pathways of central reflexes which might have influenced the initiation of ventricular fibrillation in an unknown way.

S U M M A R Y

1. Ventricular fibrillation was produced in every dog studied in these experiments by a single electric shock of 10 milliseconds duration applied during the vulnerable period of the cardiac cycle. There were no instances where fibrillation could not be produced in the dog.

2. A new cardiostimuloscope was designed and developed for the determination of the ventricular fibrillation threshold.

3. The normal V.F.T. is repeatedly consistent and reproducible in the same dog if the temperature, site of stimulating electrodes, and interelectrode distance are constant.

4. Ischaemia produces a marked drop in the V.F.T.

5. It is extremely difficult to defibrillate the heart in the presence of a major coronary artery occlusion, in the experimental animal.

6. Repeated determinations of the V.F.T. in presence of ischaemia were constant.

7. Epicardectomy immediately influenced the V.F.T. slightly.

8. Three weeks post epicardectomy the pre-ischaemia V.F.T. was higher than the initial normal V.F.T.

9. The V.F.T. in presence of ischaemia was considerably raised 3 weeks post epicardectomy.

10. This rise in the V.F.T. after epicardectomy occurred in the absence of chronic ischaemia. Thus, it is not essential to have a pressure gradient in order to achieve protection from epicardectomy.

11. Epicardectomy did increase the incidence of homo-coronary anastomoses.

12. Neurectomy immediately influenced the V.F.T. slightly.

13. One week post neurectomy the rise in the V.F.T. was more marked.

14. The late effect of neurectomy on the V.F.T. is less pronounced than the late effect of epicardectomy.

15. Neurectomy influenced the V.F.T. favourably while it did not promote coronary anastomosis.

C H A P T E R I.

SECTION B.

STUDIES ON AN ACTIVE CORONARY VASODILATOR

SECTION B. CHAPTER I.

INTRODUCTION.

In 1951 Fisher and Roch described the synthesis of a new double ring structure from two condensed pyrimidine rings. Following the introduction of this group of compounds several derivatives from this pyrimido (5, 4-d)-pyrimidine series were synthesized and certain ones were found interesting in respect to the mode of action on cardiac function.

One of these compounds, Persantin, which has the following structure: 2,6-bis di(2-hydroxyethyl) amino-4,8-bis (1-piperidyl) pyrimido-(5,4-d)-pyrimide, has been shown by Kadatz (1959) to have significant effects on coronary blood flow. Elliot (1961) has reported that Persantin increases the coronary flow in experimental animals up to 300% of normal. Bretschneider et al (1959) reported flow increases up to 400% with a 200% increase persisting for 10 minutes and 100% increases for several hours, while the myocardial O_2 consumption remains constant.

The degree of increase of coronary flow with this drug is of much greater magnitude and duration than that seen with nitrates, papaverine (Doerner, 1960) and Xanthines (Bretschneider,1959).

West (1962) found increases in coronary blood flow

to an average of 159% in normal animals without increasing cardiac contractility or cardiac work after administration of 0.2 mgm/kgm Persantin intravenously. This increased coronary flow was sustained for 20 - 30 minutes with the peak effect being reached within 3 minutes. The coronary resistance markedly decreased, the coronary venous oxygen content increased with a decrease in the coronary A-V oxygen difference. In dogs with ameroid constrictors, Persantin increased the coronary blood flow by 75% of control levels and also decreased the coronary resistance and coronary arterio-venous oxygen difference. In these dogs the decrease in coronary resistance and coronary arterio-venous oxygen difference was less than that noticed in normal dogs.

Kinsella et al (1962) arrived at similar conclusions after studying a group of normal and arteriosclerotic patients.

Vineberg et al (1962) reported an increase in survival and development of collateral coronary vessels in a group of dogs subjected to gradual ameroid coronary constriction while on Persantin in comparison to a similarly treated group of control dogs without Persantin.

The above findings seemed interesting enough to carry out further investigation on this preparation. The present study involved 3 different techniques.

Methods

A. Determination of V.F.T:

A group of 6 dogs was given two 25 mgm tablets of Persantin contained in a small meat ball 3 times a day. After a period varying from 67 - 95 days, those dogs were operated upon, the normal V.F.T. and the V.F.T. in presence of A.D.A. occlusion was determined as previously described. These values are compared with the values obtained in normal dogs from section A. These hearts were also injected, as in B.

B. Survival from Ameroid Constrictors:

A group of 20 mongrel dogs varying in weight between 40 - 50 pounds were operated upon as in Section A, Chapter VI. After retraction of the left atrial appendage, the anterior descending artery and circumflex branches of the main left coronary artery were dissected free, starting from their origins for a distance of about 1 cm. During this dissection the arteries are never held by any instrument. Small branches arising from this area of dissection were cut between ligatures. Two loops of cotton suture are passed around each vessel for traction purposes while the ameroids are slipped on to the origins of both arteries. After the ameroids are on the arteries, they are rotated so that the slotted opening faces the operator making it impossible for the ameroidsto slip out of place.

These ameroids have a central lumen of exactly

0.110 inch with a side slot that is just enough to permit a coronary artery when collapsed by traction to slide inside. The detailed description of these ameroids, their mode of action, their storage and preparation have been described by several workers from these laboratories (Litvak, 1957). After placement of the ameroid constrictors, the pericardium and the chest are closed and the animals allowed to recover. Ten of these 20 dogs were given Persantin as in A, and the other 10 served as controls.

The time of survival of each dog was recorded. After death or sacrifice of the animals, they were autopsied and the coronary arteries were injected with the "new" Schlesinger mass (Schlesinger,1957). This injection mass will not enter vessels smaller than 40 micra in diameter. The injection apparatus consists of a simple U-shaped mercury manometer with a side arm that is connected to a rubber bulb and to the bottle containing the injection mass. This bottle has an outlet near its bottom through which the mass is injected into the coronary vessels via a plastic tube and a metal cannula.

The right coronary artery is injected first, this is maintained for 5 minutes at a pressure of 120 - 140 mm Hg and X-rays are taken. The left coronary is then injected and another radiograph taken. The heart is then unrolled (Schlesinger, 1938) and a third X-ray taken.

If, after injecting the right coronary artery, no dye is present in the left, it is said that no functional anastomoses exist and the degree of collaterals is graded nil or absent. If less than 50% of the left coronary artery is filled, collaterals are graded as present. When the filling is between 50 - 75% collaterals are good and if there is more than 75% filling the degree of anastomosis is graded as complete.

After the coronary arteries are injected, all hearts are fixed in formaldahyde for 48 hours, then the ameroids are removed. Sections of the segments of the coronary arteries that were constricted by the ameroids are taken for histological studies. The degree of narrowing of each artery is recorded as a percentage of constriction of the original lumen. Sections of the myocardium of the right and left ventricles were also studied for presence or absence of myocardial infarctions.

C. Determination of the coronary back flow:

This method has been originally described by Anrep (1928) and has been used repeatedly since then as a way of evaluating the extent of coronary collaterals. This technique is simply ligating the proximal end of a coronary artery, severing the artery distal to the ligature and measuring the amount of blood flowing from the severed distal end. The artery most commonly used for determining

the coronary back flow is the circumflex branch of the left coronary artery. As such, the preparation lasts for a very short time, i.e. until the ventricles fibrillate. To prolong the time available by this method, a modification has been devised by the author and is hereby described.

Anaesthesia, preparation, positioning of the dog, 5th left intercostal space thoracotomy incision of the pericardium, and exposure of the left coronary vessels as in Section A, Chapter VI. The circumflex artery is dissected completely free from the epicardial fat and the accompanying veins for a distance of about 2 cm. starting from its origin, two #3-0 silk sutures are passed under the artery to be used for traction. The right femoral artery and vein are exposed through a longitudinal incision extending from just above the inguinal ligament to below the midthigh level. The femoral artery is dissected free and 2 sutures passed around it. The dog is heparinized at this stage using 3 mgms of heparin/kgm body weight. The distal suture around the femoral artery is tied, the proximal is held taut for traction. The artery is incised and a polyethylene tube .115" internal diameter is inserted into the abdominal aorta retrograde through the femoral arteriotomy. The suture that was held for traction is now tied around the artery and the catheter inside. This femoral artery catheter is connected through a 3-way stop cock to a transducer and a long side tube.

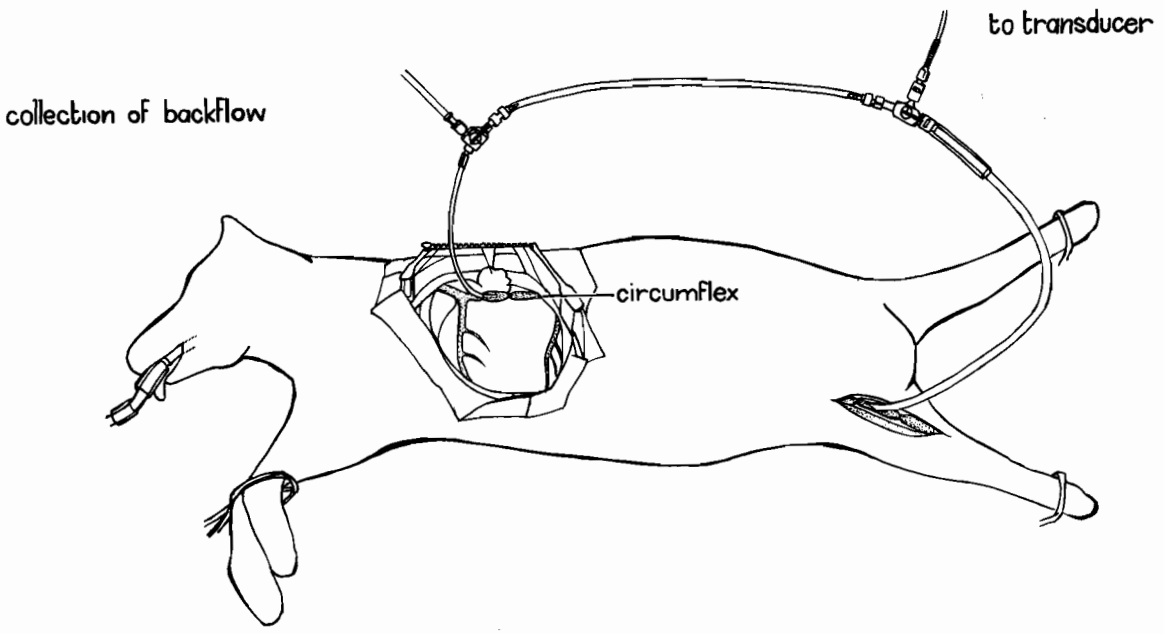

Fig. IA. Diagram illustrating the technique of collecting the coronary back flow.

The long side tube is connected to a second 3-way stop cock that in turn is connected to a polyethylene tube .066" internal diameter. The first stop cock is opened to allow filling of the long side tube and pressure recording through the transducer. The second stop cock is opened to allow filling of the terminal polyethylene tube, then closed temporarily. After this system of tubing is filled with blood, the sutures around the circumflex artery are pulled, a small incision is made in the artery as close to its origin as possible, and the polyethylene tube that is already filled with arterial blood is inserted into the distal end of the artery; at this moment the second stop cock is opened to allow perfusion of the artery by arterial blood. The tube is inserted for a distance of 1 cm. at most to avoid blocking any branches of the circumflex artery. After the polyethylene tube is in, it is secured in place by tying a suture around it. The proximal end of the circumflex artery is then ligated. By turning the second stop cock the perfusion could be stopped and coronary back flow collected. This technique provides:

1 - A stable preparation for determining the back flow;

2 - Coronary perfusion in between times of collection;

3 - Ample time to study the effect of various drugs on the back flow.

To study the relation between the blood pressure and the back flow, the femoral catheter is replaced by a

longer one that would reach the thoracic aorta. Application of a snare around the thoracic aorta distal to the tip of the femoral catheter would elevate the blood pressure of the dog mechanically and allow coronary perfusion at the same time.

The back flow was determined in 2 groups of 16 dogs each: In one group the acute effects of Persantin on normal dogs were studied by measuring the back flow before and after a single dose of 5 - 10 mgm Persantin i.v.

In the second group Persantin was given orally as in A, for periods varying from 73 - 162 days before the back flow was determined. The acute effects of intravenous Persantin were also studied in this group.

C H A P T E R I I

RESULTS AND CONCLUSIONS

Group A. (V.F.T. in Chronic Persantin Dogs)

A. Individual Summary

Dog No. 132:

This dog was started on oral Persantin on November 7, 1962 and sacrificed after 76 days on January 22, 1963. The oesophageal temperature at time of sacrifice was 37.5°C. The normal V.F.T. was 20 m. Amperes and after occlusion of the A.D.A. it was 8 m. Amperes, a drop of 60% of the normal V.F.T.

Dog No. 634:

This dog was started on Persantin on November 7, 1962 and sacrificed after 78 days on January 24, 1963. The oesophageal temperature was 38°C. The normal V.F.T. was 14 m.A., and after occlusion of the A.D.A. it was 6 m.A., a drop of 60%.

Dog No. 602:

This dog was started on Persantin on November 19, 1962 and sacrificed after 68 days on January 25, 1963. The temperature at time of sacrifice was 38°C. The normal V.F.T. was 30 m.A. and after occlusion of the A.D.A. it was 10 m.A., a drop of 66%.

Dog No. 146:

This dog was started on Persantin on November 19, sacrificed after 70 days, on January 28, 1963. The temperature at time of sacrifice was 38°C. The normal V.F.T. was 20 m.A.

EFFECT OF PERSANTIN ON V.F.T.

Dog no.	Days on Persantin	V.F.T.	V.F.T + occlusion of A.D.A.
434	70	25	5
602	68	30	10
146	70	20	7
634	78	14	6
132	76	20	8
495	94	22	8
Mean		21.8	7.3

Table I. The individual values of group A dogs.

and after occlusion of the A.D.A. was 7 m.A., a drop of 65%.

Dog No. 434:

This dog was started on Persantin on November 21 and sacrificed after 70 days on January 29, 1963. The temperature at time of sacrifice was 37.5°C. The normal V.F.T. was 25 m.A. and after occlusion of A.D.A. it was 5 m.A., a drop of 80%.

Dog No. 495:

This dog was started on Persantin on November 19, 1962 and sacrificed after 94 days on February 22, 1963. The temperature at time of sacrifice was 38°C. The normal V.F.T. was 22 m.A. and after occlusion of the A.D.A. it was 8 m.A., a drop of 66%.

The normal V.F.T. for these 6 dogs varied from 14 to 30 m.A. with a mean of 21.8 m.A. After occlusion of the A.D.A. the thresholds varied from 5 to 10 m.A. with a mean of 7.3 m.A.

The mean threshold in 29 normal dogs of Section A was 25.1 and after occlusion of the A.D.A. the mean of 24 dogs was 4.9 m.A. On injecting the left coronary artery in presence of A.D.A. occlusion, there was no filling of its branches in any instance in this group.

Group B. (Survival from Ameroids)

Individual Summary

1. Dogs with Ameroids only:

Dog No; 462:

This dog was operated upon on August 7 and survived

14 days to die on August 20. On injecting the right coronary artery the dye crossed to the left and filled the major branches of the left coronary artery. The collaterals were classified as good. Histological studies revealed that the A.D.A. was 85% occluded while the circumflex branch was more than 90% occluded. There was a left ventricular infarction.

Dog No. 642:

This dog was operated upon on June 21, 1962 and survived for 11 days to die on July 1, 1962. On injecting the right coronary artery no dye crossed to the left. This heart was not studied histologically.

Dog No. 188:

This dog was operated upon on August 7, and survived for 34 days to die on September 9. On injecting the right coronary artery no dye crossed to the left. The A.D.A. was occluded 40% while the circumflex artery was 50% occluded. There was evidence of infarction in the right and left ventricles.

Dog No. 181:

This dog was operated upon on August 7 and survived 11 days to die on August 17. The heart was not studied further.

Dog No. 132:

This dog was operated upon on August 8 and survived

for 17 days to die on August 24. On injecting the right coronary artery some dye crossed to the left. Collaterals are classified as present. Histological studies revealed 90% occlusion of the A.D.A. and 25% occlusion of the circumflex branch.

Dog No. 638:

This dog was operated upon on August 24 and survived 33 days to die on September 26. There were no collaterals, the A.D.A. was more than 90% occluded while the circumflex artery was 80% occluded. There was a left ventricular infarction.

Dog No. 657:

This dog was operated upon on August 27 and survived for more than 3 months to be sacrificed on December 19 after 112 post operative days. On injecting the right coronary the dye filled the major branches of the left coronary artery and collaterals are classified as good. Both A.D.A. and circumflex arteries were occluded for more than 90%. There was also evidence of left ventricular infarction.

Dog No. 103:

This dog was operated upon onSeptember 8, survived for 14 days to die on September 21. There were no collaterals. The A.D.A. was 85% occluded while the circumflex artery was 60% occluded. There was evidence

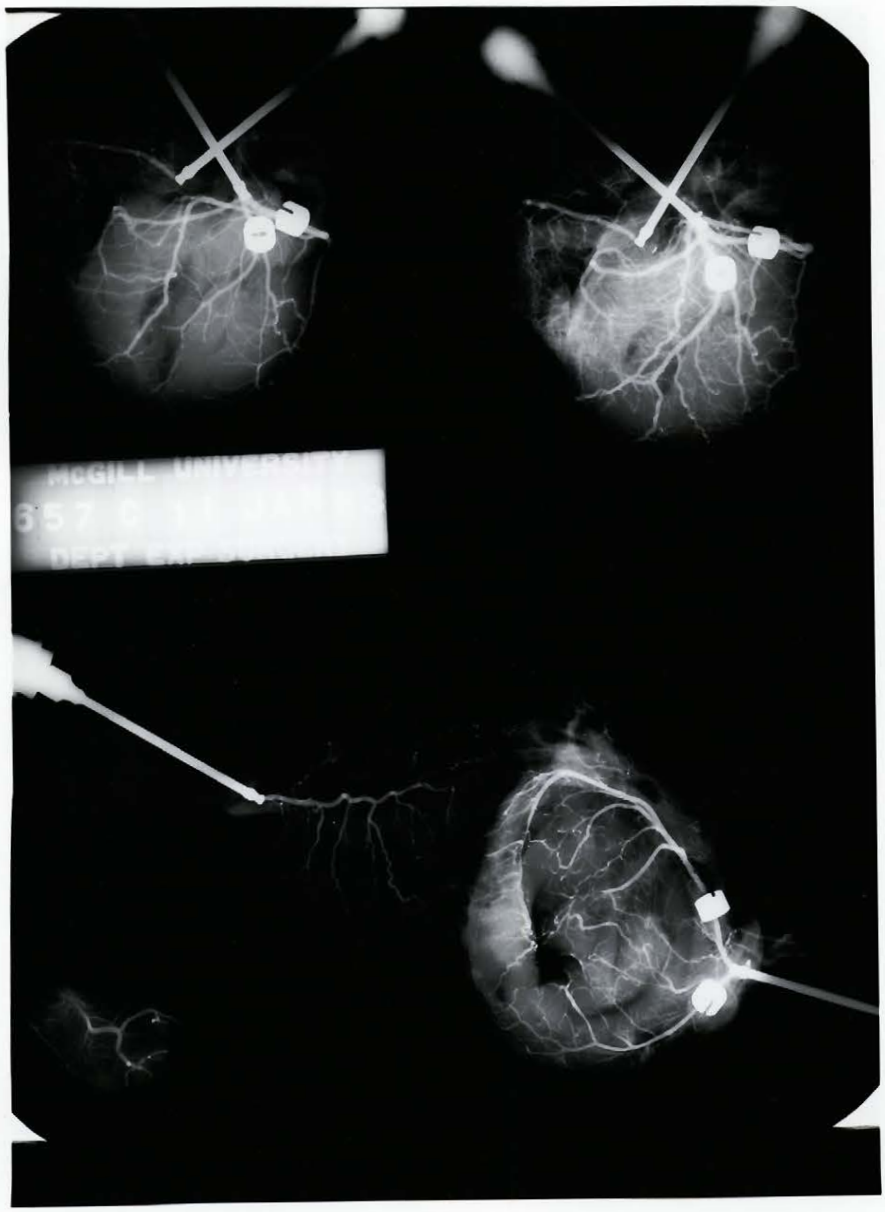

Fig. I. Reproduction of radiograph of Dog No. 657, showing filling of the left coronary artery and its major branches after injection of the right artery.

CONTROLS ONLY

Dog No.	Survival Time	Coronary Collaterals				% of Coronary Occlusion		Infarctions
		Absent	Present	Good	Complete	A.D.A.	C.C.A.	
462	14		▬	▬		85	>90	L.V.
642	11	⊠						
188	34	⊠				40	50	R+L
181	11							
132	17		▬			> 90	25	
638	33	⊠				>90	80	L.V.
657	112 S		▬	▬		>90	>90	L.V.
103	14	⊠				85	60	R+L.V.
419	20	⊠				50	50	—
656	36	⊠				70	70	—

9 Died in 21.1 days
1 Survived

Table II. Summary of the control dogs of group B.

of right and left infarctions.

Dog No. 419:

This dog was operated upon on September 17, survived for 20 days to die on October 6. There were no intercoronary collaterals. Both A.D.A. and circumflex arteries were 50% occluded and there was no evidence of infarction.

Dog No. 656:

This dog was operated upon on November 26, survived for 36 days to die on January 1. There were no intercoronary collaterals and both anterior descending and circumflex arteries were 70% occluded. There was no evidence of infarction.

Out of these 10 dogs, 9 died from the ameroids on an average of 21.1 days and 1 survived. Nine dogs were injected, 6 had no collaterals; in one collaterals were classified as present and in two they were good. In none were the collaterals complete. These results are tabulated in Table

2. Dogs with ameroids and Persantin:

Dog No. 67:

This dog was operated upon on October 1, 1962. It survived for more than 3 months and was sacrificed on

February 1, 1963, after 123 days post operative. On injecting the right coronary artery the dye filled the left coronary artery and its branches completely. Collaterals are classified as complete. The anterior descending and circumflex coronary arteries were 60% occluded. There were spotty changes in the myocardium.

Dog No. 91:

This dog was operated upon on October 11, survived for 19 days to die on October 29. There were no intercoronary collaterals. The A.D.A. was 50% occluded and the circumflex artery was 70% occluded. There was a left ventricular infarction.

Dog No. 623:

This dog was operated upon on October 26. It survived for more than 3 months to be sacrificed on February 1, 97 days post operative. Intercoronary anastomoses were complete. The A.D.A. was 40% and the circumflex artery was 60% occluded. There was also evidence of left ventricular infarction.

Dog No. 612:

This dog was operated upon on November 1. It lived to be sacrificed 92 days later on February 1. Intercoronary anastomoses were nearly complete. All major and some small branches of the left coronary artery were filled. The A.D.A. and circumflex arteries were 90% occluded. There

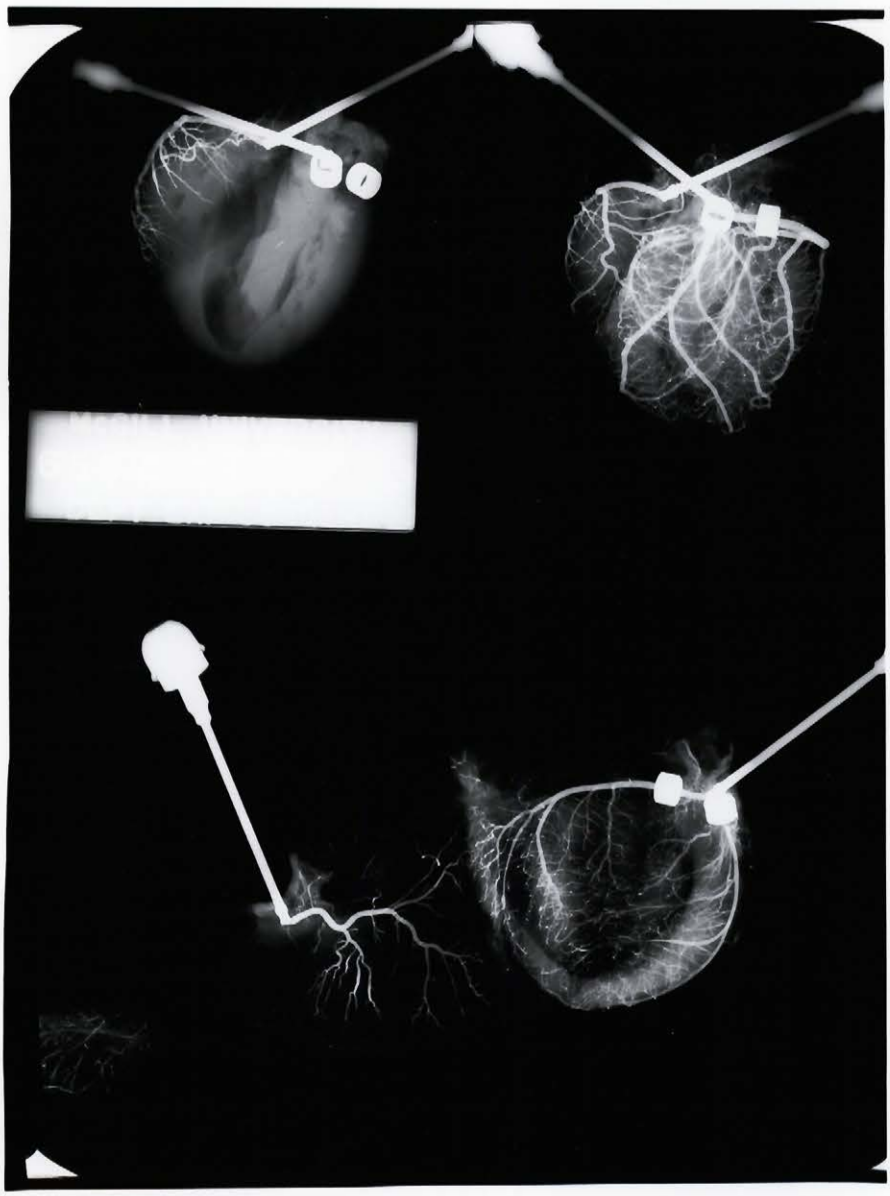

Fig. II. Reproduction of radiograph of Dog No.656, an example of complete absence of intercoronary collaterals. On injecting the right artery no dye crossed to the left.

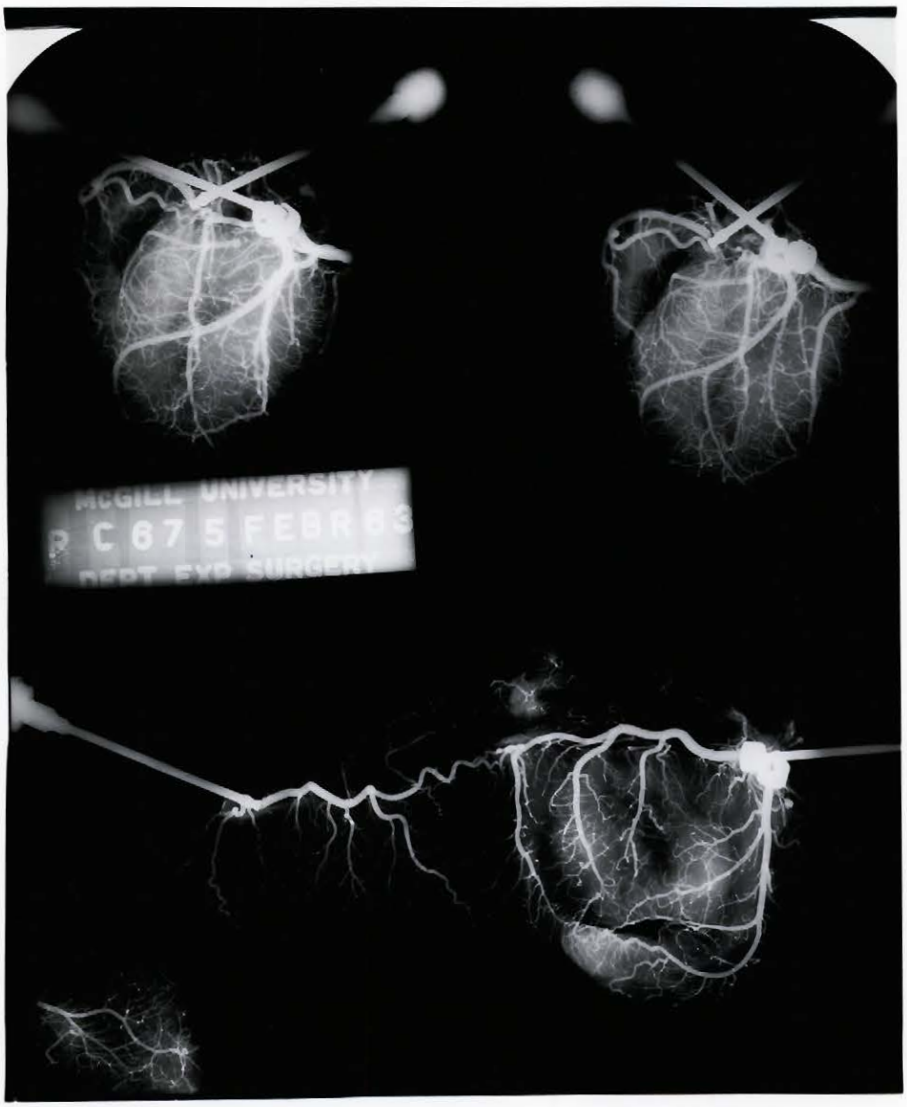

Fig. III. Reproduction of radiograph of Dog No. 67, showing complete collaterals. The left coronary artery, its major and minor branches were completely filled upon injection of the right coronary artery.

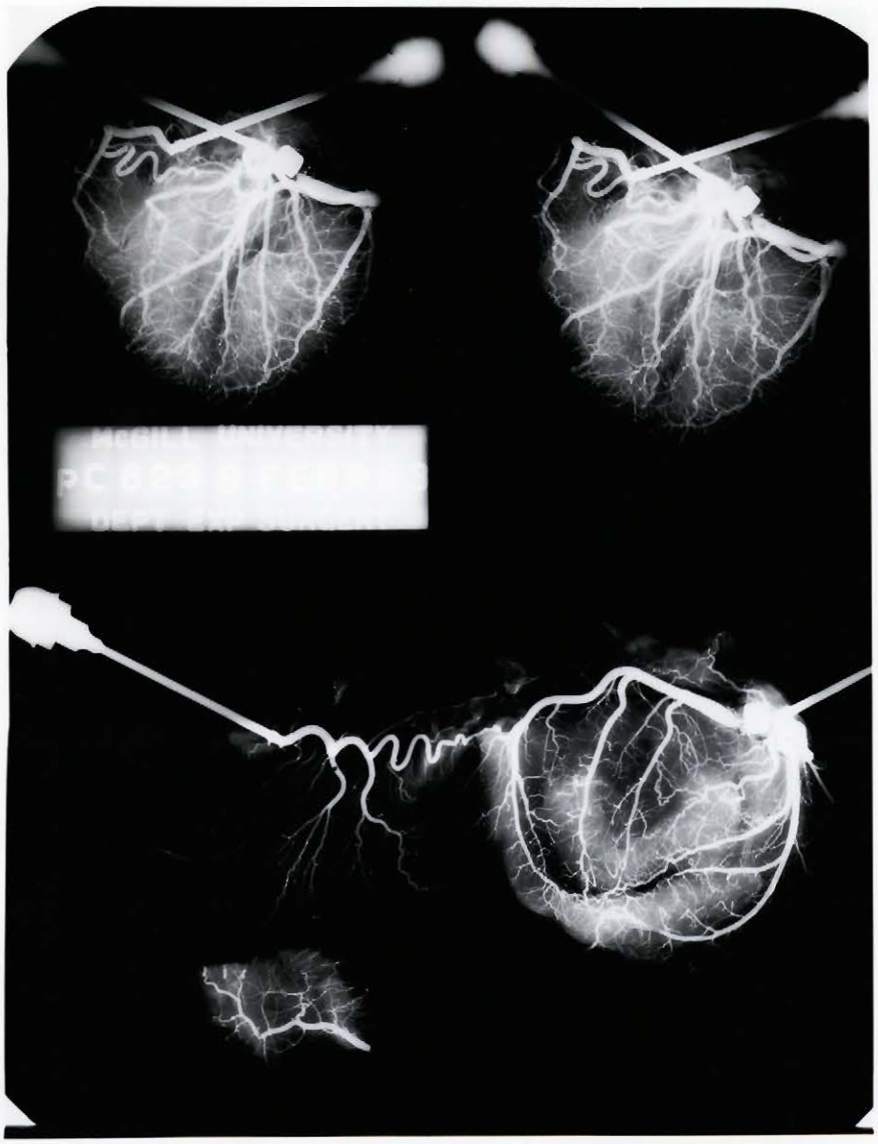

Fig. IV. Reproduction of radiograph of Dog No.623, an example of complete intercoronary anastomosis. Compare the size of these collaterals with those of Dog No.657.

was evidence of left ventricular infarction.

Dog No. 601:

This dog was operated upon on November 6 and survived for 37 days to die on December 12. Intercoronary anastomoses were classified as good. The anterior descending and circumflex arteries were 90% constricted. There was evidence of left ventricular infarction.

Dog No. 188A:

This dog was operated upon on November 6, survived 35 days to die on December 10. Intercoronary anastomoses were classified as good. The A.D.A. was 50% while the circumflex was 85% constricted.

Dog No. 616:

This dog was operated upon on November 16, survived 20 days to die on December 5. Collaterals are classified as present. The A.D.A. was 60% and the circumflex artery 30% constricted.

Dog No. 445:

This dog was operated upon on November 16, survived 24 days to die on December 9. Collaterals were just present. The A.D.A. was 70% and the circumflex 50% constricted.

Dog No. 659:

This dog was operated upon on June 13, survived 29 days to die July 11. Some dye crossed from right to

left and collaterals are classified as present.

Dog No. 665:

This dog was operated upon on June 13, survived 24 days to die on July 6. This heart was not injected.

Out of these 10 dogs, 7 died in an average time of 26.8 days and 3 survived. Nine hearts were injected and of these 9 only one had no collaterals. Collaterals are classified as present in 3, good in 2 and complete in 3. These data are tabulated in Table III.

Group C. (Back Flow Determinations)

Controls:

In 14 of the 16 control dogs the back flow varied from 1.2 to 4.7 c.c./m. In the other 2 dogs the back flow was 6.4 and 11.4 c.c./m. The mean back flow for the whole group was 3.8 cc/m. After intravenous Persantin the back flow varied from 1.3 to 6.8 cc/m. The mean value was 3.1 cc/m. This apparent drop in the back flow was accompanied by a lowering of the mean pressure from 94 mm of Hg before Persantin to 82 mm of Hg after Persantin. The individual flows, pressures and heart rate of this group are shown in Table IV.

Chronic Persantin Dogs:

In 11 dogs of this group the back flow varied

CONTROLS & PERSANTIN

Dog No.	Survival Time	Coronary Collaterals				% of Coronary Occlusion		Infarctions
		Absent	Present	Good	Complete	A.D.A.	C.C.A.	
67	S 123		▬	▬	▬	60	60	Spotty changes
91	19	⊠				50	70	L.V.
623	S. 97		▬	▬	▬	40	60	L.V.
612	S. 92		▬	▬	▬	> 90	> 90	L.V.
601	37		▬	▬		> 90	> 90	L.V.
188A	35		▬	▬		50	85	—
616	20		▬			60	30	—
445	24		▬			70	50	—
659	29		▬					
665	24							

7 Died in 26.9 days

3 Survived

Table III. Summary of the Persantin dogs of group B.

ACUTE EXPTS. (Controls)

NO.	BEFORE PERSANTIN			AFTER PERSANTIN			
	FLOW	PRESSURE	RATE	FLOW	PRESSURE	RATE	
1	3.5	125	192	3.3	105	172	10
2	2.9	66	150	2.6	59	139	5
3	1.5	81	146	1.3	80	143	5
4	4.6	105	126	4.3	100	130	5
5	3.0	76	108	2.5	64	110	5
6	4.7	89	150	4.1	76	130	5
7	1.4	60	139	1.3	64	127	5
8	4.0	93	143	4.0	78	142	10
9	4.3	96	94	3.6	80	99	5
10	1.2	138	220	1.3	108	212	5
11	3.5	104	152	3.2	90	137	10
12	2.2	80	144	1.9	69	108	10
13	11.4	79	155	6.8	55	122	10
14	6.4	88	170				
15	3.7	111	200	3.0	100	200	10
16	3.1	110	153	3.2	96	162	10
Mean	3.8	94	152	3.1	82	142	
S.D.	2.43	20.9	32	1.44	17.4	32.2	

Table IV. The individual flow, blood pressure and heart rate of the controls of Group C.

ACUTE EXPTS.
(Chronic Persantin dogs)

NO.	BEFORE PERSANTIN			AFTER PERSANTIN			
	FLOW	PRESSURE	RATE	FLOW	PRESSURE	RATE	
1	3.5	125	137	3.2	111	145	5
2	22.5	80	173	20.5	75	145	5
3	8.5	118	131	9.3	103	130	5
4	1.2	135	182	1.3	90	192	5
5	5.1	95	135	3.8	77	124	5
6	8.6	89	155	7.3	79	145	5
7	2.2	100	152	2.2	77	135	10
8	1.7	106	185	1.8	103	173	10
9	3.1	85	92	2.9	84	126	10
10	6.0	100	168	5.5	92	166	10
11	25.0	133	148	22.3	122	147	10
12	7.0	103	165	4.7	82	136	10
13	3.7	78	184				
14	12.4	140	199	11.7	117	181	10
15	3.5	122	191	3.9	93	155	10
16	4.5	103	188	3.7	70	144	10
Mean	7.4	107	162	6.9	92	150	
S.D.	7.03	19.8	28.3	6.5	16.2	19.9	

Table V. The individual flow, blodd pressure and heart rate of the chronic Persantin dogs of Group C.

from 1.2 to 7 cc/m. In the other five dogs the back flow varied from 8.5 cc to 25 cc/m. The mean value for the whole group was 7.4 cc/m.

After intravenous Persantin the back flow varied from 1.3 to 22.3 cc/m with a mean of 6.9. This drop in back flow was also accompanied by a drop of the mean pressure from 107 mm of Hg before to 92 mm of Hg after Persantin.

The individual flows, pressures, and heart rate are shown in Table VI.

EXPT.	CHRONIC PERSANTIN					CONTROL				
	DAYS	WT.	FLOW	PRESS.	RATE	EXPT.	WT.	FLOW	PRESS.	RATE
1	73	50	3.5	125	137	1	38	3.5	125	192
2	76	42	22.5	80	173	2	45	2.9	66	150
3	83	54	8.5	118	131	3	39	1.5	81	140
4	108	60	1.2	135	182	4	33	4.6	105	126
5	155	61	5.1	95	135	5	35	3.0	76	108
6	155	57	8.6	89	155	6	30	4.7	89	150
7	160	52	2.2	100	152	7	37	1.4	60	139
8	160	40	1.7	106	185	8	48	4.0	93	143
9	162	64	3.1	85	92	9	40	4.3	96	94
10	109	55	6.0	100	168	10		1.2	138	220
11	109	61	25.0	133	148	11	30	3.5	104	152
12	79	30	7.0	103	165	12	35	2.2	80	144
13	90	37	3.7	78	184	13	62	11.4	79	155
14	92	42	12.4	140	199	14	54	6.4	88	170
15	96	35	3.5	122	191	15	72	3.7	111	200
16	100	40	4.5	103	188	16	70	3.1	110	153
Mean		49	7.4	107	162		45	3.8	94	152
S.D.		10.7	7.03	19.8	28.3		13.9	2.43	20.9	32

Table VI. Comparison of the results of the control and chronic Persantin dogs of Group C.

C O N C L U S I O N S

A. In this group the mean V.F.T. dropped 66% after occlusion of the A.D.A. from 21.8 m.A. to 7.3. In the normal dogs of Section A the V.F.T. dropped 80% after occlusion of the A.D.A. from 25.1 m.A. to 4.9 m.A. This difference between both groups is probably insignificant because of the small number of dogs in the Persantin group and the wide variation between individual dogs.

B. In this group there was an increase in the survival from ameroid constriction from 10% in the controls to 30% in those treated with Persantin. There was a more appreciable increase in the incidence of intercoronary anastomosis between both groups. Intercoronary anastomoses were classified as good in 2, present in 1 and absent in 6 of the controls, while they were complete in 3, good in 2 and present in 3 among the treated dogs.

C. While the mean back flow for the treated dogs was 7.4 cc/m and that for the controls was 3.8 cc/m, the standard deviation in the first group was 7.03 which makes the difference insignificant.

Looking at the results from a different way, there were 5 dogs in the treated group with a back flow

above 8 cc, up to 25 cc while in the controls there was only one dog with a high back flow of 11.4 cc while all the rest of the group were below 7 cc.

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