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SINCLAIR, John Cameron, 1918–

THE CHRONIC IMPLANTATION OF A THERMISTOR FOR THE MEASUREMENT OF CORONARY BLOOD FLOW TRANSIENTS IN THE PIG INDUCED BY EPINEPHRINE, NOREPINEPHRINE, AND ACETYLCHOLINE.

Iowa State University of Science and Technology
Ph.D., 1966
Physiology

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1966

THE CHRONIC IMPLANTATION OF A THERMISTOR FOR THE MEASUREMENT OF CORONARY BLOOD FLOW TRANSIENTS IN THE PIG INDUCED BY EPINEPHRINE, NOREPINEPHRINE, AND ACETYLCHOLINE

by

John Cameron Sinclair

A Dissertation Submitted to the
Graduate Faculty in Partial Fulfillment of
The Requirements for the Degree of
DOCTOR OF PHILOSOPHY

Major Subject: Veterinary Physiology

Approved:

Signature was redacted for privacy.

In Charge of Major Work

Signature was redacted for privacy.

Head of Major Department

Signature was redacted for privacy.

Dean of Graduate College

Iowa State University
Of Science and Technology
Ames, Iowa

1966

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INTRODUCTION

The dynamic aspects of blood flow are being recognized more and more today as critical factors in health and disease. A knowledge of them is essential for the proper interpretation of blood pressure recordings, heart sounds, electrocardiograms, and vascular pathology.

One of the most dynamic and critical areas of blood flow is in the coronary circulation of the heart. The flow of blood in the coronary arteries is drastically reduced and may even be reversed during systole. Many attempts have been made to measure coronary blood flow. The methods used include flowmeters of various kinds; the uptake and disappearance of radioactive tracers, or nitrous oxide; cyclic movement of various foreign substances; and differential pressure recordings.

The recent microminiaturization of electronic components has made it possible to chronically implant flow transducers within the animal body. Implanting a transducer inside an artery, however, requires that such a device be made so small and so compliant that it does not obstruct the blood circulation or significantly disturb laminar blood flow. Silicone elastic compounds can be used to coat such a device to make it innocuous to the body tissues, but mechanical movement must be minimized to prevent its being embedded in endothelial tissue as well as to avoid artifacts in the flow signal.

The industrial development of a thermistor with a 0.1 second time constant in air and 0.005 inch diameter has made it feasible to fabricate a flowmeter that can be inserted inside a coronary artery of the pig. The

connecting wires and coating can be held to a diameter of less than 0.008 inch. This represents about 2% of the cross-sectional area of one of the main branches of the left coronary artery of a 22 kg pig. This research has been devoted to such a flowmeter and its use in recording blood flow transients induced by certain vasoactive hormones.

REVIEW OF LITERATURE

Anatomy of the Heart

The mammalian heart has four chambers. The right and left sides are completely separated by a septum. The right heart is a low pressure system for pumping venous blood through the lungs. The left heart accepts the oxygenated blood from the lungs and pumps it to all parts of the body. The atria on each side act as reservoirs for the blood and facilitate the filling of the ventricles. The atria have prominent appendages or auricles. The ventricles are the pump organs. Their force of contraction is regulated to a certain extent by how completely they are filled according to Starling's law. The circulating hormones, innervation, and metabolites modify the function of the ventricles within the coordinating limits of this basic law (Sarnoff and Mitchell, 1962).

The heart muscle is supplied with blood by coronary arteries that ramify upon its surface. The right and left coronary arteries typically arise from the root of the aorta just distal to the semilunar valves. The left coronary artery is larger than the right one. The left coronary artery supplies the left artrium, pulmonary conus, A-V node, His bundle, the septum and the left ventricular muscle. It anastomoses with branches of the right coronary artery at the apex and interventricular grooves. The right coronary artery supplies the right ventricle, right atrium, and S-A node. It also sends branches to the septum, A-V node, and pulmonary conus. The right coronary artery in man and the pig is relatively more important than it is in the dog. Dogs are left coronary dominant in that the left

circumflex branches supply the posterior left and right ventricles, the posterior septum, and A-V node (Gregg and Fisher, 1963).

The left coronary artery of the pig divides into a circumflex and an anterior descending branch approximately 4 mm from its origin (Lumb and Hardy, 1963). The left circumflex usually has a large descending branch. The larger arteries ramify on the surface of the epicardium giving off penetrating branches along their course. There is a relative increase in the vascularity of the myocardium from the epicardium to the endocardium. The epicardium of the dog contains 750 capillaries per mm^2 with a half-intercapillary distance of 20.5 μ. The endocardium contains 1,100 capillaries per mm^2 with a half-intercapillary distance of 16.5 μ (Myers and Honig, 1964). This increase in vascularity is associated with a phasic decrease in oxygen tension and blood flow (Kirk and Honig, 1964b).

The superficial left ventricular veins parallel the arterial branches and course toward the base of the heart to empty into the great cardiac vein anteriorly and its continuation, the coronary sinus, posteriorly. The coronary sinus empties into the right atrium. The anterior cardiac veins drain the right ventricle. They are smaller trunks that frequently empty individually into the right atrium. The deeper venous circuit communicates with both atrial and ventricular cavities via Thebesian and sinusoidal channels (Gregg and Fisher, 1963; Christensen and Campeti, 1959).

The cardiac nerves come from vagal, sympathetic, and dorsal root fibers that intermingle and tend to lose their identity within the plexuses

located above the base of the heart and between the aortic arch and tracheal bifurcation (White, 1957). The sensory afferent fibers originate in thoracic dorsal ganglia. They terminate as fine beaded nerve fibers and loops in the pericardium, connective tissue, adventitia, and walls of the heart (Gregg and Fisher, 1963). The autonomic innervation includes both an afferent and efferent vagal and sympathetic supply. The vagal parasympathetics stem from both right and left vagi and the recurrent laryngeal nerves. It supplies the great vessels superior to the heart, the inter-atrial septum, and the sino-atrial and A-V nodal areas. There are no efferent vagal fibers in the ventricles (Dawes, 1947). The sympathetic efferent outflow is largely to ventricular muscle and coronary arteries. It contains both cardiomotor and vasomotor fibers. It arises from the cervical sympathetic ganglia via the corresponding cardiac nerves.

Hemodynamic Characteristics of Coronary Blood Flow

The usual determinants of blood flow to an organ such as perfusion pressure, vasomotor tone (peripheral resistance), vascularity and viscosity, are dominated in the coronary circulation by the phasic intramural pressure of the ventricular myocardium. During systole the intramural pressure in the deeper layers of the left ventricular myocardium rises above the intraventricular pressure (Kirk and Honig, 1964a), and capillary blood flow in these layers is effectively stopped. There may be, however, an increase in venous outflow or a reverse of flow in the coronary artery (Gregg and Fisher, 1963). The rapid relaxation of the ventricles at the end of systole allows a sudden surge of blood to enter the coronary

arteries. Both the relaxation of intramural pressure and a high perfusion pressure due to facilitated venous return as well as a high aortic pressure contribute to this surge. No where else in the animal body does such a drastic change in blood flow occur.

The velocity profile of bloodflow in the proximal segments of the coronary artery shares the uniqueness of the ascending aorta in that it is relatively flat. This means that the velocity gradient close to the wall will be much steeper until a laminar, parabolic flow pattern has a chance to be established. It is quite likely that Reynold's number, which is a measure of the upper limit of non-turbulent flow, will be exceeded under these circumstances (Spencer and Denison, 1963; Kramer et. al., 1963).

The main coronary blood flow, as measured in the larger arteries, takes place during diastole though the apparent systolic flow can be appreciable. The systolic flow in the left coronary artery may be confined largely to the large arteries on the surface of the heart and to the more superficial layers of the myocardium. The flow in the right ventricle follows a pattern similar to the aortic blood pressure, so is largely determined by the perfusion pressure (Gregg, 1950).

Regulation of Coronary Blood Flow

The increases in coronary blood flow that keep pace with the metabolic needs of the heart are exerted against a tonic vasoconstrictor tone. This tone can be neural, humoral, and myogenic in origin. The increases are induced by metabolites, vasodilator nerves, hormones, and autoregulatory mechanisms (Green et al., 1963; Folkow, 1960).

The metabolic activity of the myocardium plays a key role in determining coronary blood flow (Denison and Green, 1958; Mosher et al., 1964; Bacaner et al., 1965). Though many metabolic factors have been suggested for this role, the most important factor seems to be adenosine (Berne, 1963, 1964). Most experimental work involves some cardiomotor excitation, hence the neurohumoral vasomotor effects will be masked and will only be seen transiently if seen at all (Granata et al., 1965; Rayford et al., 1965).

In the dog and cat the preganglionic β-fibers in the accelerator nerve are the vasomotor fibers of the coronary arteries. Stimulation of the adrenergic coronary constrictors produces a reduction of flow, but the oxygen consumption of the heart does not change. The A-V oxygen difference and the A-V lactate difference increase proportionately indicating no change in metabolic pattern. A true vasomotor dilator that is cholinergic in nature can also be demonstrated (Juhasz-Nagy and Szentivanyi, 1961). A transient vasoconstriction induced by sympathetic stimulation and by epinephrine has also been reported (Granata et al., 1965). Both epinephrine and norepinephrine lead to vasoconstriction in the dog after a positive inotropic effect is inhibited by dichloro-isoproterenol (Siegel et al., 1961), or by arresting the heart with K ion (Berne, 1958). There is an initial phase of reduced coronary blood flow during excitement in the dog in the presence of a decreased stroke volume and increased blood pressure (Rayford et al., 1965). On the other hand, studies with the isolated coronary arteries of pigs (Smith and Coxe, 1950),

or helical strips cut from them in the dog (Zuberbuhler and Bohr, 1965) show a relaxation response to epinephrine and norepinephrine. Similarly, the isolated, perfused, K-arrested dog heart shows a vasodilator response to isoproterenol via β-receptor sites (Klocke et al., 1965a).

There are two kinds of binding sites for catecholamines. The α-receptor is a vasoconstrictor. The β-receptor is a vasodilator, and in some nomenclatures it is considered to be a cardiomotor accelerator as well (Green et al., 1963). The relative affinity of these sites for the catecholamines and their relative abundance determine the dose-response of a given catecholamine in a given organ. The systemic hemodynamic changes reflect the integrated response of the entire organism. There is an extensive literature on the relative potency of epinephrine and norepinephrine under various experimental manipulations (Barger et al., 1961; Klocke et al., 1965b; Berne, 1964). Norepinephrine is usually considered to act primarily on α-receptors leading to vasoconstriction alone, but it may under some circumstances lead to coronary vasodilation (Zuberbuhler and Bohr, 1965; Smith and Coxe, 1950).

The rate of disappearance of injected catecholamines is determined by the amounts given, the rate and route of injection, and by the previous history of the blood vascular system. The initial uptake into the binding sites or storage sites of normally innervated blood vessels is very rapid (Potter et al., 1965). If these sites are saturated by a slow infusion of epinephrine or norepinephrine, these amines can still be detected 30 minutes after the end of infusion (Booker et al., 1962). The half-life of

a 50 μg per kg body weight injection of epinephrine or norepinephrine in the rabbit is about 60 seconds. The maximum rate of destruction is about 10 μg per kg body weight per minute in the intact animal (Lund, 1951; Axelrod et al., 1959).

The presence or functional significance of adrenergic coronary vasoconstriction is being strongly debated (Berne, 1958; Green et al., 1963). Clinical observations in cases of angina pectoris associate emotional excitement with ischemic pain (Sheffield et al., 1965; White, 1957), similarly, intracoronary epinephrine can induce an ECG pattern of myocardial ischemia in the dog (Barger, 1961). These observations suggest that an increase in sympathetic tone leads to a relative decrease in the blood supply to the myocardium.

A myogenic autoregulation of the coronary blood flow has been postulated. The mechanism of this regulation is not known but tension sensing transducers in the vascular muscle membrane have been postulated (Berne, 1964). A drop in pressure would be associated with an increase in the radius of the vessel to maintain a constant tension ($T=PR$). The increased radius would lower the resistance to flow of the viscous blood ($R=8\eta l/\pi r^4$).

The increased contractility of the heart muscle with increases in work load is associated with an increased synchronicity of muscle contraction, as well as a greater velocity of contraction, shortening of systole, and a rapid relaxation (Rushmer, 1962). All of these factors

favor diastolic coronary blood flow (Sarnoff and Mitchell, 1962), but there is a significant increase in systolic blood flow as well (Gregg and Fisher, 1963).

Methods of Measuring Coronary Blood Flow

Many attempts have been made to measure coronary blood flow. The methods used include flowmeters of various kinds; the uptake and disappearance of nitrous oxide or radioactive tracers (Klein et al., 1965; Ross and Friesinger, 1965); cyclic movement of various foreign substances (Singer, 1959); and differential pressure recordings (Greenfield and Fry, 1965).

The electromagnetic and ultrasonic flowmeters are the only flowmeters that are at present suitable for chronic implantation (Kramer et al., 1963). They both require very good electronic instrumentation for a satisfactory signal to noise ratio and frequency response (Gessner and Bergel, 1964; O'Rourke, 1965; Philips and Davila, 1965). The electromagnetic flowmeter measures the mean flow rate across the diameter of the vessel. The latest miniature models do not require vessel cannulation (Kolin and Kado, 1959; Khouri and Gregg, 1963), but they may disturb the blood flow pattern (Fox et al., 1964). It is not known how the ultrasonic flowmeter response is affected by the velocity profile (Franklin et al., 1959b; Franklin, 1965). It too will cause disturbances due to a rigid constriction of the blood vessel.

The electromagnetic flowmeter signal produced by the motion of a conducting fluid across the lines of a magnetic field is at right angles

to both the field and the flow. It gives an instantaneous mean velocity averaged across the outside diameter of the blood vessel. Its frequency response is limited only by the electronic circuitry. This method of measuring flow assumes a uniform electrical conductivity of blood and wall. The vessel also needs to be surrounded by insulating material. The artifact due to quadrature voltage, which is an a.c. voltage induced by the alternating magnetic field (transformer component), can be largely eliminated. There is also a need for electrostatic shielding of the pick-up electrodes, due to stray capacitance. The response of this flowmeter is directional.

The ultrasonic flowmeter is lightweight and simple but requires very complex electronic instrumentation. A phase difference modification of the design of Kalmus is described and discussed in some detail by Wetterer (1963). Cylindric, ceramic 'transducers' are placed about 1 inch apart around the vessel wall. They are arranged to transmit and receive ultrasound (400 kc/sec) alternately upstream and downstream at a rate of 75 per sec. The phase differences between these signals are detected by phase meters and used as a measure of the difference between the sound transit times. The velocity of sound in blood is about 1.5×10^5 cm/sec, so it travels 1 cm in about 7 μ seconds. A flow velocity of 1 cm/sec changes the transit time by about $\pm 5 \times 10^{-11}$ second. An assessment of the base line is still a difficult problem.

Franklin *et al.* (1959a) use two barium titanate crystals. At a switching rate of 800 times per second, the crystal gives a train of 3

mc/sec sound bursts at a repetition rate of 12,000 per second. The transit-time voltage converter generates a ramp voltage with a constant slope of 40 volts per μ second. This ramp terminates when the other crystal is excited by the sound, so this gives a measure of transit time. The response is independent of the velocity profile within ± 5%.

MATERIALS AND METHODS

Fabrication of Device

The thermistor device as shown in Figure 1 is composed of three parts. The probe (Figures 2, 3 and 6) that is inserted into the artery, the cable (Figures 2 and 6) that acts as an electrical conduit, and the skin connector (Figure 4) that permits the device to be attached to an external recorder.

The cable is made by coiling a double strand of platinum alloy wire[1] into a coil about 1 mm in diameter with the apparatus shown in Figure 8. Two 5-foot lengths of wire are used for an 18-inch cable. The coils are rinsed in isopropyl alcohol and blotted. They are then dipped in 4120 primer,[2] drained, and air dried. The coils are suspended vertically in 3 mm glass tubing which has been coated with silicone.[3] The deaerated potting compound[4] is slowly injected into the tube from a syringe so as to avoid trapping bubbles. Silicone tubing[5] is used with the syringe. The

---

[1]Platinum alloy wire #851, 2.2 mil, class H insulation, Sigmund Cohn Corp., Mount Vernon, N. Y.

[2]Primer #SS-4120, General Electric, Waterford, N. Y.

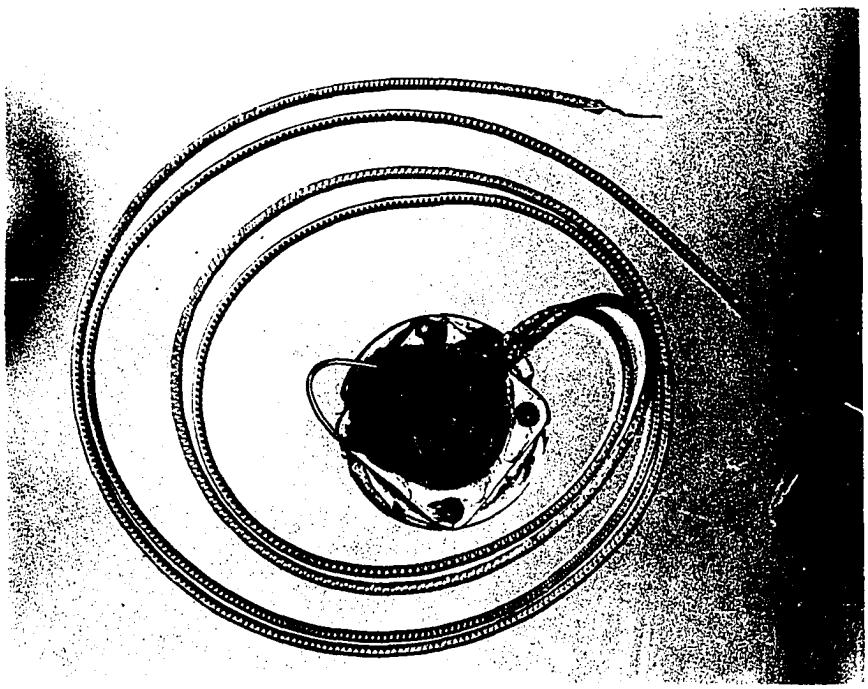
[3]Siliclad, Clay-Adams, Inc., New York, N. Y.

[4]Potting compound #RTV-615, General Electric, Waterford, N. Y.

[5]Vivosil, Medical grade, Becton, Dickinson and Company, Rutherford, N. J.

Figure 1. Double thermistor device showing the coronary and aortic leads attached to the base of the skin connector. The bare wire on the side of the connector is the silver ground wire

Figure 2. Close-up of a probe. The clear potting compound allows the wire coils inside the cable to be seen



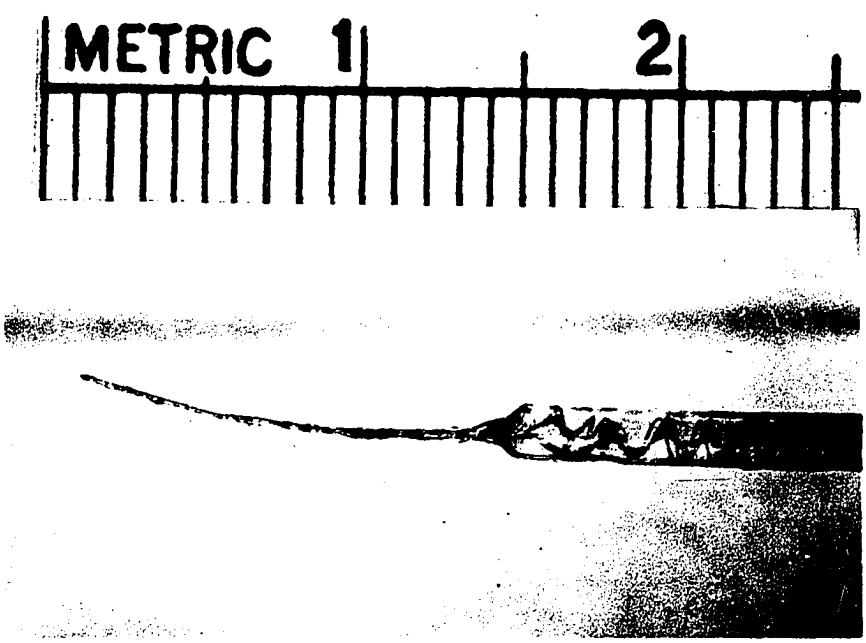
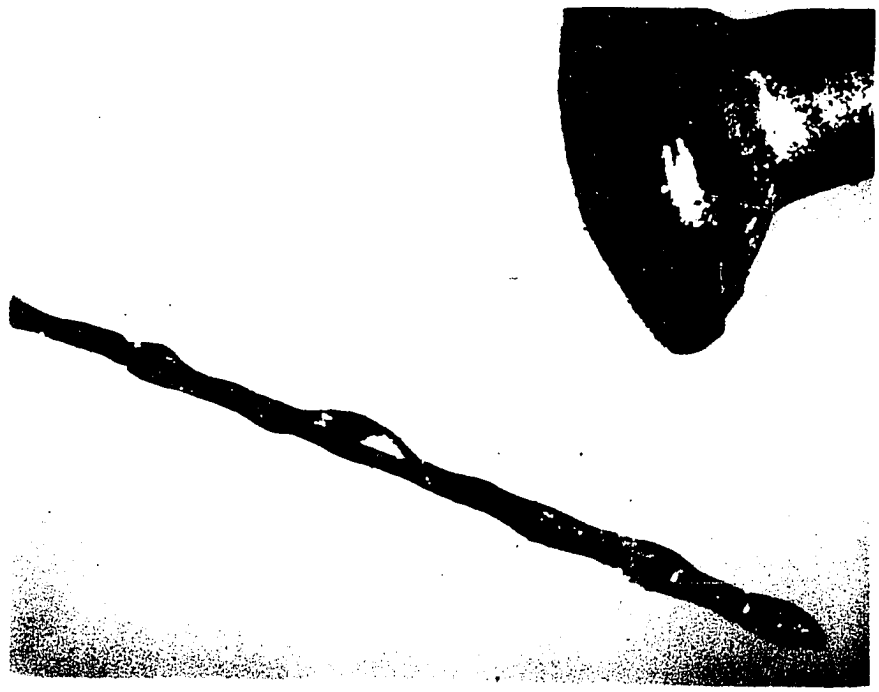

METRIC 1
2

Figure 3. Photomicrograph of the tip showing the dark thermistor and its two lead wires wrapped around the probe wire. The head of a pin is seen for size comparison

Figure 4. Chassis connector and stainless steel flange used for the skin connector



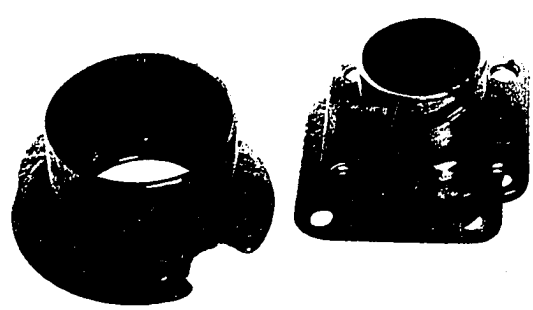


Figure 5. Schematic drawing of the left side of the pig heart showing the approximate locations of the principal branches of the left coronary artery. The left auricle is reflected with clips. RS-restraining sutures, PA-pulmonary artery, RA-right auricle, LA-left auricle, RV-right ventricle, LV-left ventricle, A-implant site on the left circumflex coronary artery, B-implant site on the left anterior descending coronary artery

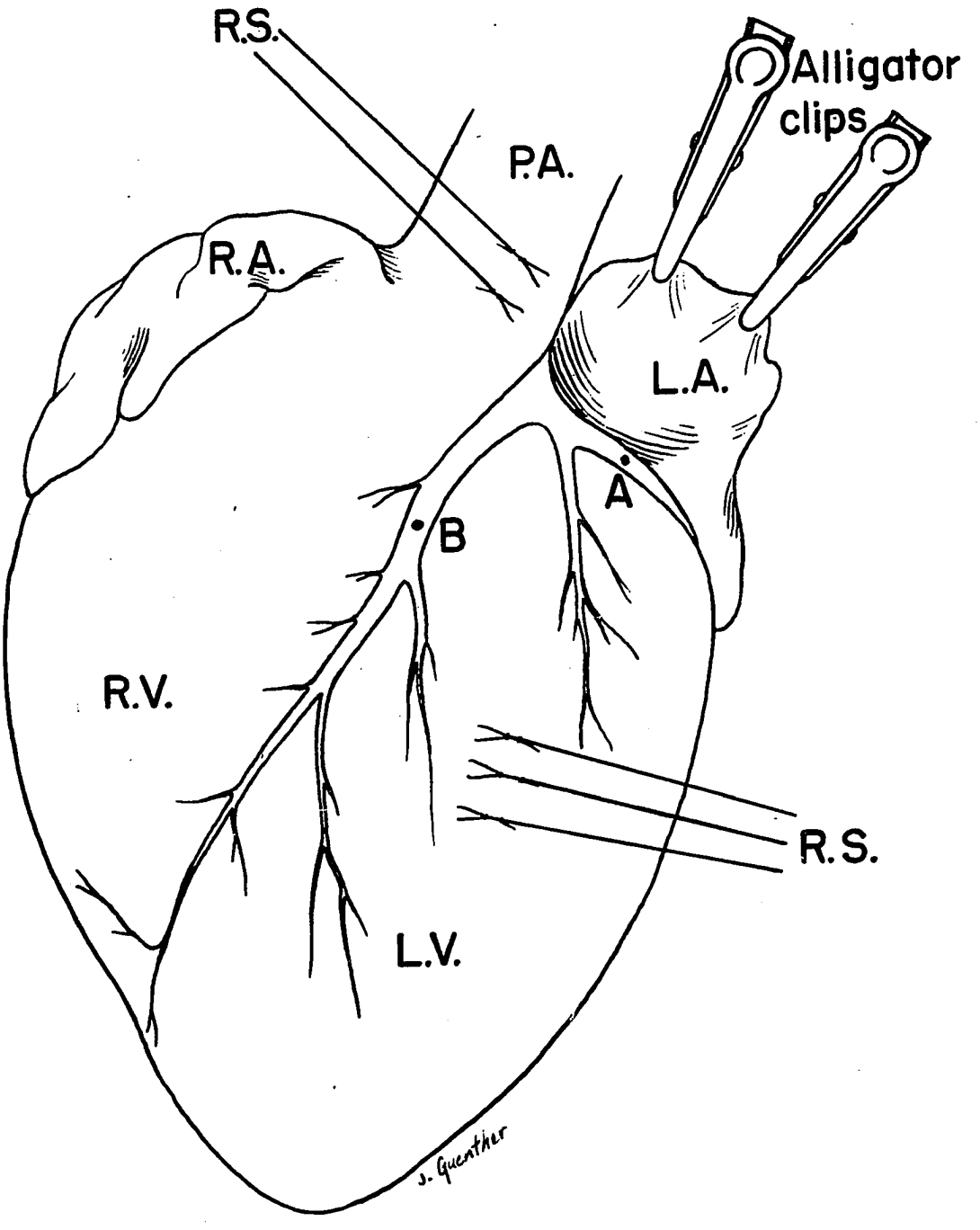
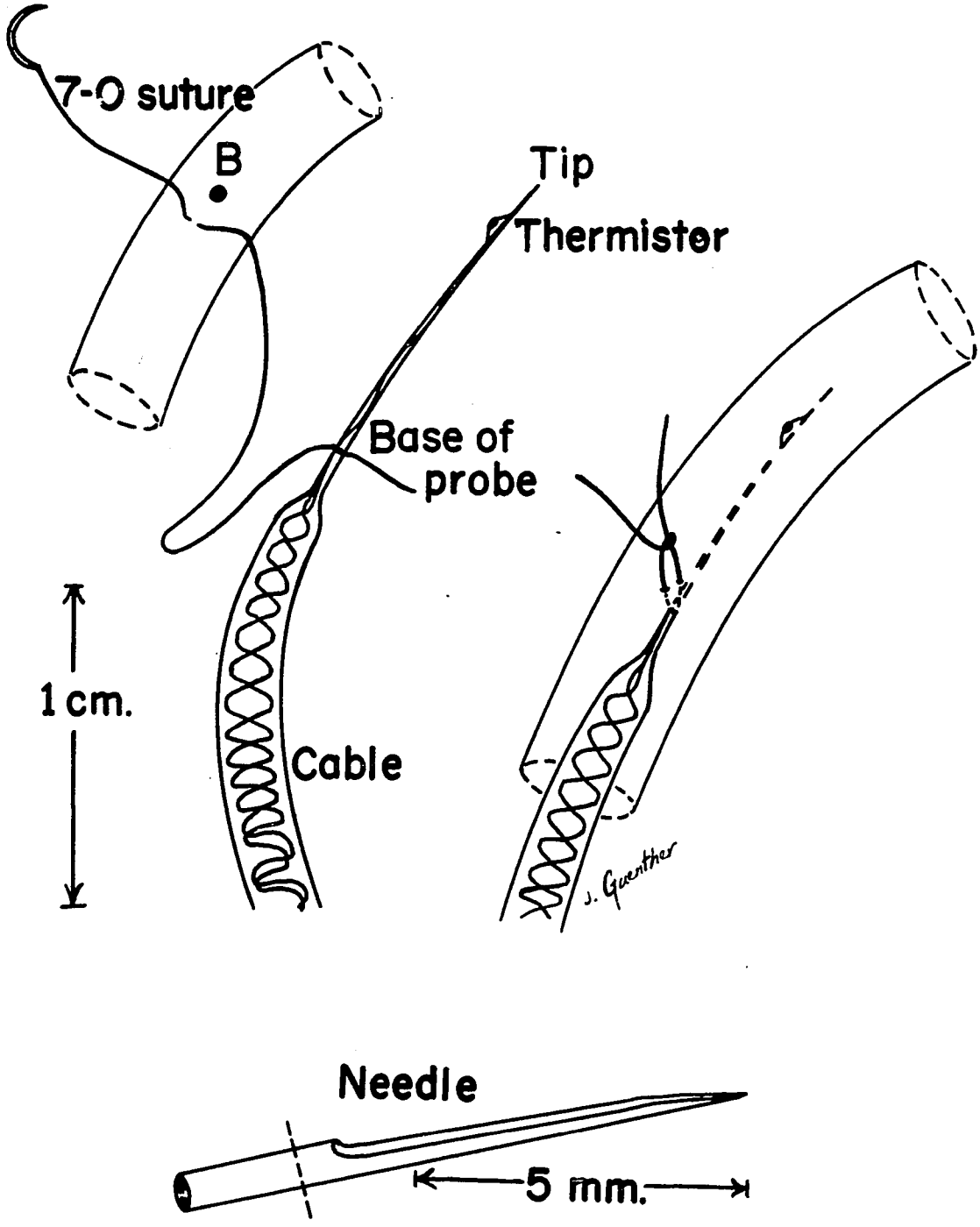

R.S.
Alligator clips
P.A.
R.A.
L.A.
A
B
R.V.
R.S.
L.V.
J. Guenther

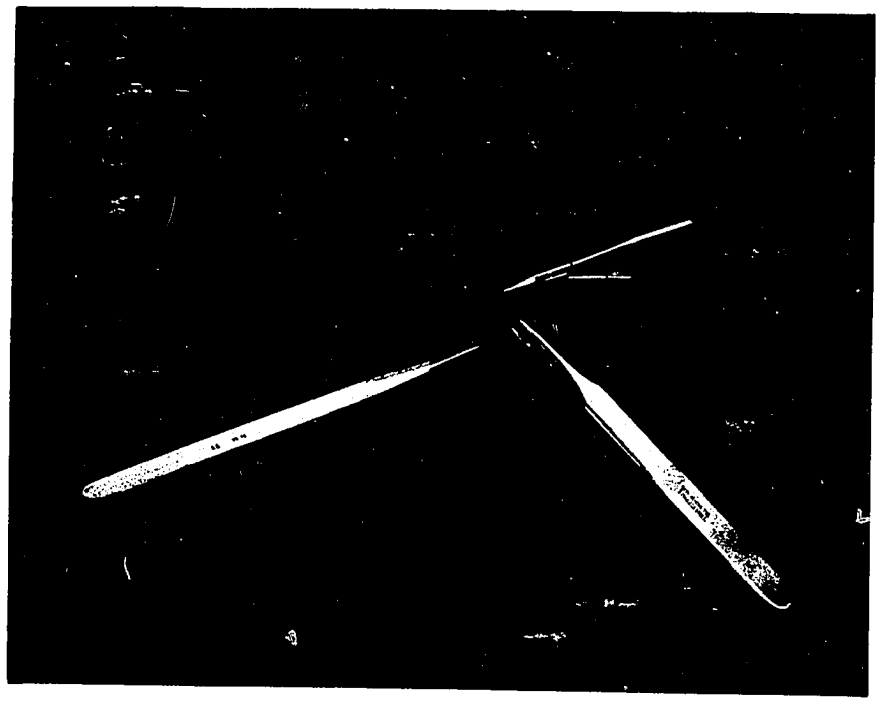
Figure 6. Schematic drawings showing the technique of implantation within a coronary artery. After the probe is inserted into the artery with the help of the needle, the 7-0 suture is pulled tight and tied firmly in place

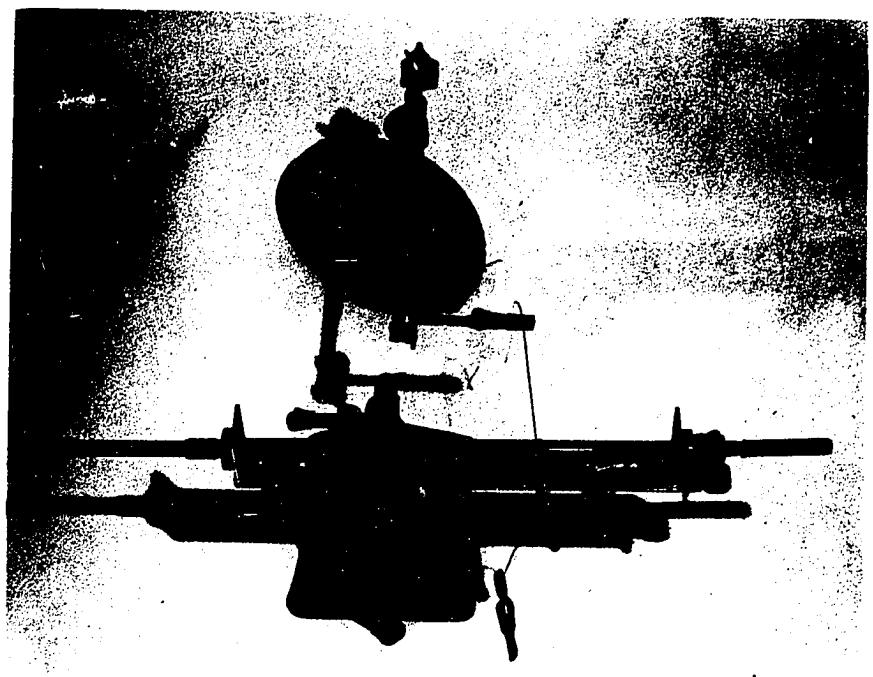

7-0 suture
B
Tip
Thermister
Base of probe
1 cm.
Cable
J. Guenther

Needle
5 mm.

Figure 7. Instruments used to mount the thermistor on the probe. The tweezers are used for stripping insulation, making ties, and winding the thermistor lead wires. The scissors are used for trimming the tie strands

Figure 8. Composite view of the instrument used for winding the wire coils. The top bulldog clip guides the wire into place. It is self-tracking. The other clip is tied to the guide clip and holds it at an appropriate angle. The rubber covered alligator clip is a tension device. The axis wire is attached at both ends with pin vises and is under tension. The pin vises are centered in ball-bearings





potting compound is allowed to solidify overnight and is then placed in the oven for 30 minutes. This and all subsequent heat treatments are done in an oven preheated to 135° C. One must use caution and wrap the tubes in paper, because the glass will shatter. The shattered glass is removed and the cable is rinsed in water. One end of the wires is straightened and dip-coated with varnish[1] and then baked for 2 hours.

To make the probe, the wires are cut to 13 and 22 mm lengths, stripped of insulation at the tips, and tinned with solder with the help of flux.[2] The soldering is done with a drop of solder on the tip of a magnetic soldering iron. The solder is kept just above its melting point by adjusting the line voltage with a voltage regulator. The surface of the solder is cleansed with a thread before each use. These and all subsequent manipulations are done under a dissecting microscope.

One end of the thermistor[3] is tied (Figure 7) to the short wire. This and all subsequent ties are made with a strand taken from a 2 cm piece of Vetafil[4] suture. The thermistor lead wire is wound around the cable wire several times (Figure 3). This joint is etched with flux and soldered. The soldered joint is etched with flux, cleaned with xylene, coated with varnish, and baked for one hour. The cable wires are tied

---

[1]Sylgard #1377, Dow Corning Corp., Midland, Mich.

[2]Duzall, All-State Welding Alloys Co., Inc., White Plains, N. Y.

[3]Veco Micro-Bead #42A402C, Victory Engineering Corp., Springfield, N. J.

[4]Dr. S. Jackson, Washington 11, D. C.

together and the thermistor is wound around the long wire. This second joint is now etched and soldered. It is then etched, cleaned, coated, and baked as described before. Additional ties are made where necessary. The entire tip is dipped in 4004 primer[1] and baked for 15 minutes. The tip is now dipped in a 50:50 mixture of dry xylene and silastic.[2] It is air dried for 1 hour and baked 1 hour. The tip is now dip-coated with potting compound and baked for 30 minutes. The tip is again coated with the xylene and silastic mixture, then baked for 30 minutes.

The skin connector is made by fitting a stainless steel flange around the chassis connector (Figures 1 and 4). The two cables and a 5 cm length of bare silver wire are soldered to the connector. The silver wire acts as a ground wire. The flange and connector base are coated with potting compound and silastic to waterproof and insulate them.

The device is now ready for testing. It can be sterilized for surgery by placing in the oven for two hours. It can also be chemically sterilized.

Calibration of Device

The calibration of the thermistors was done on a rotating drum 10 cm in diameter. The thermistor probe tip was rigidly held 3 mm from the edge of the drum and about 12 mm below the surface of the fluid. The fluid used was 20% sucrose by weight and 0.4% sodium chloride. The viscosity of

---

[1]Primer #SS-4004, General Electric, Waterford, N. Y.

[2]Medical adhesive #891, Dow Corning Corp., Midland, Mich.

this fluid at 25° C is approximately that of blood plasma (1.7 centipoise). Changes in voltage across the recorder[1] bridge circuit[2] with changes in D.C. current at a constant flow rate were used to calculate $\Delta R/\Delta I$. The changes in voltage with changes in flow rate at 40 μA of current were used to calculate $\Delta R/\Delta F$. The voltage is a log function of the flow rate (Figure 9).

The insulation of the device was tested in this same fluid with a one volt square wave taken from the calibrating circuit of the oscilloscope.[3] A wire from the calibration jack was immersed in the fluid. If the square wave was picked up by the probe, it was rejected.

The time constant was calculated from the rise time of one of the fast transients seen when the rotating drum is suddenly stopped (Figure 10a). One such spike was considered to be one-half of an idealized sine wave. $T = 1/2\pi f$.

---

[1]Grass Polygraph, Model 5, Grass Instruments, Quincy, Mass.

[2]The bridge circuit had 20 K ohm, 1% resistors in the base of each arm. The thermistor arm was balanced with a 25 K ohm potentiometer on the other arm. The current source was a 9-volt battery in parallel with a 50 K ohm potentiometer used as a gain control.

[3]Oscilloscope #502, Tektronix Inc., Portland, Oregon.

Figure 9. Calibration curves for a representative pair of flowmeter devices. A minimum flow rate is necessary before any change in heat dissipation occurs

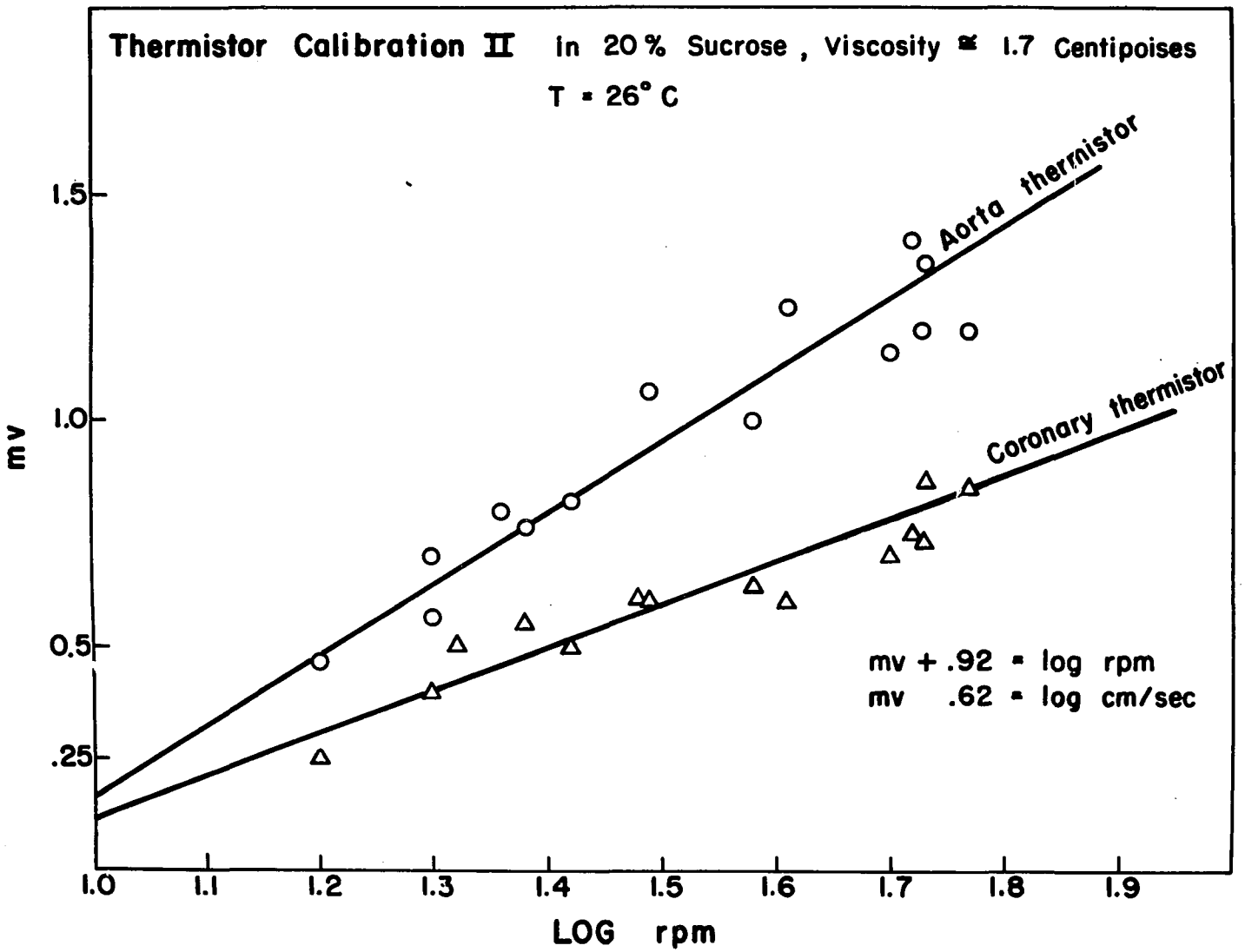
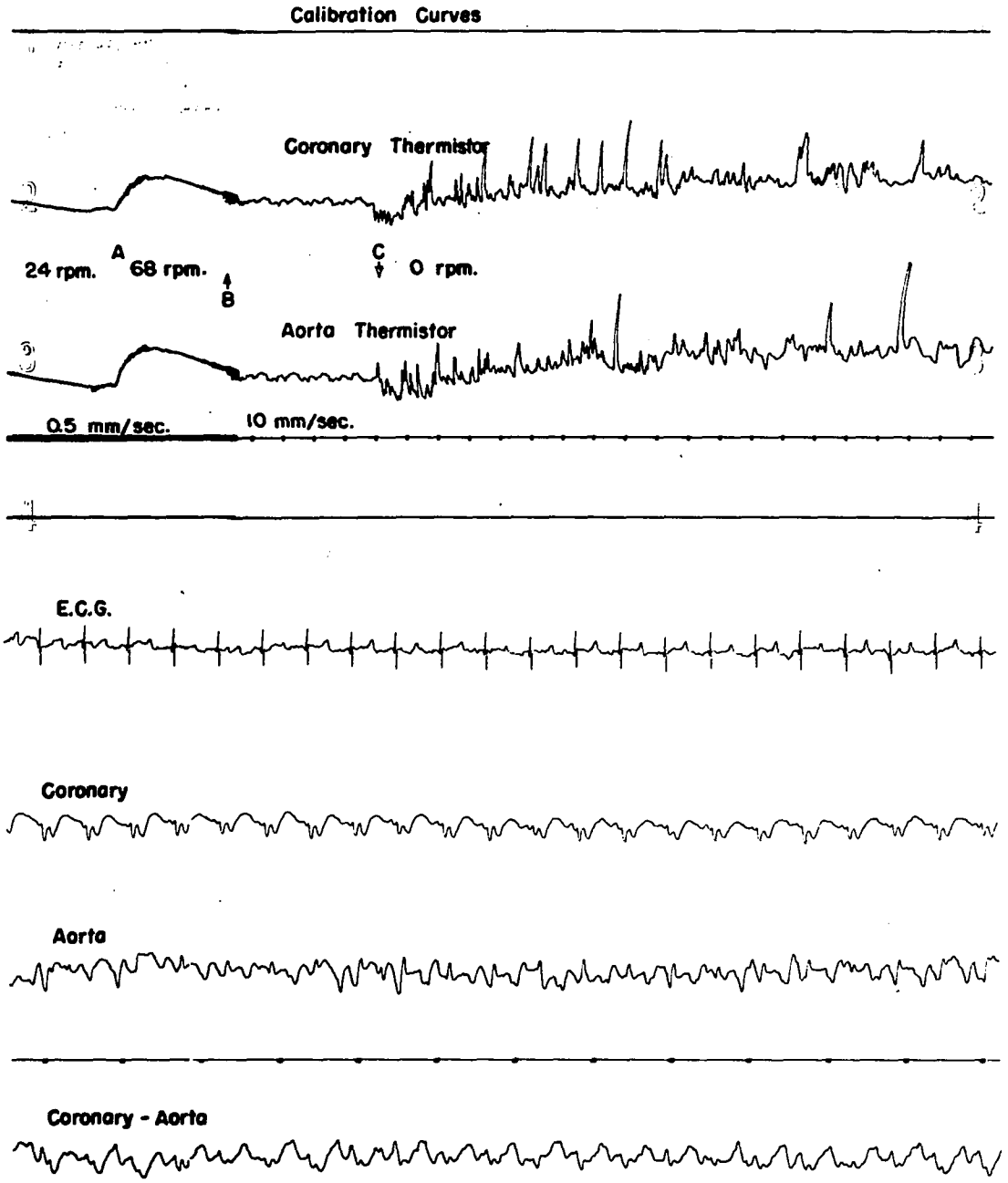

Thermistor Calibration II In 20% Sucrose, Viscosity ≅ 1.7 Centipoises
T = 26° C
Aorta thermistor
Coronary thermistor
mv + .92 = log rpm
mv .62 = log cm/sec
mv
1.5
1.0
0.5
.25
1.0
1.1
1.2
1.3
1.4
1.5
1.6
1.7
1.8
1.9
LOG rpm

Figure 10a. Representative thermistor response during a calibration recording. The drum rotation is changed from 24 to 28 rpm then stopped completely. It takes a long time for the fluid to stop moving

Figure 10b. Normal thermistor response to phasic coronary and aortic blood flow. An upward deflection of the pen indicates a cooling of the thermistor by an increase in blood flow. A sharp rise in coronary blood flow coincides with the T wave of the ECG. The aortic probe does not give the response one would expect. Perhaps it is being deflected by the blood flow


Calibration Curves
Coronary Thermistor
24 rpm.
A
68 rpm.
B
C
0 rpm.
Aorta Thermistor
0.5 mm/sec.
10 mm/sec.
E.C.G.
Coronary
Aorta
Coronary - Aorta

Surgical Procedure for Implantation of Device

A pig[1] weighing about 22 kg or a dog[2] weighing about 14 kg was given a preoperative injection of 0.65 mg Atropine[3] and 100 mg Promazine.[4] Thirty minutes later the animal was anesthetized with 30 mg sodium pentobarbital[5] intraperitoneally per kg body weight. When the animal was deep enough to permit it (Stage III, plane 1), it was laid on its right side, clipped and scrubbed for aseptic thoracic surgery (Cholvin, 1961). A #28 endotracheal tube was inserted and an ear vein was cannulated with a 24 guage hypodermic needle on the end of a long polyethylene tube for the injection of additional amounts of pentobarbital. An oxygen respirator was put in place and the chest cavity was opened between the 4th and 5th ribs (Figure 11). The pericardium was incised and retracted with sutures. During these procedures care was taken to keep the tissues moist with physiological saline and to minimize blood loss.

The left atrium was retracted with atraumatic alligator clips (Figure 5). The heart surface was restrained by sutures. A portion of the left

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[1]Pigs from the ISU Swine Nutrition farm, fed a 16% protein diet, ad libitum. This diet consisted of 76% yellow corn, 12% soy-bean meal, 5% fish meal, 5% alfalfa meal, 1.5% steamed bone meal, and 0.5% salt.

[2]Mongrel dogs from local sources, fed a diet of 25% crude protein, 7% crude fat, and 5% crude fiber.

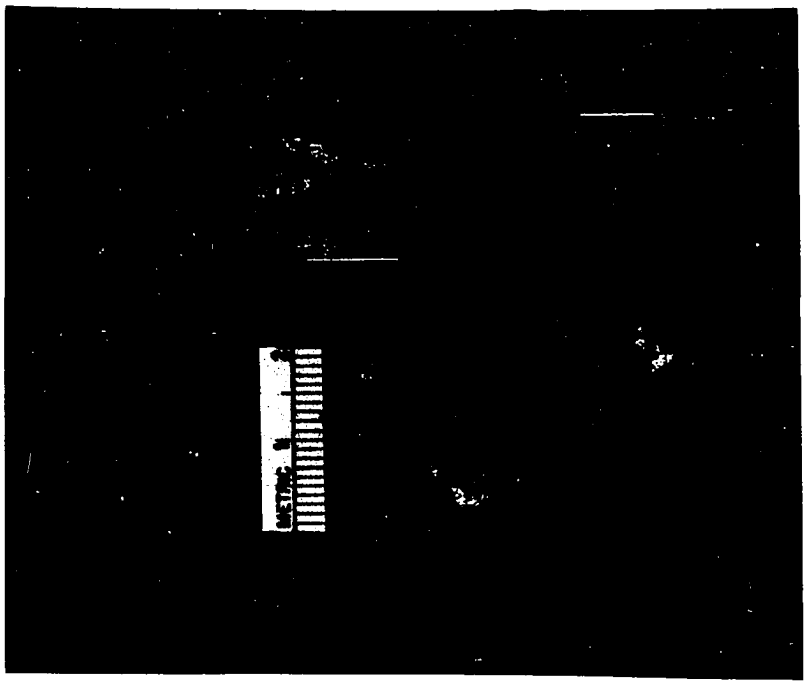
[3]Atropine, 0.5 mg per ml, Fort Dodge Laboratories, Inc., Fort Dodge, Iowa.

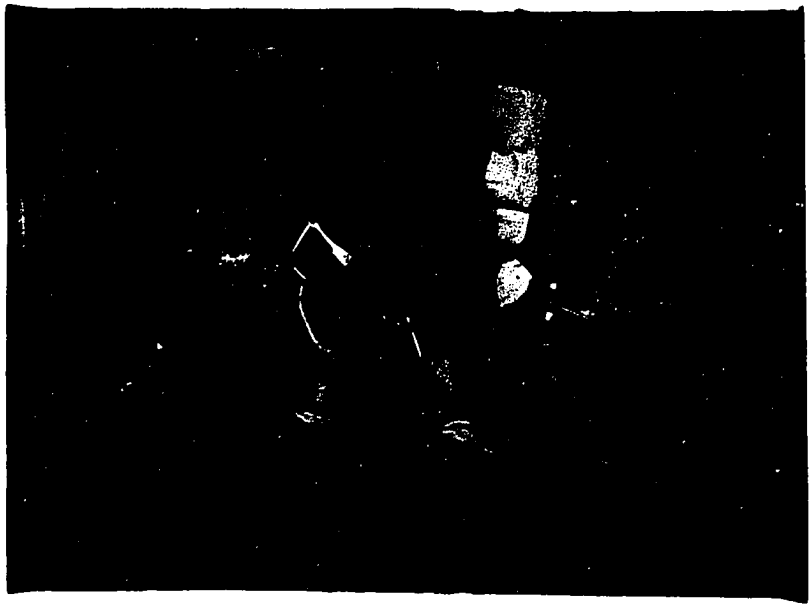
[4]Promazine Hydrochloride, 50 mg per ml, Fort Dodge Laboratories, Inc., Fort Dodge, Iowa.

[5]Halatal solution, 1.0 grain per ml, pentobarbital sodium, Jensen-Salsbery Laboratories, Kansas City, Mo.

Figure 11. View of the implantation surgery. Standard sterile operative procedures are used

Figure 12. Surface view of the heart two days after implantation. The connective tissue ensheathment of the device is well along





circumflex or descending coronary artery close to their bifurcation and free of overlying muscle or veins was exposed by incising the surface connective tissue. Every effort was made to maintain the coronary circulation during the implantation. No ligatures were placed around the arteries or veins to avoid traumatizing them or rupturing small tributaries.

A loop of suture[1] was placed in the wall of the artery about 1 mm distal to the site chosen to insert the thermistor probe (Figures 5 and 6). The other end of the loop was tied to the base of the probe. A 27 gauge hypodermic needle tube, which had been ground off on one side to form a U-shaped channel and given a long tapering point (Figure 6), was inserted into the lumen of the artery and held in place while the probe tip was threaded down the needle. The needle was removed and the suture was pulled tight, thus holding the probe in place. The suture was firmly tied (Figure 6). The cable was sutured to the surrounding connective tissue close to the base of the probe. Large, loose loops of cable were laid on the surface of the heart and sutured so as to minimize mechanical stress on the probe during contraction of the heart (Figure 12). A thermistor probe was similarly inserted into the descending aorta just anterior to the azygous vein.

During the completion of the operation, loose coils of cable and a drainage tube were left in the thoracic cavity and brought out between the

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[1]Cardiovascular suture #7-0.

ribs. The incision was closed in layers with interrupted sutures. The cables were allowed to lie loosely underneath the skin. The lateral skin incision was extended dorsally and a one-inch diameter core of skin was removed for the cable connector. The connector was held in place with a purse-string suture (Figure 15). The air was removed from the thoracic cavity through the drainage tube by means of a syringe. The antibiotic[1] was given intramuscularly.

The post-operative recovery of the animal was judged by its alertness; by whether it was able to breath normally, stand, move about, eat and drink; by the texture and color of the skin; by the appearance of the incision; and by the blood pressure and electrocardiogram.

Both the dogs and pigs were kept in separate, large dog cages. They were separated to prevent them from chewing on one another's connectors.

Procedure for Measuring Drug Effects

The animal was allowed to recover for 1 or 2 days from the effects of prolonged anesthetization and to allow the connective tissues and endothelium to anchor the device in place (Figures 12, 13 and 14). The connective tissue ensheathment reduces and damps the mechanical artifacts caused by the heart and lungs.

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[1]Longicil-S, 150,000 units benzathine penicillin-G, and 250 mg dihydrostreptomycin sulfate per ml, Fort Dodge Laboratories, Inc., Fort Dodge, Iowa.

Figure 13. View of the probe inside the coronary artery three weeks after implantation. The base of the probe is heavily coated with endothelium

Figure 14. Picture of an aortic probe three weeks after implantation. The ensheathment reduces the sensitivity of the device and increases its tendency to bend with changes in blood flow and thereby reduces its effective time constant

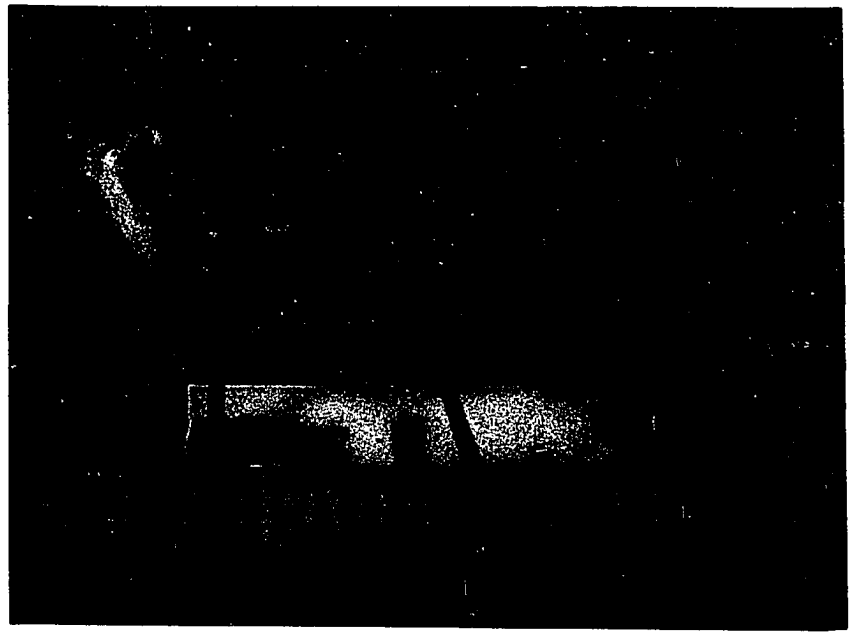

Figure 15. Pig on the day after surgery. He is able to stand but favors his left foreleg

Figure 16. Experimental drug setup showing the method of injecting the hormones; and recording the blood pressure, ECG., and coronary blood flow

The animal was again anesthetized with sodium pentobarbital. The left carotid artery was cannulated for the recording of blood pressure with a Statham strain guage.[1] Heparinized saline[2] was used in the pressure apparatus, and was used to flush the cannula every 10 to 15 minutes. The left epigastric[3] or left cephalic[4] vein was exposed and cannulated with polyethylene tubing filled with heparinized saline and attached to a 3-way stopcock for the injection of the drugs and for the periodic flushing with saline. The stopcock was kept in a neutral position to prevent blood from backing up into the tubing. The animal was connected for lead II ECG recording with sharp stainless steel pins (Figure 16).

The thermistor bridge was balanced for a D.C. current level of 40 μA. An input time constant of 0.1 second was used to reduce the effects of slow temperature changes. An upper frequency response of 3 or 15 cps was used. The gain was set for a 1 to 2 cm deflection. This can be any setting from 0.01 to 0.1 mv per cm depending on the state of arousal of the animal and on how close the thermistor is to the center of the artery. The animal was kept lightly anesthetized. The current to the thermistor

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[1]Statham Pressure Transducer #P23AC, Grass Instruments, Quincy, Mass.

[2]Heparin, 3000 USP units per liter, Heparin sodium injection USP., Organon Inc., West Orange, N. J.

[3]Anterior, superficial epigastric vein.

[4]Cephalic vein of the forearm.

may be turned off after each run, especially if the ECG response suggests that the insulation has been damaged during implantation. This is shown by a shift of the ECG base line when the current is turned on or off.

The J_{11} jack on each thermistor channel was connected to a third driver amplifier for a coronary minus aorta differential recording. The J_{11} and J_{12} jacks on the blood pressure channel were connected to another driver amplifier set for 0.1 cps to dampen the pulse and give a mean pressure recording.

When a stable response of all channels was obtained, the drug was quickly injected and flushed with saline. At least ten minutes were allowed between each injection. The drugs were given in various sequences and in variable amounts. The smallest doses were given first. Epinephrine[1] and norepinephrine[2] were used in doses of 0.005 to 2.5 µg per kg body weight. Acetylcholine[3] was given in doses of 0.5 to 5.0 µg per kg body weight.

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[1]Epinephrine Hydrochloride, Wolins, Mineola, N. Y.

[2]Norepinephrine, Nutritional Biochemical Corp., Cleveland, Ohio.

[3]Acetylcholine chloride, Nutritional Biochemical Corp., Cleveland, Ohio.

RESULTS AND DISCUSSION

Characteristics of Device

The thermistor is a semiconductor material with a large temperature coefficient (Sapoff and Oppenheim, 1963). An increase in temperature greatly increases the density of current carriers and so lowers the resistance. Its total resistance as used here is a function of the nominal resistance, the current flowing through it, the temperature of the blood, and the velocity of blood flow. Forty μa of current will raise the temperature of the 20 K ohm thermistor about 0.6° C above body temperature. The resistance will drop about 3.9% for each 1° C rise in temperature. A flow signal of 1 mv represents an increase in resistance of about 50 ohms. The flow velocity determines how rapidly heat is removed from the surface of the thermistor, and thus how effectively the thermistor is cooled by the blood.

A flowmeter which lies inside the blood stream poses certain unique problems. It is more apt to disturb the flow it is supposed to measure, both by the heat it dissipates and by its physical size; it may be inactivated by blood clots or tissue overgrowth; and its response may be distorted by the pulsating blood flow (Taylor, 1958; Pieper, 1964).

Muller (1954) has theoretically shown that at present, exact mathematical calculation of the forces exerted on a body immersed in a streaming fluid is impossible even in the case of steady flow. In the range of high Reynold's numbers, friction must be considered, for the force exerted on the body is due to a thin boundary layer of fluid

(Prandtl's theory). Within this layer, the velocity gradient perpendicular to the body surface is very high and is a function of the viscosity. The boundary layer is stable up to Reynold's numbers of about 900 (Reynold's number = velocity x radius x density/viscosity). In pulsatile flow the blood is nonhomogeneous and Reynold's numbers vary from zero to several thousand (Kramer et al., 1963). Under these conditions, the response of the thermistor will be unpredictable.

The thermistor flowmeter has certain advantages over other implantable flowmeters. It records instantaneous flow rates at the surface of the probe. There are no intervening tissue layers or averaging effects to mask or distort the flow signal. It uses simple circuitry and is free of ECG or magnetic field artifacts. It can also record temperature gradients and so can be used as a measure of cardiac output by thermal dilution methods (Cooper et al., 1963; James et al., 1965).

The probe of the device which is placed inside the artery must be so small, strong, and flexible that the use of a platinum alloy wire is mandatory. Considering this requirement, the fabrication of the device and its reuse are facilitated by using this same wire for the cable. The diameter of the probe wire is chosen to withstand the manipulations of implantation. The compliance of the probe in turn fixes the minimum compliance that can be tolerated in the cable. It is necessary for the maximum flexibility of the cable to choose a wire coil that matches the compliance of the cured potting compound. The coil can be made more flexible by increasing the diameter of the coil, using a smaller wire,

or by including more loops per unit length. It is usually desirable to keep the overall size of the cable as small as possible. A cable 1 mm in diameter is quite strong and can be made very flexible by the above considerations.

If one wishes to avoid the necessity of aligning the coil inside the glass tubing, the inside of the tubing can be coated with a thin film of potting compound and cured before the wire coil is inserted. Alternatively, the cable can be dip-coated with silastic or potting compound after it is removed from the glass tubing. Any low viscosity silicone resin that is waterproof and is a good insulator can be used as a potting compound (Colwell, 1963). A suture can be tied close to each end of the coil to prevent the wire from pulling out of the cable during the fabrication of the device. A few millimeters of braiding would serve the same purpose (Colwell, 1963), but would hinder the reuse of the cable.

The most difficult part of the fabrication is the coating of the tip. Various materials (varnish, primers, silastic, and potting compound) were tried in all conceivable combinations. It was learned that the potting compound and the silastic would bond to themselves and to one another, if the undercoat was properly primed and cured. The combination of materials finally adopted gives a probe which is flexible and waterproof.

Implantation of Device

Four dogs and 13 pigs were implanted to learn what sort of probe design and technique of implantation were best. The connectors were attached to the skull with screws at first, but the neck flexing pulled the probes out of the artery. It was also difficult to maintain aseptic conditions when the cables were threaded under the skin to the skull. Septic conditions could rapidly destroy the silicone elastic cable. Insulated stainless steel wire was used in the beginning, but the cable lasted only a few days before breaks occurred in it. The coils of fine, insulated, platinum alloy wire embedded in silicone rubber were entirely satisfactory. Cables made in this way could be removed intact after several months in the animal. Several of the connector and cable assemblies were used over again after the thermistor probe was repaired.

The longest survival of a functional probe was three weeks. The device itself was intact but the intra-arterial probe was partially walled off with endothelium (Figures 13 and 14). This 'walling-off' process can be well along after only one day, if the probe is digging or rubbing against the endothelium. Hence, the probe inside the artery needs to be relatively long and flexible, though this kind is very difficult to implant without damaging it. Suturing the probe base firmly to the wall of the artery helps to keep the probe from rubbing against the endothelium.

Several of the implanted tips were found to have perforated the coronary artery twice. If the thermistor could be centered with a diagonal double perforation, so that the tip protrudes from the underside of the artery, this could be one way of staying in the center of the lumen. The motion of the heart during surgery, however, makes it impossible to achieve this. The field of view is also obstructed by the loss of blood during the time that the channeled needle is in place. Another way of centering the device is by placing flexible bristles on the tip of the probe like the spokes of a wheel. These bristles would also tend to anchor the tip in place and help prevent it from pulling out during surgery. Centering would minimize any mechanical artifacts due to the motion of the heart and the arterial pulse. It would also retard an endothelial overgrowth of the tip and would thus prolong its useful life. An electronic zero flow could be determined by using a reference thermistor implanted near the spine where it would be shielded from mechanical motion and thermal gradients due to muscle contraction, respiration, or blood flow. Occluding the artery would not give a true zero flow (Gregg et al., 1965).

Coronary Blood Flow

The normal pattern of coronary blood flow changes during the cardiac cycle is shown in Figure 17. An upward deflection of the recorder pen indicates a cooling of the thermistor as a result of an increase in blood flow. A sharp rise in coronary blood flow coincides with the T wave of the ECG (electrocardiogram), the electrical

indication of ventricular relaxation. Coronary blood flow decreases at the start of ventricular contraction, signaled by the QRS complex of the ECG. Though the thermistor response is non-directional, the systolic flow peak is probably forward flow (Gregg, 1950).

The velocity of blood flow as measured by the thermistor will vary with the thermistor's distance from the center of the vessel because of the parabolic velocity profile which is characteristic of laminar flow (Wetterer, 1963). If the thermistor is assumed to be in the axis of the vessel with a constant value for the radius (R) of the vessel, but in fact it is not in the center, the absolute flow rate will be underestimated. For example, if the thermistor is at a distance of $R/\sqrt{2}$ from the axis, the measured flow rate will be only 1/4 what it should be.

If a vasodilation of a large artery occurs with little or no change in the small arteries, then this change will cause a decrease in the blood flow velocity in the large artery and will look like a vasoconstriction to the thermistor. In a similar way, a uniform vasoconstriction of both large and small arteries will not be detected. A relatively large increase in large artery diameter would have to occur to mask even a small vasodilation in the small arterioles due to the surface area effect. The greatest resistance to flow, shear stress, of a viscous fluid in a tube is found near the walls where the velocity gradient is the steepest. When a large artery divides into a number of smaller arteries, there is a large increase in lateral surface area even

though there may be only a small increase in total cross-sectional area. Hence, there will be a net increase in resistance to flow. This question, concerning vasomotor changes at the site of implantation could be answered by measuring these changes (Cholvin, 1961).

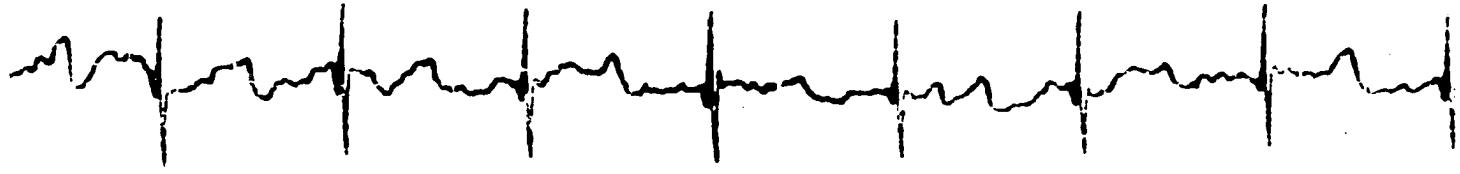
It is significant to note that though the electromagnetic method of measuring blood flow does not permit an increase in the diameter of the artery, primary coronary vasoconstriction has, nevertheless, been detected by the electromagnetic method. The time course and magnitude of the coronary blood flow changes that were found in the dog (Gregg et al., 1965) are similar to the results obtained in the pig with a thermistor.

A total of 93 hormone tests were done on 6 pigs. Typical responses are shown in Figures 18, 19 and 20). The hormones used in this study can affect coronary blood flow by changing the vasomotor tone of the coronary arteries, the phasic intramural pressures, and the perfusion pressure. Their effects on heart rate, blood volume, myocardial contractility, venous return and peripheral systemic resistance indirectly affect these quantities.

The mean height of the coronary thermistor response for a given respiratory cycle was measured on the recording (Figures 18, 19 and 20). This height was used to find an approximate, relative flow on the calibration curve (Figure 9). These calculations are only relative, minimal approximations, because the thermistor may not have been in the center of the artery, and the flow in the coronary arteries may not

Figure 17. Magnified view of Figure 10b to show the coronary blood flow changes during the cardiac cycle. Though the thermistor response is non-directional, the systolic peak is probably forward flow

E.C.G.



Coronary

Figure 18. Hemodynamic changes induced by 5-10 μg doses of epinephrine. The initial decrease in coronary blood flow in experiment A is inhibited in B. A is the response to epinephrine alone. B is the response to epinephrine following a preinjection of norepinephrine

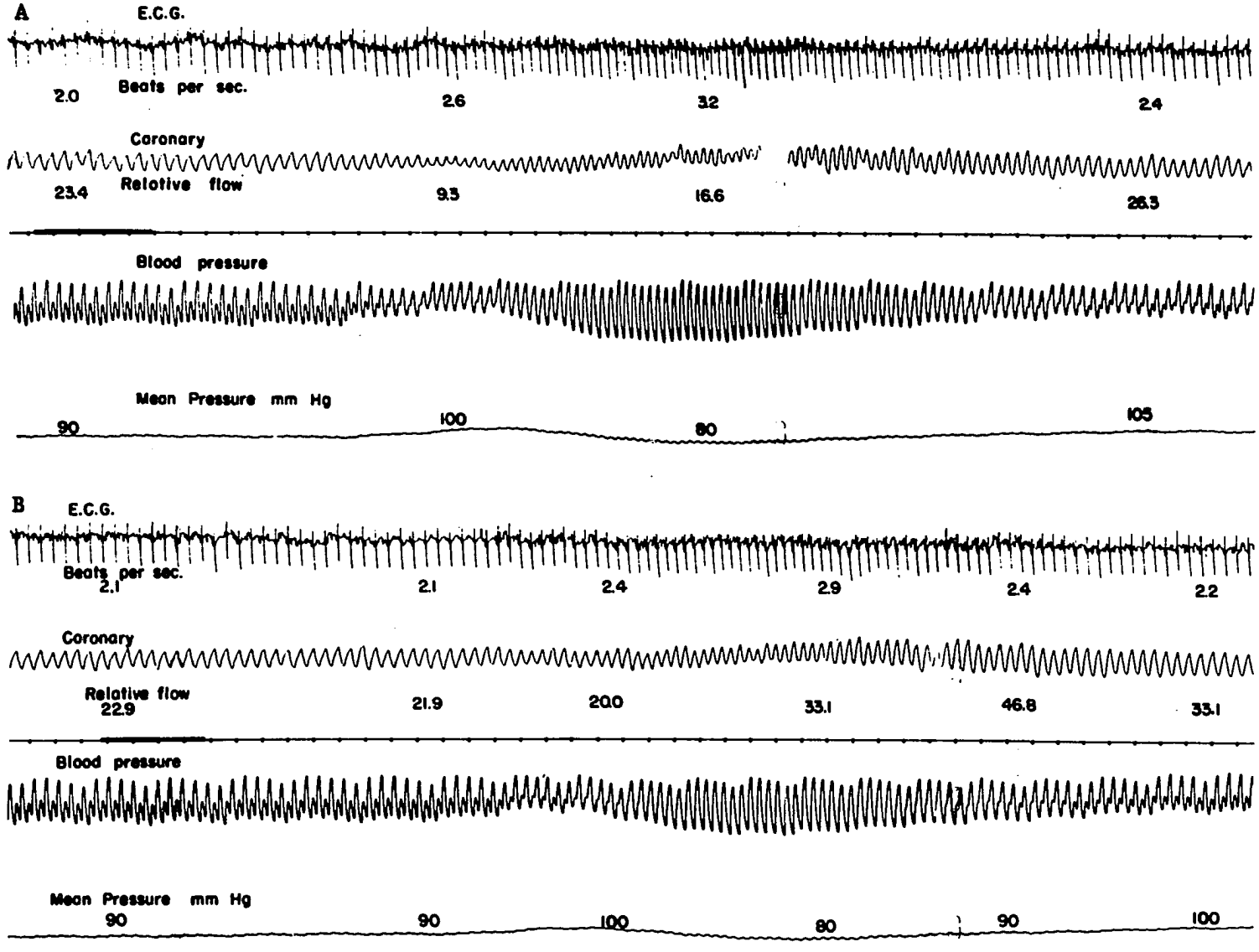

A
E.C.G.
Beats per sec.
2.0
2.6
3.2
2.4
Coronary
Relative flow
23.4
9.3
16.6
26.3
Blood pressure
Mean Pressure mm Hg
90
100
80
105
B
E.C.G.
Beats per sec.
2.1
2.1
2.4
2.9
2.4
2.2
Coronary
Relative flow
22.9
21.9
20.0
33.1
46.8
33.1
Blood pressure
Mean Pressure mm Hg
90
90
100
80
90
100

Figure 19. Hemodynamic changes induced by 20-30 μg doses of acetylcholine. The decrease in coronary blood flow which follows the period of hypotension in experiment C is inhibited in D. A is the response to acetylcholine alone. B is the response to acetylcholine following a preinjection of norepinephrine

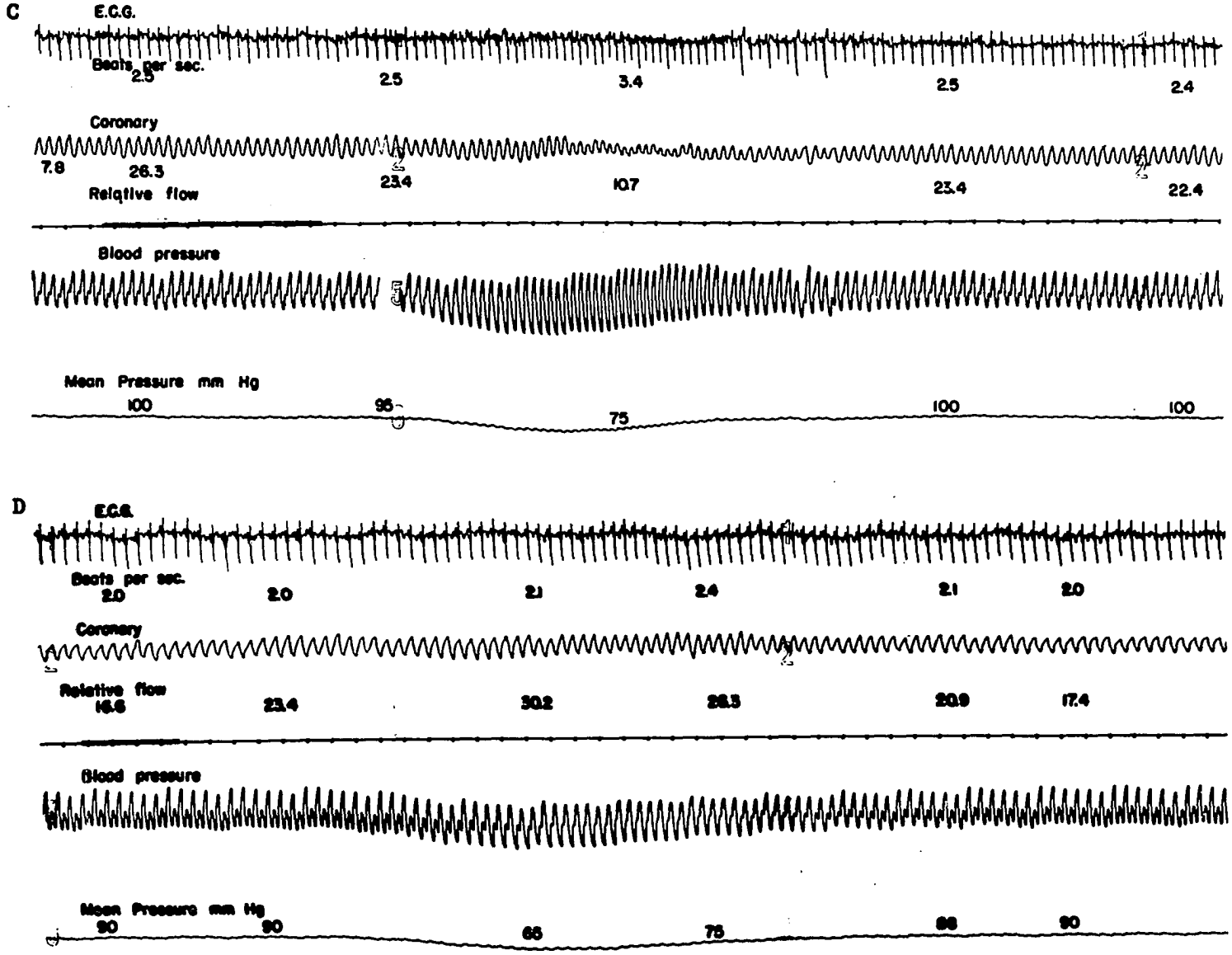
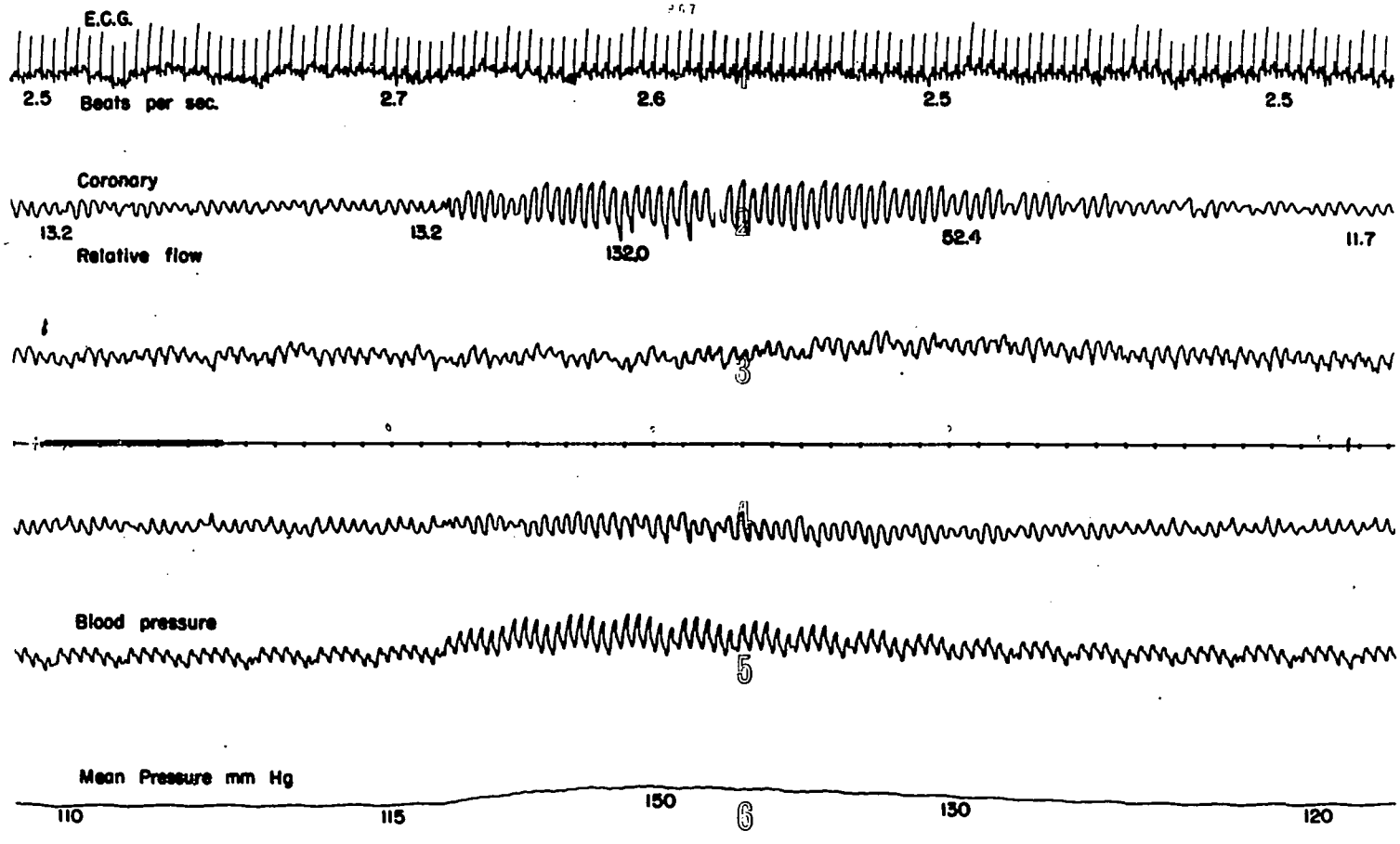

C
E.C.G.
Beats per sec.
2.5
2.5
3.4
2.5
2.4
Coronary
7.8
26.3
23.4
10.7
23.4
22.4
Relqtive flow
Blood pressure
Mean Pressure mm Hg
100
95
75
100
100
D
E.C.G.
Beats per sec.
2.0
2.0
2.1
2.4
2.1
2.0
Coronary
Relative flow
16.6
23.4
30.2
28.3
20.9
17.4
Blood pressure
Mean Pressure mm Hg
90
90
66
76
88
90

Figure 20. Hemodynamic changes induced by 10 µg dose of norepinephrine


E.C.G.
2.5
Beats per sec.
2.7
2.6
2.5
2.5
Coronary
13.2
13.2
132.0
52.4
11.7
Relative flow
Blood pressure
Mean Pressure mm Hg
110
115
150
130
120
1
2
3
4
5
6

have dropped to zero at any time during systole (Gregg et al., 1965). In addition, the 3 cps upper frequency cut-off used to facilitate the voltage measurements would distort the flow pattern and underestimate total flow. Though the absolute blood flow is not known, it should be proportional to the flow as it is calculated here. Hence, any conclusion drawn from these relative changes in blood flow should be valid.

Epinephrine given in 5-10 µg doses, experiments A and B in Figure 18, induced a tachycardia and peripheral vasodilation that increased the pulse pressure but had little effect on the peak systolic pressure. The mean pressure rose slightly, then fell as the peripheral vasodilation took effect. The mean pressure, pulse pressure and tachycardia slowly returned to normal as the effects of the hormone wore off. This whole sequence of events occurred in about 60 seconds. The coronary blood flow in "A" decreased before there was any appreciable change in the other hemodynamic factors. This vasoconstrictor effect was transient, however, because an autoregulatory increase in coronary blood flow, associated with increased cardiac effort, would mask it. The surprising thing is that this vasoconstrictor effect of epinephrine could be inhibited. This was not known at the time these experiments were done so that no specific statements relative to the time course or magnitude of this inhibition can be made.

Acetylcholine given in 20-30 µg doses in experiments C and D (Figure 19) induced a drop in mean pressure and diastolic pressure followed by a reflex tachycardia and return to normal pressure. In

experiment C the coronary blood flow decreased with the start of the secondary tachycardia and returned to normal pressure. This secondary drop in coronary blood flow was inhibited in experiment D. There was also less secondary tachycardia in experiment D. The drop in coronary blood flow at a time when adrenergic and or sympathetic nervous activity was increasing is similar to the response seen in experiment A. The inhibition of this coronary vasoconstriction in both experiments B and D follows a preinjection of norepenephrine. No experiments have been done as yet to prove that norepinephrine does, indeed, have this effect.

Norepinephrine given in a 10 μg dose (Figure 20) induces a brief rise in blood pressure with little change in pulse pressure or heart rate. There is a large, transient increase in coronary blood flow. Though there is a greater driving pressure, the principal factor responsible for this increase is probably the augmented metabolic activity of the myocardium.

The only way that these transient decreases in coronary blood flow could be artifactual would be by a local vasodilation of the coronary artery at the site of implantation. No such large artery response to epinephrine or sympathetic activity that is not accompanied by vasomotor changes in the arterioles is known to the author.

How this study relates to the <u>in vitro</u> studies of Smith and Coxe (1950), and Zuberbuhler and Bohr (1965) is not known. They have found that isolated coronary arteries are relaxed with solutions of epinephrine

and norepinephrine in concentrations of 10 µg per liter; and 0.1 µg or 0.01 µg, respectively.

SUMMARY AND CONCLUSIONS

The fabrication of a chronically implantable thermistor device is described. It has an effective time constant of 0.02 second. It is suitable for the measurement of intra-arterial coronary blood flow transients in the quiet, unanesthetized pig. It consists of a probe that projects into the lumen of the artery, a skin connector for external recording, and a flexible silicone elastic cable that acts as an electrical conduit. This device can remain intact in the animal body for several weeks but the probe may become ensheathed with endothelium. The operative procedures are also very difficult. There are uncertainties relative to vasomotor changes at the site of implantation and to the position of the thermistor within the velocity profile across the diameter of the vessel. Thus no knowledge of absolute flow rate is possible, but it should be proportional to the flow as it has been measured here. Hence, any conclusion drawn from these relative changes in blood flow should be valid.

The transients induced by 0.5 to 1.5 μg acetylcholine, and 0.1 to 1.0 μg epinephrine and norepinephrine per kg body weight are shown. A primary vasoconstriction due to epinephrine or a secondary vasoconstriction following acetylcholine hypotension can be inhibited by a preinjection of norepinephrine.

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