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Continuous measurement of oxyhemoglobin concentration by reflection oximetry and its use in controlling an artificial heart

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CONTINUOUS MEASUREMENT OF OXYHEMOGLOBIN CONCENTRATION BY REFLECTION OXIMETRY AND ITS USE IN CONTROLLING AN ARTIFICIAL HEART

by

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TABLE OF CONTENTS

TABLE OF CONTENTS (Continued)

INTRODUCTION

The development of an artificial heart poses many problems, one of which is control to maintain homeostasis and meet the changing physiological and metabolic requirements of the subject. Another is an appropriate method of instrumentation. The purpose of this study is twofold. The objective of Part I is to design a reflection oximetry system with the capability of continuous measurement of the arterial, venous or arteriovenous difference in oxyhemoglobin concentration during extracorporeal cardiopulmonary bypass and artificial heart studies. Part II consists of the investigation of venous and arteriovenous difference in oxyhemoglobin concentrations as parameters to control the output of an artificial heart.

The continuous measurement of the oxyhemoglobin concentration has been shown to be important in the diagnosis of left-to-right intracardiac shunts (13, 14, 17, 19). Venous oxyhemoglobin concentration is a good indication of tissue perfusion, therefore it is a useful parameter to monitor during extracorporeal cardiopulmonary bypass for open heart surgery. With the advent of artificial hearts it has been necessary to find methods to determine how efficiently these devices are functioning as substitutes for the natural heart. Here again the concentration of arterial and venous oxyhemoglobin may be useful indicators of both pulmonary gas exchange and tissue perfusion.

Reflection oximetry is based on the reflection properties of blood at two different wavelengths (805 and 660 mμ). The oxyhemoglobin concentration is the per cent of the total hemoglobin which is oxygenated. At approximately 660 mμ the largest difference in the amount of light reflected is observed between oxyhemoglobin and reduced hemoglobin. At 805 mμ, the isobestic point of blood, all hemoglobin appears essentially the same. The ratio of the amount of light reflected at these two wavelengths is thus proportional to the oxyhemoglobin concentration. A flexible fiber optic transmission line is used to transmit the information from the blood. This approach permits the point of measurement to be near the chest and also keeps the instrumentation back out of the way. Canine and ovine blood are used to calibrate the oximeters since these are the two species of experimental animals used for the study.

Previous investigations by this group (8, 51, 52) have shown that it is possible to use right and left atrial pressures to control blood flow through an artificial heart. In Part II of this study, an investigation is made to determine if the venous and arteriovenous difference in oxyhemoglobin concentrations along with left atrial pressure can be used as parameters to control the output of an artificial heart.

Modeling has provided a means of representing and studying various physiological systems and the interaction of physiological mechanisms. Guyton et al. (22, 23, 24) and

Grodins (21) have developed various models to illustrate and describe how the cardiovascular system might be under chemostatic control. A model is developed in Part II of this thesis which helps to illustrate how oxyhemoglobin concentration might be an integral part of cardiovascular control. The model also illustrates how the venous and arteriovenous difference in oxyhemoglobin concentrations are used to control the stroke volume of an artificial heart.

The control studies first illustrate how the system functions under steady-state conditions. Various methods are then used to perturb the animal-machine system in an attempt to show how the system might compensate to meet various physiological and metabolic requirements.

This study has been done in conjunction with a group project which has as its major objective the development of an implantable artificial heart for use in experimental animals.

PART I. CONTINUOUS MEASUREMENT OF OXYHEMOGLOBIN CONCENTRATION BY REFLECTION OXIMETRY

REVIEW OF THE LITERATURE

History of Reflection Oximetry

Reflection oximetry had its beginning in 1949 when Brinkman and Zijlstra (7) introduced their haemoreflector. By means of this instrument the oxyhemoglobin concentration of blood samples could be determined more rapidly than by any other means. The method had an accuracy in the same order as Van Slyke's procedure and spectrophotometric methods. Almost simultaneously with the haemoreflector Brinkman and co-workers developed a two color reflection oximeter ("cyclops") for use on patients, especially for observing changes in arterial oxyhemoglobin concentration during thoracic surgical interventions.

In 1953 Rodrigo (47) discussed the methods of Brinkman and Zijlstra (7). He pointed out the advantages which reflection oximetry has over colorimetric methods which use transmitted light. He also discussed the reflection theory by Dreosti (9) and its application to Brinkman's haemoreflector.

In 1956 Mook and Zijlstra (41) adapted a standard "cyclops" oximeter to use on a cuvette, which was directly connected to a cardiac catheter. Measurements with this instrument indicated that the amount of reflected light varied with the flow rate of blood through the cuvette. Further experiments showed the amount of light reflected to be

dependent on the degree of rouleaux formation.

In 1960, Polanyi and Hehir (45) demonstrated that the ratio of light reflected by a nonhemolyzed blood sample at two suitable wavelengths (805 and 660 mμ) was a linear function of the oxyhemoglobin concentration. The reflection oximetry system which they developed provided an absolute determination of oxyhemoglobin concentration as in the absorption method and it was shown to be of definite practical value for in vitro measurements.

In 1961, Ware et al. (58) discussed the importance of determining the oxyhemoglobin concentration during cardiac catheterizations and cardiopulmonary bypass. They determined the oxyhemoglobin concentration in 34 patients who underwent cardiac catheterization, open heart surgery, brochoscopy, and thoracotomy. Blood samples were compared by reflection oximetry, standard spectrophotometric procedures and manometric techniques. The instrument used was the reflection oximeter developed by Polanyi and Hehir which utilizes two wavelengths (805 and 660 mμ) and heparinized whole blood. They showed that the instrument provided oxyhemoglobin concentration values which were independent of temperature and hemodilution, as well as cell size, shape and origin. They also showed that there was no significant difference in the standard deviation between

Van Slyke, Beckman[1] and reflection oximeter determinations of oxyhemoglobin concentration.

In 1962, Enson et al. (13) described an oximeter which employed two bundles of flexible glass fibers to conduct appropriately filtered light into the blood. The light was diffusely reflected by the blood out of the blood stream for the determination of oxyhemoglobin concentration or dye concentration within blood flowing past the tip of either an arterial needle or a cardiac catheter which contained both bundles. The ratio of the intensities of the reflected light at two wavelengths was linearly related to the oxyhemoglobin concentration (I_{R805}/I_{R660}) and dye concentrations (I_{R900}/I_{R805}).

In 1964, Kapany and Silbertrust (35) developed a fiber optics spectrophotometer for in vivo oximetry. They also investigated the angular scattering and other optical properties of blood with different oxyhemoglobin concentrations.

In the same year Edgington and Cholvin (11, 12) performed a series of experiments to determine the effects of flow, pressure and oxyhemoglobin concentration on the intensity of reflected light at 632.8 mμ. They showed that the intensity of light reflected was velocity dependent below a critical velocity. Reversal of flow caused a change in reflected light

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[1]Model D. U. spectrophotometer, Beckman Instrument Co., Inc., Fullerton, California.

which was attributed to different flow patterns and the geometric arrangement of the cells in the region of the catheter tip. Pulsatile pressure variations were shown to have no direct effect on reflected light intensity. They concluded that the intensity of light reflected from whole unhemolyzed blood was dependent upon the length of rouleaux present and, as such, was shear rate dependent. The intensity of light reflected at 632.8 mμ was linearly related to the oxyhemoglobin concentrations between 40 and 100 per cent for constant hematocrits.

In 1965, Gamble et al. (19) expanded on the technique of Enson and co-workers by improving the design of the catheter tip to avoid artifactual changes in oxyhemoglobin concentration caused by proximity of the catheter tip to the endothelial surface. They also incorporated an automatic device which computed the ratio of the light intensities and reported the oxyhemoglobin concentration in as little as 0.07 seconds.

In 1965, Frommer et al. (17) described several clinical applications using a modification of the reflection oximetry system developed by Enson et al. (13, 14). The system permitted study of phasic changes in the pulmonary arterial oxyhemoglobin concentration during respiratory maneuvers. The oximeter also permitted continuous measurement of the pulmonary arterial oxyhemoglobin concentration before, during and after muscular exercise.

Fiber Optics

Optical fibers efficiently transmit light and images around bends and in controlled paths with little loss of energy. In recent years fiber optic catheters have become popular in reflection oximetry (11, 12, 13, 14, 17, 19).

The history and application of fiber optic principles, properties and design considerations have been described by Siegmund (50), Edgington (11), Kahl (34), and Aron and Arlan (1). The basic mechanism that makes optical fibers behave the way they do is known as total internal reflection (34). Light striking the end of a glass fiber or rod will be totally reflected from the sides as it travels toward the exit at the other end. As a light ray enters the end of the fiber at a given angle, it is refracted and travels toward the outer surface. When it reaches this interface between the fiber and the surrounding medium, it may be again refracted or reflected. If the angle at which it is incident to the interface is greater than some critical angle, as measured from the perpendicular, it will be totally reflected and cannot escape, as shown in Figure 1. A light ray entering at an angle which causes it to be incident at less than the critical angle will penetrate and leave the fiber. The critical angle depends on the ratio of the indices of refraction of the two media that affect the light; for example, the glass that makes up the fiber or rod and the air that surrounds the glass. Contamination degrades

the surface of the glass fiber, so for protection it is clad with another glass. It also provides a uniform surface at which total reflection can take place. Thus, the critical angle will depend on the refractive indices of two different glasses, one a core glass and the other a cladding glass.

Kahl (34) indicates that one of the great advantages of optical fibers is their light-gathering power. This property, termed the "numerical aperture", is dependent on the maximum cone or acceptance angle at which the fiber can trap and reflect light. It equals sin θ_1 in Figure 1, and by Snell's Law is expressed: NA = sin $\theta_1 = \sqrt{n_1^2 - n_2^2}$, where n_1 and n_2 are the indices of refraction of the core and cladding glasses respectively, and the incident ray is traveling in air. It can be seen that the greater the difference in the indices, the greater the acceptance angle will be. Aron and Arlan (1) indicate that the range of numerical apertures available in fiber optics is limited only by the material from which the fibers can be made. Bundles which transmit visible light, can be made of selected pairs of glasses, which provide numerical apertures up to 1.2. Materials such as arsenic trisulfide glass which are used in bundles which transmit infrared light have higher refractive indices, and it is therefore possible to obtain larger numerical apertures for the same coating-to-core refractive index ratio. Slight changes in the refractive index will cause very rapid changes in NA (34). Some typical

values for combinations of commercial glasses include:

$n_1 = 1.700$; $n_2 = 1.512$; NA = 0.78; $\theta_1 = 51^\circ$

$n_1 = 1.650$; $n_2 = 1.560$; NA = 0.54; $\theta_1 = 32^\circ$

Kahl (34) and Edgington (11) have discussed the principal optical factors which affect light transmission in a single fiber. These include: the absorption coefficient of the core glass and reflection losses at entrance and exit faces. Thus in attempting to ascertain the light transmission, the nature of the incident light should be known. The wavelength will determine the absorption coefficient, and the angle of incidence will determine the reflection losses and amount of contact with the absorbing medium. The angle of incidence also determines the optical path length of the fiber and consequently, the absorption losses. Therefore light losses encountered include entrance and exit losses and internal losses. Losses encountered when light enters the fibers are a function of the numerical aperture of the optical fibers and the angle of incidence of light striking the end as illustrated in Figure 1. There are also additional losses at the ends due to imperfections in polishing. The process of internal reflection of the light from one end to the other accounts for the internal losses. Therefore light transmission with fiber optics is a function of the length of the fibers.

The gross transmission of a fused array of fibers is further affected by the ratio of the cross-sectional surface

area represented by the core glass to the total cross-section of the array (34). This is called the "packing fraction", and can range from 60 to 85 per cent.

Fiber optic bundles are available from several manufacturers. They come in diameters from .020 to .500 inch (.51 to 12.7 mm.) and in lengths up to six feet (1.83 m.), with individual fiber diameters ranging from 10 to 75 microns. The bundles usually have a numerical aperture of about 0.50 and transmit only visible and near infrared light. Manufacturers indicate that in a typical fiber about 70 per cent of the light striking the end enters the fibers and about 10 per cent of this is lost for every foot of length.

INSTRUMENTATION

The Oximetry System

The oximetry system consists of a light source which is focused on the transmitting hub of a fiber optic transmission line. The fiber optic transmission line conducts the light to the blood-glass interface. The light which enters the blood is scattered by the red blood cells and other cellular components of the blood, illuminating the area around the tip of the fiber optic transmission line. Kapany and Silbertrust (35) have indicated that many other parameters, in addition to the oxyhemoglobin concentration, determine the optical properties of blood. These parameters include the velocity of flow, whether the flow is laminar or turbulent, the temperature of the blood, and the hematocrit or the total number of red blood cells per unit volume. The reflected light is transmitted back up the transmission line through the two receiving bundles. The amount of reflected light at 805 and 660 mμ is measured by photocells which are components of a wheatstone bridge. Figure 2 is a schematic representation of the optical portion of the system.

The light source[1] is mounted in a socket[2] in an aluminum

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[1]#1493 (6.5v, 2.75a) General Electric Company, Chicago, Illinois.

[2]D. C. Bay, Candelabra Socket, Allied Electronics, Chicago, Illinois.

box. The light is focused by means of an achromatic lens[1] on the transmitting end of the fiber optic transmission line. Figure 2 also illustrates the lamp and condensing system. The power supply for the lamp consists of a constant voltage transformer[2]. Figure 3 is a circuit diagram of the power supply.

The procedure for construction of the fiber optic transmission lines was similar to that described by Edgington (11). The major difference was that it contained two receiving bundles rather than a single one which Edgington describes.

The glass fibers used to construct the transmission line were taken from bundles of incoherent optical fibers[3]. Figure 4 is a photograph of a bundle of loose glass fibers which make up the transmission line.

Construction of the transmission line was begun by taking the flexible fiber optic bundle and cutting it in the center to make two bundles, each approximately 18 inches (45.8 cm.) in length. The intact end was preserved while the fibers at the loose end were separated into three bundles in such a manner that the fiber ends of each bundle were uniformly dispersed at the intact end. Each of the three bundles was kept

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[1]#6387, Edmund Scientific Company, Barrington, New Jersey.

[2]#30882, Sola Electric Co., Chicago, Illinois.

[3]#40, 644, American Optical Company, Southbridge, Massachusetts.

intact by tying it with a piece of thread. The bundles were passed into a "Y" connector[1], the receiving bundles in one branch and the transmitting bundle in the other. Each of the three bundles was inserted into a piece of polyethylene tubing[2]. This permits adequate room for the fibers and allows the catheter to flex to a small radius without serious danger of fiber breakage.

Transparent epoxy resin[3] was then spread over the ends of the fibers and a short piece of irradiated polyvinyl shrinkable tubing[4] was heated until it had shrunk down to tightly enclose the bundle of fibers. This process forced the fibers at the tip into a closely packed bundle approximately circular in cross section and left the spaces between the fibers filled with epoxy compound. A thin coating of adhesive[5] was then placed on the surface of the shrinkable tubing and the polyethylene tubing forced over this to create a watertight seal at the tips of the transmission line. A piece of shrinkable tubing was placed over the polyethylene tubing to prevent light

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[1]#T5307, Scientific Products, Chicago, Illinois.

[2]Intramedic PE330, Clay Adams Inc., New York, New York.

[3]#40674, Edmund Scientific Co., Barrington, New Jersey.

[4]Alphex Wire Co., New York, New York.

[5]Miracle Adhesive, Miracle Adhesive Corp., Bellmore, New York.

from entering the fiber optics from the outer walls of the catheter. This tubing was inserted inside the ends of the "Y" connector and epoxyed in place. This prevents any stress from being applied to the fibers. The "Y" connector was wrapped with black tape to prevent light from entering at this point.

The tips thus formed were then polished using a series of abrasives[1]. The abrasives used were alundum (#220, 320, 400, and 600), #305 emery, red jewelers rouge, cerium oxide and barnesite. The abrasives were used in this order. Polishing was done on a manila folder, mixing a small amount of water with each abrasive and changing areas frequently. The polished ends were observed under a light microscope. Polishing reduces the end losses created by total internal reflections.

Coaxial connectors[2] were modified and used to attach the transmitting and receiving branches of the fiber optic transmission line to the light source and photocell receiving system. The centers of the receptacles were enlarged and epoxyed in place on the transmitting and receiving hubs of the transmission line. The plugs were fastened to the light source and photocell receiving system. Figure 5 is a photograph of the fiber optic transmission line with the connectors.

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[1]Edmund Scientific Co., Barrington, New Jersey.

[2]#45000, 46025, Amphenol coaxial connectors, Allied Electronics Corp., Chicago, Illinois.

Later studies used commercially manufactured fiber optic transmission lines[1]. Compression fittings were used to attach this transmission line to the light source and photocell receiving unit. As a precaution against clotting, the tip of the transmission line which made contact with the blood was treated with a silicone solution[2].

The end of the transmission line which makes contact with the blood was placed in a "T" connector[3]. The branches of the "T" were cut off so the inside diameter was about 3/8 inch (.95 cm.). A coaxial connector[4] was used to attach this end of the transmission line to the "T" connector by the method previously described. A rubber grommet and a small teflon collar permit a water tight seal when the transmission line is placed in the "T" connector. Figure 6 is a photograph of the commercial transmission line and the "T" connector.

The receiving system was also constructed in an aluminum box. Light reflected from the blood is transmitted by the two receiving branches of the fiber optic transmission line which attach to the box by means of coaxial connectors. The light then passes through two filters.[5]

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[1] #F18024, Donner Electronics, Inc., Melrose, Massachusetts.

[2] Siliclad, Clay Adams Inc., New York, New York.

[3] #T5305, Scientific Products, Chicago, Illinois.

[4] BNC type, Amphenol coaxial connector, Allied Electronics, Inc., Chicago, Illinois.

[5] S-1, S-1(NIR), Baird Atomic, Inc., Cambridge, Massachusetts.

The filters are multi-layer, all dielectric interference filters which transmit light of high spectral selectivity. One filter, S-1, has a peak wavelength of 660 mμ, with a bandwidth at half peak transmission of 1.45-1.55 per cent of the peak position. This indicates a bandwidth of 9.5-10.2 mμ. This filter with standard long wavelength blocking to 800 mμ has a maximum peak transmission of 40-45 per cent. However additional blocking is required, so a blocking piece[1] is added to increase long wavelength blocking to 1200 mμ. This gives a maximum peak transmission of 35-45 per cent for the 660 mμ filter and blocking piece combined. The other filter, a S-1 (NIR), has a peak wavelength of 805 mμ. It has a maximum transmission of 35-45 per cent with standard blocking to 1200 mμ. This filter has an approximate bandwidth at half peak transmission of 1.45-1.70 per cent of peak position. This indicates a bandwidth of 11.7-13.7 mμ. Transmission outside the pass band for both filters is 0.1 per cent.

These filters were selected because of the spectral transmission characteristics of oxyhemoglobin and reduced hemoglobin in the visible and infrared regions of the spectrum as illustrated in Figure 7 (30-31, 60). Light reflected from the hemoglobin at 805 mμ indicates the amount of blood in the optical path and is independent of the degree of oxygenation

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[1]Baird Atomic Inc., Cambridge, Massachusetts.

of the blood. This is because oxygenated and reduced blood transmit light of this wave-length to almost the same degree. This is called the isobestic point of blood. The percentage transmission of red light (600-750 mμ) is very different for oxygenated and reduced hemoglobin. Hence the amount of light reflected by the hemoglobin of the blood is a function of the amount of blood and both amount and degree of oxygenation of the blood. If the amount of blood is constant, light reflected at 660 mμ is a function of the oxyhemoglobin concentration of the blood.

Matched photoconductive cells[1] (photocells) were placed behind the filters to determine changes in reflected light. The photocells were made of cadmium selenide and have a peak spectral response of 690 mμ. The spectral sensitivity of these photocells is shown in Figure 8. The fact that the sensitivity is approximately equal at 660 and 805 mμ is helpful for design considerations. The response time (time required to reach 63 per cent of the final value) of the cell at a light level of 0.01 foot candles is 1.1 seconds for an increase, and 0.12 seconds for a decrease, in brightness.

The photocells make up two of the components of the wheatstone bridge which is shown in the circuit in Figure 9. Resistors were selected to correspond to the actual

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[1]#CL604L, Clairex Corp., New York, New York.

operating range of the photocells. The 100K potentiometer is for calibrating the wheatstone bridge. This is the design for the oximeter used in venous blood. A similar unit was constructed to determine the concentration of oxyhemoglobin in arterial blood. The box was made light tight by sealing all seams and cracks with black tape. The power supply for the bridge consists of two mercury batteries[1], which together provide 2.7 volts. Figure 10 illustrates the entire oximetry system.

The Switching System

A switching system (20) was constructed which provides two modes of operation, manual or automatic. The system was capable of manual switching between arterial, venous or the arteriovenous difference in oxyhemoglobin concentration. The automatic mode provided automatic switching between arterial and arteriovenous difference in oxyhemoglobin concentration.

The switching circuit incorporates a hybrid timing circuit as shown in Figures 11 and 12. The circuit is considered hybrid in that it utilizes a unijunction transistor in conjunction with a PNP transistor. The junction transistors form a conventional flip-flop with the unijunction transistor serving the timing and triggering functions. Each time the unijunction transistor conducts, the discharge current from the

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[1]#RM-42R, Mallory Battery Co., Tarrytown, New York.

capacitor C_T develops a pulse across R_A which triggers the flip-flop from one state to the other. Thus it switches from arterial to the arteriovenous difference in oxyhemoglobin concentration.

In the non-symmetrical multivibrator, the timing capacitor C_T is charged through the resistor R_{T1} or R_{T2} which is connected to the positive collector. The diodes isolate the other resistor from the timing capacitor. The two parts of the period (t_1,t_2) can thus be set independently by R_{T1} and R_{T2} and may differ by as much as 1000 to 1. This enables variable recording periods for the arterial and arteriovenous difference in oxyhemoglobin concentrations in the automatic mode.

EXPERIMENTAL METHODS

In Vitro Methods

In vitro studies were conducted to determine the effect of hematocrit, flow velocity, and species difference on the function of the oximetry system at various levels of oxygenation of the blood.

The pumping system developed by Edgington and Cholvin (11, 12) was used for these experiments. A block diagram of the system is shown in Figure 13. It consists of two pumps with piston-cylinder arrangements which can be filled with blood and driven at constant flow rates from one cylinder to another. Each cylinder consists of a 3-1/2 inch (8.9 cm.) inside diameter plexiglass cylinder fitted with a Bellofram[1] seal over a 3-1/4 inch (8.3 cm.) diameter piston. This system, by avoiding the use of a tight fitting piston cylinder arrangement, reduces friction and potential trauma to blood normally associated with sliding parts. Each cylinder has a rod attached to it so that each can be driven either manually or by the drive system described below. The cylinders were connected together by 3/8 inch (.95 cm.) inside diameter glass tubing, the "T" connectors for the oximetry systems and a filling "T".

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[1] #4-350-350DCC, Bellofram Corporation, Burlington, Massachusetts.

The drive system used to drive the blood from one cylinder to the other, consists of the drive mechanism from an infusion pump[1] mounted so it can be driven by a variable speed motor.

The flow velocity of the blood passing the tip of the fiber optic transmission line in the "T" connector was determined by loading one cylinder with water and emptying it via a piece of rubber tubing into a graduated cylinder. The linear flow velocity was then calculated as follows:

$$\text{Linear Flow Velocity} = \frac{\text{Volume Flow Rate}}{\text{Cross Sectional area of the "T"}}$$

This system permits a range of linear flow velocities from 3-40 cm./sec. at the point where the transmission line is placed in the "T" connector.

Prior to placing the transmission lines in the "T" connectors they are calibrated by immersing them in a concentrated liquid magnesia[2]. This provides a calibration for the wheatstone bridge, since it gives a reflection standard which can be repeated. The transmission lines were inserted into the "T" connectors so that light would strike the blood perpendicularly to the path of flow.

Approximately a liter of blood was obtained from canine, ovine or bovine donors and was heparinized with 24 mg. of heparin per liter of blood. The blood was divided into two

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[1]Model 600-9000, Harvard Apparatus Co., Dover, Massachusetts.

[2]The Chas. H. Phillips Co., New York, New York.

portions in infusion bottles; one portion was reduced and the other fully oxygenated. Oxygenation and reduction of the blood were accomplished by bubbling oxygen and nitrogen respectively into the blood through tubing with a fritted termination. Foaming of the blood was prevented by treating the infusion bottles and blood with an antifoam agent[1]. This treatment decreased the efficiency with which the blood was oxygenated and reduced. There was probably a very thin layer of the agent on each of the red blood cells which may have hindered gas transport or diffusion. It is possible that reflectivity was also affected by this thin silicone layer. By mixing quantities of oxygenated and reduced blood, blood of any desired oxyhemoglobin concentration could be obtained for use in the pumping system. This allows the determination of constant flow effects for various levels of oxyhemoglobin concentration.

In a typical experimental run one portion of treated blood was placed in the pump system and residual air expelled as rapidly as possible. The flow velocities were then varied in steps from 3-38 cm./sec. Before and after each series of velocity runs at one level of oxygenation a sample was drawn anerobically. The oxyhemoglobin concentration of these samples was determined spectrophotometrically[2] and the average of the

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[1]Antifoam A spray, Dow Corning Co., Midland, Michigan.

[2]Method of Edgington (11), Beckman Model DU, Beckman Instrument Co., Inc., Fullerton, California.

two oxyhemoglobin concentrations taken as the oxyhemoglobin concentration for that series of runs. The oxyhemoglobin concentration of the blood in the system was then altered by addition of a quantity of blood from the remaining portion and the above procedure repeated.

In a similar manner studies were conducted to determine the effect of hematocrit on the function of the oximeter. In order to obtain lower hematocrits a 5 per cent dextrose solution was used to dilute the blood. Hematocrits from 14 to 41 per cent were studied in canine blood and 15 to 25 per cent in ovine blood. A linear flow velocity of approximately 20 cm./sec. was used for these studies.

The bridge voltage from each oximeter was recorded unfiltered on a direct ink writing recorder[1]. The procedures used to facilitate anaerobic handling of blood samples and determination of the oxyhemoglobin concentration were essentially those described by Edgington (11).

In Vivo Methods

The in vivo studies were designed to continuously monitor the arterial, venous, and arteriovenous difference in oxyhemoglobin concentrations during extracorporeal cardiopulmonary bypass and in artificial heart studies.

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[1]Model 5 or 7 polygraph, Grass Instrument Co., Quincy, Massachusetts.

Valve implant procedures

Monitoring the oxyhemoglobin concentration during extracorporeal cardiopulmonary bypass was done in conjunction with procedures in which the mitral or tricuspid valve of dogs was replaced with an artificial valve. The anesthesia used for these procedures consisted of induction with a thiobarbiturate[1] and maintenance with nitrous oxide and methoxyflurane[2]. A positive-negative phase respirator[3] and an anesthetic machine[4] were used to ventilate the lungs with 100 per cent oxygen and to administer the methoxyflurane and nitrous oxide.

The following cannulations were made to connect the heart-lung machine for extracorporeal circulation while the valve was replaced. A femoral vein and jugular vein were cannulated for venous return and a carotid artery and femoral artery for infusion. Prior to making the cannulations the dog was heparinized (3 mg./kg. body weight). The venous blood was oxygenated by a bubble oxygenator column[5] after which it passed through silicone treated sponges which defoamed the

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[1]Surital, Parke, Davis and Co., Detroit, Michigan.

[2]Metofane, Pitman Moore, Division of the Dow Chemical Co., Indianapolis, Indiana.

[3]Model 8, Bird Corporation, Palm Springs, California.

[4]Heidbrink Kinetometer, Ohio Chemical and Surgical Equipment Co., Madison, Wisconsin.

[5]Kimray, Inc., Oklahoma City, Oklahoma.

blood. The oxygenated blood passed down a helical tube where it could be heated or cooled by a triple temperature heat exchanger[1]. The oxygenated blood was returned to the animal by means of a carotid artery and femoral artery. Roller pumps were used to pump the venous blood to the oxygenator and return the oxygenated blood from the helix to the animal. Figure 14 is a diagram to show where the oximeters were placed to monitor the arterial and venous oxyhemoglobin concentrations. The extracorporeal circuit was primed with a 5 per cent dextrose solution (approximately 700 cc.). Other parameters monitored were the electrocardiogram, electroencephalogram, thoracic esophageal or venous blood temperature[2], aortic pressure[3], and mean blood flow rate in the extracorporeal circuit. A direct ink writing recorder[4] was used to record these parameters. Biochemical and hematological determinations performed were total hemoglobin, plasma free hemoglobin, hematocrit, blood pH, arterial P_{O_2}, and arterial P_{CO_2}. A slow intravenous infusion of buffer[5] was maintained in an attempt to keep the

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[1]Kimray, Inc., Oklahoma City, Oklahoma.

[2]#43TD Telethermometer, Yellow Springs Instrument Co., Inc., Yellow Springs, Ohio.

[3]#9927 P23AC Strain guage transducer, Statham Transducers Inc., Hato Roy, Puerto Rico.

[4]Model 5 or 7 polygraph, Grass Instrument Co., Quincy, Massachusetts.

[5]Trishydroxymethylamino methane (TRIS), Nutritional Biochemicals Corp., Cleveland, Ohio.

blood pH within a normal range (10). Following the transition to the extracorporeal circuit the preparation was cooled to 29° C. After the artificial valve was implanted the animal was rewarmed to 37° C.

During these procedures attempts were made to show how changes in blood flow, arterial pressure, and body temperature affect the oxyhemoglobin concentration.

Artificial heart procedures

Many of the procedures for the artificial heart studies were similar to those for the valve studies. The anesthesia was essentially the same, except that muscle relaxants were used in place of or in combination with a thiobarbiturate. A thoracotomy was performed through the fifth intercostal space. Heparin was given initially at a level of 3 mg./kg. body weight and repeated at 1.5 mg./kg. every two hours. Cannulations for cardiopulmonary bypass were essentially the same as for the valve studies. The other femoral vein was isolated for infusion of fluids and taking blood samples. The venae cavae were constricted with umbilical tape and tygon tubing when the transition was made to the heart lung machine. The preparation was cooled and the ventricles removed for connection of the artificial ventricles. Cannulas were then inserted into the anterior and posterior vena cavae, the pulmonary artery, left atrium, and aorta and secured with umbilical tape. The cannulas contained catheters for monitoring

inlet and outflow pressures. The cannulas were connected to the artificial ventricles by means of bubble traps and buffer chambers. In some of the later studies a stainless steel blood heat exchanger[1] was placed between the left atrium and the input to the left artificial ventricle. It was used to recover the animal from hypothermia following cardiopulmonary bypass and also to maintain blood and body temperature during the artificial heart studies. One oximeter was placed in the cannula leading from the left atrium to the input of the left artificial ventricle and the other in the cannula leading from the right atrium or vena cavae to the imput of the right artificial ventricle. Figure 15 is a block diagram which illustrates the placement of the oximeters and other equipment with relationship to the artificial hearts. Other parameters monitored during the artificial heart studies were the electrocardiogram, electroencephalogram, aortic blood pressure, pulmonary arterial blood pressure, right atrial or vena caval blood pressure, left atrial pressure, esophageal or venous blood temperature, instantaneous flow rate through the artificial ventricles, and integrated flow rate. Biochemical and hematological determinations were essentially the same as for the valve studies. The same buffering procedure was used as described for the valve procedures. The system was primed

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[1]10 inch unit, Lytron, Inc., Woburn, Massachusetts.

with a 5 per cent dextrose solution (approximately 1000 cc.) through the bubble traps and all bubbles removed from the system.

The ventricles used for these studies have been described by Cholvin et al. (8) and Swift (51). They were made of polytetrafluorethylene[1] and silicone medical grade rubber[2] and were designed to conform to the functional performance of a 20 kg. dog.

The artificial heart studies also demonstrated how the blood flow velocity, arterial pressure, body temperature and pulmonary ventilation are related to the arterial and venous oxyhemoglobin concentrations. Arterial oxyhemoglobin concentration was used as an indication of pulmonary function and ventilation and venous oxyhemoglobin concentration as an indication of tissue perfusion.

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[1]Teflon, E.I. Dupont de Nemours, Wilmington, Delaware.

[2]Silastic 372, Dow Corning Corporation, Midland, Michigan.

RESULTS AND DISCUSSION

In Vitro Studies

Results of in vitro studies conducted to determine the relationship between the bridge voltage and the linear velocity of flow at the tip of the transmission line are shown in Figure 16. The graph indicates the bridge voltage vs. linear velocity of flow at several different levels of oxyhemoglobin concentration of the blood. These studies indicate that for velocities from 3-38 cm./sec. the accuracy of the reflection oximetry system is only slightly affected. Others (13, 14, 35) have reported similar results with a two wavelength system. The maximum change at the high level of oxygenation is 25 mv. which represents a change of 4 per cent in the oxyhemoglobin concentration. The response at the low level of oxyhemoglobin concentration indicates a similar change.

A one wavelength system, similar to that described by Edgington and Cholvin (11, 12) is more dependent on the flow velocity of blood. Enson et al. (13) discuss the reasons why a two wavelength system is not dependent on flow velocity. As flow velocity increases, there is an axial accumulation of cells (13, 61). There is also less rouleaux formation of the red blood cells as the velocity increases and more light is reflected due to a larger surface area of the red blood cells (11, 61). At low flow velocities more of the red blood cells exist in rouleaux formation and thus the surface area for

reflection of light is less. These effects are measured and have a marked influence on the signal output of a one wavelength oximeter. However, the incorporation of two wavelengths provides a system which is essentially independent of the geometry of the red blood cells at the blood-glass interface. Changes in reflectivity due to changes in the geometry of the red blood cells are essentially equally recorded at both wavelengths. Therefore the signal output, the ratio of the reflectivity at the two wavelengths, is affected much less by blood flow velocity. The bridge voltage in Figure 16 is a function of the ratio of reflectivity at 805 and 660 mμ and is thus also essentially independent of the linear velocity of blood flow.

Studies were also carried out to investigate the effect of hematocrit on the bridge voltage. In canine blood, a change in hematocrit from 41 to 14 per cent caused approximately a 5 per cent change in the bridge voltage or oximeter reading. A similar change was observed in ovine blood as the hematocrit was varied from 25 to 15 per cent. Figures 17 and 18 illustrate the results of the hematocrit studies. The bridge voltage which is an indication of the oxyhemoglobin concentration is essentially linear in the region from 35 to 98 per cent oxyhemoglobin concentration.

Enson et al. (13) studied the effect of hematocrit on the measurement of the oxyhemoglobin concentration by reflection

oximetry. They measured the intensity of reflected light at 805 and 660 mμ and the ratio of intensities at various hematocrits. They found that the intensity of reflected light increased as the hematocrit increased to a value of 45-50 per cent, but beyond this range of values it decreased. The ratio, however, remained stable between 30 and 80 per cent hematocrit. Edgington and Cholvin (11, 12) also reported that light reflectance was a function of hematocrit when a single wavelength was used.

It was also possible to study the effect of species difference on the oximeter output. Canine and ovine blood were used since these were the experimental animals used in the in vivo studies. Figure 19 illustrates the effect of species difference at a hematocrit of approximately 21.4 per cent. A comparison was made between canine and ovine blood at hematocrits of approximately 25.6, 21.4, and 14.5 per cent. The oxyhemoglobin concentration was varied from 32-100 per cent. Throughout this range only minor variations were observed between canine and ovine blood.

In Vivo Studies

Continuous monitoring of the arterial and venous oxyhemoglobin concentrations provides an indication of tissue perfusion and pulmonary function. Theye and Tvohy (55) have emphasized the importance of mixed venous oxygen levels during general anesthesia and have illustrated how venous oxygen

levels reflect changes in the oxygen transport system. Theye and Tvohy (55) have shown that when Equation 1, the Fick equation, is rearranged into Equation 2, it illustrates the mixed-venous oxygen content is related directly to arterial oxygen content and inversely to the ratio of oxygen uptake and cardiac output.

$$\text{Cardiac output} = \frac{O_2 \text{ uptake}}{(\text{Arterial-mixed venous}) \ O_2 \text{ content}} \qquad (1)$$

$$\text{Mixed venous } O_2 \text{ content} = \text{Arterial } O_2 \text{ content} - \frac{O_2 \text{ uptake}}{\text{Cardiac output}} \qquad (2)$$

Thus a decrease in mixed-venous O_2 indicates a change in the O_2 transport system which includes a reduction of arterial O_2 content or reduction of cardiac output relative to O_2 uptake, or a combination of both. Similar considerations apply to the interpretation of an increase in mixed-venous O_2.

Theye and Tvohy indicate that knowledge of mixed-venous O_2 content alone does not provide a quantitative estimate of arterial O_2 content, O_2 uptake, or cardiac output. However, it does make possible certain deductions about relations within the O_2 transport system. For example, if mixed-venous O_2 content is normal (15±1 ml./100 ml. blood) no profound disparity exists in arterial O_2 content or in the relation of cardiac output to O_2 uptake. If mixed-venous O_2 content is abnormally low, for example 10 ml./100 ml. blood, a disparity exists in the O_2 system. Further laboratory or clinical observations

are necessary to determine the nature of the disparity. The abnormality might be: (1) reduced arterial O_2 content (anemia, low inspired O_2 tension, CO poisoning and so on, or (2) low cardiac output relative to metabolic consumption of O_2 (myocardial failure, coronary occlusion, hypovolemia, hyperthermia, shivering and such), or (3) a combination of (1) and (2).

Guyton (22) indicates that normally, about 97 per cent of the oxygen transported from the lungs to the tissues is carried in chemical combination with hemoglobin in the red blood cells. The remaining 3 per cent is carried in a dissolved state in the water of the plasma and cells. Theye and Tvohy (55) report that the difference in content of O_2 in physical solution between arterial and mixed venous blood is .2 ml. of O_2/100 ml. of blood. The oxyhemoglobin concentration is thus a good indication of the O_2 content of the blood.

The oxyhemoglobin concentration was monitored during extracorporeal cardiopulmonary bypass in 22 procedures. Nine of the procedures were valve studies, the other thirteen were artificial heart studies. The oxyhemoglobin concentration provided a good indication of tissue perfusion and oxygenation of the blood. The arterial oxyhemoglobin concentration remained essentially constant since the oxygenation of the venous blood was quite efficient in the bubble oxygenator. Therefore any changes in the mixed-venous oxygen levels or venous

oxyhemoglobin concentration indicated a change in blood flow or oxygen uptake. Figure 20 illustrates continuous monitoring of the venous oxyhemoglobin concentration during partial cardiopulmonary bypass for replacement of the tricuspid valve in a dog. Figure 21 illustrates continuous monitoring of the arterial and venous oxyhemoglobin concentrations during complete cardiopulmonary bypass for an artificial heart study. Figure 20 indicates a venous oxyhemoglobin concentration which ranges from 54 to 57 per cent. Figure 21 indicates, respectively, arterial and venous oxyhemoglobin concentrations of 94 and 60 per cent. The small pulsations are probably due to flow transients associated with the roller pumps since the points of measurement were in close proximity to them.

During cardiopulmonary bypass it was possible to study the effects of changes in aortic blood pressure, instantaneous blood flow, and body temperature on the venous oxyhemoglobin concentration.

Figure 22 illustrates the effect of a change in aortic blood pressure on the venous oxyhemoglobin concentration. As the aortic pressure first increases to 90/45 mm. Hg and then decreases sharply to 35/25 mm. Hg corresponding changes are seen in the venous oxyhemoglobin concentration. Since the arterial oxyhemoglobin concentration remains essentially constant during cardiopulmonary bypass, the changes in venous oxyhemoglobin concentration in Figure 22 are probably

associated with changes in blood flow. This indicates that the changes in aortic pressure are probably associated with changes in blood flow. Figure 22 thus helps to indirectly confirm the relationship of cardiac output to mixed-venous oxygen levels or venous oxyhemoglobin concentration which Theye and Tvohy have discussed. As the flow rates changed during cardiopulmonary bypass, corresponding changes were observed in the venous oxyhemoglobin concentration. This will be illustrated much better in the discussion of continuous monitoring of the oxyhemoglobin concentration in the artificial heart studies. The sharp rise in the venous oxyhemoglobin concentration in Figure 22 which follows about 9 seconds after the initial drop in the aortic pressure is difficult to explain. It may be associated with a sudden relaxation of the arterioles and precapillary sphincters to permit an increased flow of oxygenated blood.

Body temperature changes influenced the venous and arteriovenous difference in oxyhemoglobin concentrations during cardiopulmonary bypass. In the initial stages of bypass, the blood was cooled by the heat exchanger. As the venous blood or esophageal temperature dropped from approximately 36° C. to 32° C. the venous oxyhemoglobin concentration increased from 55 to 65 per cent as shown in Figure 23. Attempts were made to maintain flow rates at constant levels during this period of time, however reduced flow rates usually resulted at lower

temperatures due to lower metabolic requirements by the tissues. As shown in Figure 23, there is a lag of about 120 seconds before the oxyhemoglobin concentration begins to change. This time lag can be attributed to at least two factors. One factor is the circulation time from the helix where the blood is heated or cooled to the point of measurement in the venous cannula before the blood enters the roller pump. The time lag is also a function of the time required to cool the tissues. Since the arterial oxyhemoglobin concentration does not change during hypothermia, the arteriovenous difference in oxyhemoglobin concentration decreases during hypothermia. Similar observations were also noted at the end of cardiopulmonary bypass when the animal was rewarmed. Figure 24 illustrates the effect of hyperthermia on the venous oxyhemoglobin concentration.

The oxyhemoglobin concentration was monitored during 31 artificial heart studies. In addition to providing an indication of tissue perfusion and pulmonary function continuous monitoring of the oxyhemoglobin concentration provided a basis for many other interesting physiological observations.

Figure 25 illustrates continuous monitoring of the arterial and venous oxyhemoglobin concentrations during an artificial heart study. In this procedure the points of measurement of the venous and arterial oxyhemoglobin concentrations were in the input cannulae to the artificial ventricles as

illustrated in Figure 15. In Figure 26 the point of measurement of the arterial oxyhemoglobin concentration was at the output of the left artificial ventricle or in the aortic cannula. In this case there is a marked increase in the pulsatile blood flow at the point where the arterial oxyhemoglobin concentration is measured; however, there is little change in the signal from the oximeter. Other workers have also discussed the effect of pulsatile flow on the measurement of the oxyhemoglobin concentration. Enson et al. (13) indicate the signal at each wavelength is affected by pulsatile blood flow. They attribute (2, 3, 4, 54) it to a change in the orientation of the red cells and to a lesser degree to axial accumulation of the cells during axial acceleration of blood flow. Enson et al. have shown that the light reflected at both wavelengths is equally sensitive to this phenomenon, in that the same percentage of change occurs with pulsation in both signals. Therefore, the ratio which he obtained, and the oxyhemoglobin concentration derived therefrom, was unaffected by pulsatile flow throughout the heart cycle.

Figure 27 illustrates the operation of the switching system and timing circuit in an artificial heart study in a sheep. This system enables continuous monitoring of the arterial, venous, or arteriovenous difference in oxyhemoglobin concentration on the same channel. The automatic mode provides a means of observing the arterial and arteriovenous

difference in oxyhemoglobin concentrations. In Figure 27 the arterial oxyhemoglobin concentration is 90 per cent and the venous oxyhemoglobin concentration 59 per cent. Therefore the arteriovenous difference in oxyhemoglobin concentration is 31 per cent.

Figure 28 illustrates the effect of changing the oxygen content of the inspired air during an artificial heart study. In this procedure a change was made from 100 per cent oxygen to a mixture of 15 per cent oxygen and 85 per cent nitrogen. The change caused a gradual decrease in the arterial and venous oxyhemoglobin concentrations, with the decrease in the venous oxyhemoglobin concentration beginning about 50 seconds after the onset of the decrease in the arterial oxyhemoglobin concentration. In Figure 28 and 29 the pulmonary arterial pressure has a negative phase. This might have some adverse effects on the pulmonary vessels. Figure 29 illustrates the return to 100 per cent oxygen from the 15 per cent oxygen mixture. Again the venous oxyhemoglobin concentration begins to rise approximately 50 seconds after the initial rise in the arterial oxyhemoglobin concentration. This time lag can probably be attributed to at least three factors. First, there is the partial circulation time from the point of measurement of the arterial oxyhemoglobin concentration in the left atrial cannula to the point of measurement of the venous oxyhemoglobin concentration in the right atrial cannula. Second, the tissues

can utilize the reservoir of dissolved oxygen in the blood. Third, the time lag is also a function of the metabolic rate, which is probably somewhat lower than normal since the venous blood temperature is approximately 32° C.

Figure 30 illustrates pulmonary failure during one of the artificial heart studies. The arterial oxyhemoglobin concentration has decreased sharply from approximately 95 to 55 per cent and the venous oxyhemoglobin concentration shows a steady decline from approximately 50 to 42 per cent. Associated with the decrease in arterial and venous oxyhemoglobin concentrations is a decrease in the aortic pressure. This may be an example of autoregulation and vasodilatation to permit increased blood flow to increase the transport of oxygen to the tissues.

During this same procedure some interesting oscillations were observed in the arterial oxyhemoglobin concentration. Figure 31 illustrates these oscillations. Ventilation of the lungs was being controlled by the Bird respirator. As the inspiratory pressure increased to 20 cm. of water, the arterial oxyhemoglobin concentration decreased. The exact cause of these oscillations was not determined. Decreasing the inspiratory pressure from 20 to 15 cm. of water decreased the amplitude of the oscillations. The oscillations may be associated with increased blood flow through a nonfunctioning area of the lung during inspiration. Guyton (22) indicates that normally 1 or 2 per cent of the total cardiac output fails to pass through the pulmonary capillaries but instead is shunted through non-aerated vessels either in the lungs themselves or in the heart.

He also states that in some diseases of the pulmonary circulation the shunted blood amounts to more than 50 per cent of the cardiac output. Hildebrandt and Young (29) discuss the influence of lung mechanical properties on pulmonary circulation. They have reported that inflation of the lungs tends to distend not only the airways but also the larger vessels. The small vessels (principally gas-exchanging in function) are located within the interalveolar septa and consequently are not enlarged by tissue or surface forces, but are flattened or "squeezed" by a rise in alveolar pressure. Inspiration in Figure 31 may be associated with flattening of the normal pulmonary capillaries giving rise to reduced blood flow through them. The larger pulmonary vessels draining these capillaries may dilate and empty less oxygenated blood into the left atrium. However, the blood flow through the nonfunctioning area of the lung may remain the same, or increase, thus giving rise to the decreased arterial oxyhemoglobin concentration. The very sharp decrease in the arterial oxyhemoglobin concentration is associated with manual increases in the inspiratory pressure to 25 or 30 cm. of water.

Figure 32 illustrates the relationship between the venous oxyhemoglobin concentration and cardiac output. An increase in cardiac output or blood flow from the artificial ventricle provides transportation of more blood and thus more oxygen to the tissues. The extraction rate by the tissues is essentially

the same. The circulation time is decreased. Thus, there is an increase in the reserve of oxygen in the form of oxyhemoglobin in the venous blood. On a cellular basis less oxygen is taken from each red blood cell as it completes the circuit through the body.

During an abrupt decrease in cardiac output, a marked decrease was observed in the venous oxyhemoglobin concentration. In addition to the decrease, oscillations or large fluctuations were also seen in the venous oxyhemoglobin concentration. Figure 33 illustrates this phenomenon. Frommer et al. (17) also reported a similar phenomenon in some studies on man. These fluctuations might be attributed to actual changes in the oxyhemoglobin concentration caused by variable venous mixing. The placement of a fiber optic catheter in the veins of different organs and tissues and simultaneously recording the venous oxyhemoglobin concentration from various tissues might help to confirm this hypothesis.

SUMMARY

It has been shown that reflection oximetry is a practical method for continuously monitoring the oxyhemoglobin concentration during cardiopulmonary bypass and artificial heart studies.

The reflection oximeter used is essentially independent of the velocity of blood flow, hematocrits between 15 and 40 per cent, and pulsatile changes in blood flow. The reflection properties of canine and ovine blood are essentially the same.

In vivo studies indicate that continuous monitoring of the oxyhemoglobin concentration can provide useful information about adequacy of tissue perfusion, flow rates and oxygenation of the blood during cardiopulmonary bypass. The venous oxyhemoglobin concentration increases with decreasing body temperature, provided constant flow rates are maintained. This indicates decreased metabolic requirements by the tissues. Conversely, tissue requirements are greater as the body temperature rises and thus the venous oxyhemoglobin concentration falls at constant flow rates. Flow rates also influence the oxyhemoglobin concentration. High or increasing flow rates tend to increase the venous oxyhemoglobin concentration and decrease the arteriovenous difference in oxyhemoglobin concentration for a constant temperature. Low flow rates have the opposite effect.

The incorporation of reflection oximetry in the artificial heart studies has also shown that venous oxyhemoglobin concentration may be an indication of adequate tissue perfusion. Arterial oxyhemoglobin concentration on the other hand provides useful information about the respiratory system and oxygenation of the venous blood. The arteriovenous difference in oxyhemoglobin concentration is an indication of the amount of oxygen extracted by the tissues as the blood completes the circuit.

PART II. THE USE OF OXYHEMOGLOBIN CONCENTRATION AS A MEANS OF CONTROLLING AN ARTIFICIAL HEART

REVIEW OF THE LITERATURE

Autoregulation of Blood Flow

The term "autoregulation" means regulation of blood flow through each local tissue in response to the tissues metabolic needs. A review of the historical background of autoregulation has been given by Johnson (33). Probably the earliest experiments which gave evidence of an autoregulatory type of behavior were reported by Bayliss in 1902 (5). Bayliss reduced arterial pressure by stimulation of the depressor nerve or compression of the aorta and observed accompanying changes in the volume of the hind limb of dogs and cats. He noted that while the fall in blood pressure continued, there was a passive diminution in volume of the hind limb; but when blood pressure was restored, the limb expanded and exceeded its control volume. Bayliss theorized that vascular relaxation had occurred during the period of reduced pressure and became evident when blood pressure was restored. Since the limb was denervated, the response could not have been due to a vasodilator nerve reflex and might therefore represent a local response.

Bayliss also observed a contraction of isolated segments of carotid artery with elevation of internal pressure. In 1921 Wachholder (57) investigated this phenomenon with isolated segments of carotid artery and observed rhythmic contractions 8 to 20 seconds after elevation of internal

pressure. Fog (15) and Nicoll and Webb (42) also saw dilatation of arterioles with pressure reduction and contraction with pressure elevation during in vivo studies of the pial vessels of the cat and the vessels of the bat wing, respectively.

In 1946 Selkurt (49) reported the first studies on renal autoregulation based on examination of the pressure-flow relationship in the kidney. Winton (59) also observed the phenomenon of autoregulation in isolated kidneys and noted that it was somewhat attenuated by cooling the kidney to 3 to 12° C.

In 1949 Folkow (16) reported a series of experiments on the effect of local changes in arterial pressure on blood flow, primarily in the hind limb but also in the intestine.

To date autoregulation has been described in kidney (49), skeletal muscle (16), brain (46), intestine (32), myocardium (6), and liver (56).

Hamilton (27, 28) has indicated that the primary function of the heart is to supply an adequate stream of oxygenated blood to the body. Transportation of other nutrients and wastes is an easy task compared to the transportation of oxygen. Thus, even in the resting state, one fourth of the blood's oxygen is depleted as the blood passes through the body and goes back to the lungs; whereas it picks up only one eighth of its content of carbon dioxide on the same trip.

The nutrients and wastes such as blood sugar and urea have an even smaller arteriovenous difference in proportion to blood content.

Hamilton indicates that oxygen transport is the strategic function of the circulation. In exercise the peripheral resistance is half that in rest; in a study of the effects of exercise the arterial pressure increased 50 per cent, and the cardiac output more than doubled while the oxygen consumption increased about sixfold. The fact that the heart rate doubled cannot be due to a lowered peripheral resistance because the arterial pressure has just increased. Nervous and hormonal stimulation of the heart, arising directly from the excitement of the effort, seem to play a prepotent role over the reflex slowing which usually accompanies a rise in pressure. The decreased peripheral resistance and pressure influences of excitement cause the heart to accelerate and to empty more completely.

The nervous tensions of anxiety and other emotional states also alter the peripheral resistance, and this alteration, acting through the secretion of epinephrine and the direct action of the sympathetic system, is different in different species.

Autoregulation of blood flow in response to the tissues metabolic needs has been emphasized by Guyton et al. (22, 23, 24). Ordinarily, autoregulation maintains flow through each

tissue almost exactly at that level required to supply the tissues needs for nutrients, no more, no less. They explain this mechanism by the fact that blood supplying each local tissue area flows first through very small arterioles and meta-arterioles before passing into the capillaries. The arterioles have a strong muscular coat, the meta-arterioles are surrounded by sparse but highly active smooth muscle fibers and, finally, at each point where a capillary leaves a meta-arteriole a small muscular precapillary sphincter surrounds the origin of the capillary. The smooth muscle of each of these structures ordinarily has a high degree of intrinsic tone. Even without nervous impulses or humoral stimulation, the smooth muscle remains contracted to a considerable degree. Various local factors in the tissues can cause this smooth muscle to relax or to contract, thereby increasing or decreasing the blood flow through the local area. Guyton et al. (22, 23, 24) points out that it is by means of these local factors that each local tissue controls its own blood flow.

They believe the oxygen concentration in the tissues is a primary regulator of local blood flow in most organs--the less oxygen concentration, the greater the flow. Their reasons for believing this are:

(1) They have perfused mixtures of arterial and venous blood through isolated dogs legs and found that the flow increased 2-1/2 fold as the blood became very

venous in character.

(2) Animals were prepared surgically so that one lung could be used to respire the animal and the other lung used as an oxygenator or deoxygenator to prepare blood for perfusing the dogs hind limb. The results with deoxygenated blood were identical with those found with venous blood. They felt this approach permitted them to rule out other factors in venous blood besides oxygen deficiency which might cause an increased flow.

(3) Minute arteries isolated from a number of different tissues respond to changes in oxygen in exactly the same way that local tissues do. Increased oxygen in the blood causes constriction; decreased oxygen causes dilatation. The smaller the artery, the greater the intensity of this effect, indicating that the minute arterioles, meta-arterioles and precapillary sphincters could be extremely sensitive to slight alterations in local oxygen concentration.

(4) Oxygen is the most nearly "flow-limited" substance that is commonly transported in the blood. The blood flow can decrease as much as 10-fold and still transport adequate quantities of essentially all the other substances normally transported to or from the tissues besides oxygen, such substances as carbon dioxide, amino acids, glucose, and fatty acids. However,

> a decrease in blood flow of only 50 per cent causes enough diminution in oxygen transport to decrease oxygen utilization by the tissues about 20 per cent. Further decrease in blood flow below the 50 per cent level causes serious oxygen deficiency in most tissues of the body.

Guyton (22) indicates that the mechanism by which oxygen concentration regulates blood flow may be through the precapillary sphincters. Smooth muscle requires oxygen to remain contracted. Thus it might be assumed that the strength of contraction of the precapillary sphincter increases with an increase in oxygen concentration. When the oxygen concentration rises above a certain level, the precapillary sphincters begin to contract, and according to the law of Laplace it closes completely. This cuts off the blood flow to the local area. As the tissues consume oxygen, the concentration of oxygen decreases, finally decreasing low enough that the precapillary sphincter begins to relax. Once relaxation starts and the pressure begins to overcome the strength of the sphincter, the vessel opens completely because of the effect of the law of Laplace. Now, blood flows rapidly through the capillary again until the oxygen concentration rises once more to a level high enough to cause another cycle of precapillary sphincter constriction. The precapillary sphincter closes again, the oxygen concentration in the local area falls, the sphincter opens again, and the process continues indefinitely.

Guyton also discusses the vasodilator theory which has been suggested by other investigators (22) as an explanation for metabolic autoregulation of local blood flow. According to this theory, the greater the rate of metabolism or the less the availability of nutrients to a tissue, the greater becomes the rate of formation of a vasodilator substance. The vasodilator substance then supposedly diffuses back to the precapillary sphincters, meta-arterioles, and arterioles to cause dilatation. Some of the different vasodilator substances that have been suggested are carbon dioxide, lactic acid, adenosine, histamine, potassium ions, and hydrogen ions. Guyton states that some physiologists place much faith in adenosine as a possible dilator substance. Some of the vasodilator theories assume that the vasodilator substance is released from the tissue in response to oxygen lack. For instance, it has been demonstrated that oxygen lack can cause both lactic acid and small amounts of adenosine to be released from the tissues, substances that can cause vasodilation.

In 1955, Nicoll and Webb (42) studied the action of individual muscle cells forming precapillary sphincters. They were able to show that the availability of oxygen was a prime determinant in the activity of the muscle cells. The duration and magnitude of the contraction phase of the sphincter compared with its activity when sufficient oxygen was present, but were sharply reduced with oxygen-poor mixtures. Shortly

after shifting to 100 per cent helium, the sphincters appeared to lose their ability to constrict.

Guyton et al. (23) have postulated a mechanism based on the vasomotion studies of Nicoll and Webb (42). It illustrates that an oxygen control system can perform the known control functions of autoregulation. It is assumed the strength of the precapillary sphincter of a capillary supplying a tissue area is a positive function of the amount of ATP in the sphincteric muscle and that this, in turn, is a function of the P_{O_2} in the tissue. Thus it is assumed there is a proportionality between strength and oxygen:

$$S = k_5 O_e$$

It is then assumed that the diameter (D) of the sphincteric opening is equal to a maximum value (k_2) minus a factor proportional to the closing force (C_F) of the vessel, or

$$D = k_2 - k_3 C_F$$

Thus the closing force of the vessel is a function of the strength of contraction of the sphincteric muscle and diameter of the vessel in accordance with the Law of Laplace,

$$C_F = \frac{k_4 S}{D}$$

Next it is assumed the flow through the vessel (F) is proportional to the fourth power of the diameter:

$$F = k_1 D^4$$

The rate of change of oxygen in the tissues $\frac{dO_e}{dt}$ equals the rate of entry of oxygen into the tissue $\frac{dO_{e_i}}{dt}$ minus the rate of metabolic usage of the oxygen $\frac{dO_{e_o}}{dt}$, or

$$\frac{dO_e}{dt} = \frac{dO_{e_i}}{dt} - \frac{dO_{e_o}}{dt}$$

The rate at which oxygen enters the tissue is proportional to the product of blood flow times the oxygen delivered to the tissue by each unit of blood. The oxygen delivered is proportional to the P_{O_2} in the arterial blood (O_a) minus the P_{O_2} in the tissues (O_e), if we assume linearity of the oxyhemoglobin saturation curve. Thus,

$$\frac{dO_{e_i}}{dt} = k_7 F\ (O_a - O_e)$$

Studies have been done on the analog computer by Guyton et al. (23) to show that this mechanism will maintain tissue P_{O_2} reasonably constant despite severe changes in tissue metabolism or in arterial pressure. They have also shown that this mechanism will cause a typical autoregulation curve when the arterial pressure is changed through a full spectrum.

By means of this analysis they have demonstrated that an oxygen-demand mechanism for regulation of local blood flow can duplicate the known types of autoregulation in all or most tissues besides the brain and kidney. It can also duplicate the known pattern of vasomotion at the precapillary sphincters.

Modeling of the Cardiovascular System

Modeling is a relatively new approach to the representation of physiological systems. Milsum (40) has given an excellent description of modeling and its applications. He defines modeling as the quantitative analysis of qualitative verbal modeling which is represented schematically by information-flow diagrams. The diagram generally contains only mathematical symbols and is generally called a block diagram.

The information-flow diagram or block diagram consists of a set of blocks interconnected by directed lines which indicate unidirectional cause-effect relationships. The lines represent variables which are relevant to the desired analysis and which are usually physically measurable in the real system.

Milsum defines a mathematical model as an abstract representation of physical phenomena. For a physiological system the model may be a concise way of quantifying the interacting behavior of physiological mechanisms which have a more or less clearly defined functional goal. Since model interactions are often very complex, electronic computers are often utilized. The analog computer is particularly valuable because it sets up an electrical analog of the system via the equations of the mathematical model. It also provides a flexible tool for parameter manipulations, etc.

There are at least two major approaches to modeling. The first approach consists of writing equations for well-established physical processes from a priori knowledge. The second approach is empirical. Cause-effect relations are derived from experimental data, since actual phenomena are not understood. With respect to biological control systems, Milsum points out that neural and hormonal phenomena must generally be modeled by the empirical approach, and often there is not satisfactory experimental data even for this.

Guyton et al. (22, 23, 24) have indicated that circulatory autoregulation, the ability of each individual tissue to regulate intrinsically its own blood flow in accordance with its needs, is an important mechanism controlling cardiovascular hemodynamics. They imply that a feedback stimulus exists from each tissue to the local blood vessels to control their degree of vasodilation. Their studies indicate that oxygen is the feedback stimulus in most tissues. Many tissues of the body automatically increase their blood flow when the oxygen concentration in the tissue decreases.

Guyton (22) also points out that many other feedback factors have been proposed for autoregulation in the tissues, such as histamine, potassium, bradykinin, carbon dioxide, and intra-arterial pressure. However only one of these has been proved: carbon dioxide has been shown by several investigators to be the major feedback stimulus for cerebral

circulatory autoregulation.

Koch (36) has investigated some of the properties of autoregulatory systems by looking at the forms of solutions obtained from idealized models.

He devised a model for autoregulation through changes in extravascular pressure. This model shows an increase in vascular resistance with increasing arterial pressure throughout the pressure range. The model also allows some specific predictions as to the effects of changes in effective osmotic pressure and the form of relationships between vascular resistance and interstitial pressure as functions of arterial pressure.

Koch investigates two models in which vascular resistance is a function of flow. He points out that although these models generate autoregulatory processes, vascular resistance does not increase throughout the whole pressure range.

Two models of autoregulation by the myogenic reflex were analyzed by Koch. A model in which there is mechanical feedback between the contractile element and the sensor cannot produce autoregulation, but one in which there is no such feedback may produce autoregulation.

Grodins (21) has described the mammalian cardiovascular system as a very complex hydrodynamic system whose many parameters are continuously operated upon by neural and humoral controlling signals. He has shown that the respiratory

system functions by means of a control system which can be considered a multiple chemostat. He also attempts to study the cardiovascular system from the point of chemostatic control, particularly from the point of regulation of oxygen levels in the body.

The cardiovascular system perfuses the lumped-tissue reservoir with fresh blood at a rate required to keep tissue (mixed venous) P_{O_2} and P_{CO_2} at or near normal levels. From this standpoint, the controlled variables would be tissue (mixed venous) P_{O_2} and P_{CO_2} and the manipulated variable would be cardiac output. The block diagram of the cardiovascular chemostat illustrated by Grodins is shown in Figure 34.

Grodins has also suggested that cardiac output may not be regulated by mixed venous composition directly, but indirectly through systemic arterial pressure. The systemic arterial pressure is a product of cardiac output (Q) and systemic peripheral resistance (R_S):

$$P_{AS} = QR_S$$

Grodins isolates the controlled system of Figure 34 and adds a "mechanical section" to it as in Figure 35. In particular systemic vascular beds, it is known that the arteriolar resistance varies with local tissue (venous) composition as a direct chemical effect independent of nerves. This action for the lumped systems has been indicated by the dashed arrows in Figure 35. Grodins points out that monitoring P_{AS} in the

system of Figure 35 provides information about mixed venous composition. This indicates that feedback from mixed venous composition is indirect via P_{AS} as shown in Figure 35.

The circulatory chemostat is different from the respiratory chemostat. The various parallel components of the tissue reservoir are active elements with very different functions, therefore Grodins suggests that each might have a chemostat of its own.

The tissue reservoir can be divided into a number of parallel circuits. In doing this the distribution of the total cardiac output among the several circuits depends upon the individual circuit resistances. A block diagram for this new isolated controlled system appears in Figure 36. Figure 36 shows that P_{AS} is a measure of $(O_2)_V$ which represents tissue P_{O_2}. If P_{AS} is kept constant by manipulating Q, then the flow through each parallel circuit depends only upon the resistance of that circuit and thus upon its chemical output. Therefore, each parallel element, as well as the entire lumped tissue block acts as a chemostatic mechanism.

The control system is thus an adaptive one, i.e., it can adjust its controlling operations to changes in controlled-system conditions. For example, the brain and the heart (as well as skeletal muscle during exercise) are favored, an arrangement having obvious survival value.

Grodins summarizes his concept of the steady-state cardiovascular chemostat in the block diagram of Figure 37. The transfer functions of certain blocks are represented by graphs, which he regards as rough qualitative guesses. They indicate that the arterioles of the various systemic vascular beds respond differently to local chemical feedback and to vasomotor nerves. The system might work as follows: Suppose that $(O_2)_A$ were reduced by breathing a low-oxygen mixture. This would first reduce all of the n venous (O_2) values by the same amount. This via the direct chemical feedback loops, would reduce $R_1, R_2, \ldots . R_n$ by various amounts. The resulting fall in R_S would reduce P_{AS} and this, in turn, would increase Q and/or increase arteriolar resistance in selected areas.

Artificial Hearts

The national annual death toll of approximately one million persons per year from heart disease has caused people to believe that there is a need for the development of an artificial heart.

The history of the present effort to develop artificial hearts can be found in the "Transactions of the American Society for Artificial Internal Organs"[1]. In a presidential address at the third annual meeting of the ASAIO in 1957,

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[1]Volumes I-XII, Georgetown University Printing Dept., Washington 7, D.C. 1955-1966.

Dr. Peter Salisbury urged that a serious, protracted effort be undertaken in this area.

The development and clinical use of heart-lung machines for extracorporeal use have led to the development and implantation of artificial heart devices inside the body. Since 1957, artificial heart devices have been developed by several groups. Kusserow (37), Nose (43), Fry (18), Lindgren (39), Cholvin et al. (8) and Hall et al. (25, 26) have recently discussed artificial heart research and major problems in this area.

The development and implantation of an artificial heart poses many problems (8, 25, 26). It must be made of durable, biologically tolerable materials which are flexible and capable of unfailing performance over hundreds of millions of cycles. Synthetic materials such as silicone rubber and teflon are relatively nonreactive and promote a minimum amount of clotting. Dacron and nylon velour surfaces permit a strong mechanical bond for the coagulum, enabling the blood to make contact with a surface which is autologous tissue. This helps to prevent embolization and blood destruction. Heparin has been chemically combined with a number of plastic surfaces rendering them nonthrombogenic (38). A suitable power source is also necessary to operate an artificial heart. Compressed gases have been most widely used in the past, however biological, mechanical, electromagnetic and hydraulic sources have

also been investigated. There are also many surgical problems associated with the implantation of an artificial heart. Hemorrhage may occur at the anastamoses between living tissue and synthetic materials. Infection is a problem where lead wires and tubes must pass through the body wall. Other phenomena which occur during the operation of an artificial heart include acid-base imbalance, red blood cell destruction and coagulation of the blood, denaturation of the proteins in the blood, and cyclic collapse of the great veins and atria. Postoperative problems include lung edema and liver engorgement with blood resulting from unequal minute volume output from the artificial ventricles.

In addition to the design and implantation of an artificial heart, it is also necessary to provide a means for control. The normal heart utilizes a combination of neural, hormonal and chemical control which serve to change the pulse rate, stroke volume, blood pressure and oxygen content of the blood. In 1963 Pierce et al. (44) described a servomechanism which used venous pressure as a parameter to control the output of an artificial ventricle. He selected this parameter because experimental and clinical studies indicated that venous pressure assumes control when neural and/or hormonal mechanisms are attenuated. Venous pressure was measured with a pressure transducer and compared with an "ideal" venous pressure, usually 0 mm. Hg. An error signal was generated,

amplified, integrated with respect to time and fed into a programable d-c power supply. The power supply output operated the artificial ventricle whose pump output was controlled by setting the venous pressure.

Nosé (43) has pointed out that control of a pump system for a two chamber heart must be separate and independent. It is also necessary to provide sufficient blood flow or ischemia of the tissues will result. Nosé emphasizes that the feedback system which drives the pump should be sensitive to venous pressure. The driving system of the artificial heart used at the Cleveland Clinic which Nosé has described is governed by the right and left atrial pressures. The system utilizes the NASA servomechanism which incorporates electronic control of the air pressure to drive the artificial heart.

Swift et al. (51, 52, 53) and Cholvin et al. (8) have also described an artificial heart and power control system in which compressed air provides the power medium and the feedback control is based on venous pressure regulation. The control system functions to keep the inlet blood pressure to each artificial ventricle within a reference zone. The system uses an adjustable meter relay to perform the level sensing function. Upper and lower pressure limits can be set anywhere within a 40 mm. Hg pressure range and the reference zone can be as small as 0.3 to 0.4 mm. Hg. The upper and lower limit switching functions of the meter relay determine the

direction of rotation of the control motor. The control motor is connected to a bleed-off valve in the air line. Altering the position of the needle valve in the exhaust line changes the air pressure available to the artificial ventricle and thus changes the stroke volume. The reference zone or "dead zone" permits small changes in venous pressure without activation of the control circuit. The system also possesses a sampling circuit which permits variable control circuit activation and correction periods.

Hall et al. (25) has indicated that the flow rate of an artificial heart should be so regulated that the venous pressure is maintained at about 10 mm. Hg and the peak aortic pressure is kept below 150 mm. Hg. The ventricular stroke volume should be such that normal pulse rates can be maintained. The artificial heart system should have great flexibility in input and output to meet changes in physiological and emotional states. It should also be responsive to small changes in the system.

At present the major emphasis has been concerned with pressure feedback systems. In addition to a pressure and flow feedback system a chemical feedback system has been under development by the NASA group (43).

THE USE OF OXYHEMOGLOBIN CONCENTRATION AS A PARAMETER TO CONTROL THE STROKE VOLUME OF AN ARTIFICIAL HEART

If tissue oxygen demand is a factor causing autoregulation of blood flow, it may be possible to regulate cardiac output by maintaining an optimum venous or arteriovenous difference in oxyhemoglobin concentration. As the venous oxyhemoglobin concentration decreases it is necessary to increase cardiac output. When venous oxyhemoglobin concentration decreases, vascular resistance decreases, arterial pressure decreases and normally cardiac output increases. This increases blood flow to the tissues, increases venous oxyhemoglobin concentration, vascular resistance increases, arterial pressures increase, and thus cardiac output decreases again.

In a similar manner it may be possible to use the arteriovenous difference in oxyhemoglobin concentration to control cardiac output, providing the arterial oxyhemoglobin concentration remains essentially constant. If we assume the arterial oxyhemoglobin concentration remains constant at approximately 97 per cent and the venous oxyhemoglobin concentration decreases to less than 70 per cent then we have an increase in the arteriovenous difference in oxyhemoglobin concentration. Again, the mechanism is to increase cardiac output in order to bring the arteriovenous difference in oxyhemoglobin concentration back to 27 per cent. In a similar manner the cardiac output should be decreased when the arteriovenous

difference in oxyhemoglobin concentration decreases with the arterial oxyhemoglobin concentration remaining constant at 97 per cent.

These are some of the feedback mechanisms which may control cardiac output in the normal animal. In the animal with its heart replaced with an artificial heart these feedback mechanisms and control systems are not quite as functional. Therefore, it is necessary to incorporate some means of control for an artificial heart so that it can meet various physiological and metabolic requirements.

The artificial heart system used in this study was essentially that described by Cholvin et al. (8) and Swift et al. (51, 52, 53) which was used for the in vivo studies in Part I. In previous studies Swift has used left and right atrial pressures to control the output of the respective ventricles.

In this study an attempt was made to use venous oxyhemoglobin concentration and arteriovenous difference in oxyhemoglobin concentration as parameters to control the stroke volume of the artificial ventricles.

Instrumentation

The feedback control system responds to the amplified d-c output voltage from the wheatstone bridge of the oximeter. This signal from the wheatstone bridge was amplified with a

differential operational amplifier[1]. The amplifier was used as a differential bridge amplifier with a variable gain of one to six. The circuit diagram is shown in Figure 38. It has facilities to balance the signal on the meter relay and to vary the current to it.

The output of the differential amplifier, displayed on the 0 to 1 milliampere meter relay, represents the oxyhemoglobin concentration. A change of 0.1 milliamperes represents approximately a 10 per cent change in the oxyhemoglobin concentration. The amplified d-c level of the output from the oximeter is sensed by a double set-point meter relay. It can actuate the control motors at either an upper or lower limit of oxyhemoglobin concentration. There is an adjustable intermediate "dead zone" within which the oxyhemoglobin concentration can vary without control circuit activation. Thus, the control system does not operate when the oxyhemoglobin concentration and ventricular output are adequate. As the venous oxyhemoglobin concentration reaches either of the limits, the stroke volume is altered by changing the bleed-off rate in the air line which powers the artificial ventricles. The bleed-off valve is controlled by a small low r.p.m., d-c shunt motor which is incorporated into the feedback control system circuit. The motor controls a

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[1]Model 106, Analog Devices, Inc., Cambridge, Massachusetts.

needle valve in the system. As the speed of the control motor is varied, the response time of the control system is changed. This bleed-off needle valve in the exhaust line allows fine control of the oxyhemoglobin concentration and thus permits control of the output of the artificial ventricles. The control circuit functions to maintain the oxyhemoglobin concentration in a preset reference zone.

The sampling circuit was also used during the control studies to give a combination of an open and closed loop system. It permitted periodic sampling of the oxyhemoglobin concentration and corrections could be for a specified length of time. Various sampling rates and correction periods were studied in an endeavor to find the best animal-machine combination.

Methods of Controlling the Artificial Ventricles with Oxyhemoglobin Concentration

Various combinations of control were studied in an attempt to see if the venous and/or arteriovenous difference in oxyhemoglobin concentrations could be used as parameters to control the stroke volume of the artificial ventricles. The following combinations of control were studied:

(1) Venous oxyhemoglobin concentration was used to control the stroke volume of the right artificial ventricle. The left ventricle was operated manually. This provided a means of equilibrating the two ventricles in

order that they would pump equal minute volumes.

(2) Venous oxyhemoglobin concentration was used to control the stroke volume of the right artificial ventricle. Left atrial pressure was used to control the stroke volume of the left artificial ventricle. In theory this approach would maintain adequate tissue perfusion by maintaining a normal venous oxyhemoglobin concentration. It would prevent pooling of blood in the pulmonary circulation by maintaining a normal left atrial pressure.

(3) Venous oxyhemoglobin concentration was used to control the stroke volume of both artificial ventricles. This was done by paralleling the d-c control motors and thus the speed of the motors was the same. The attempt here was to provide nearly equal and simultaneous control of the stroke volume.

(4) The arteriovenous difference in oxyhemoglobin concentration was used to control the stroke volume of the right artificial ventricle. The left ventricle was operated manually. With this approach and the following two it was necessary to periodically check the individual arterial and venous oxyhemoglobin concentrations. Control with the arteriovenous difference in oxyhemoglobin concentration was based on the assumption that oxygenation of the venous blood in the lungs would be quite efficient. Control circuit activation would be due

primarily to changes in the venous oxyhemoglobin concentration.

(5) The arteriovenous difference in oxyhemoglobin concentration was used to control the stroke volume of the right artificial ventricle. Left atrial pressure was used to control the stroke volume of the left artificial ventricle. Again it is assumed the arterial oxyhemoglobin concentration will remain essentially constant and that control circuit activation is due to changes in the venous oxyhemoglobin concentration. By this method it may be possible to provide adequate tissue perfusion by maintaining a normal arteriovenous difference in the oxyhemoglobin concentration. Pooling of blood would be prevented in the pulmonary circulation by maintaining a normal left atrial pressure.

(6) The arteriovenous difference in the oxyhemoglobin concentration was used to control the stroke volume of both artificial ventricles. This required paralleling the control motors as described in the third procedure.

The system was put into operation by setting the rate, duty cycle, and inlet air line pressure to give a satisfactory flow rate and aortic pressure. The sampling circuit was set to the desired sampling rate and correction period. The animal-machine system was then placed in the control mode.

In this mode, the system attempts to keep the oxyhemoglobin concentration and/or left atrial pressure within the reference zone.

Methods of Perturbing the System

The animal-machine system was first permitted to function under steady-state conditions for a period of time. After a period of control under these conditions the system was subjected to different perturbations. Various methods were used to perturb the system to study the use of oxyhemoglobin concentration as a parameter to control the stroke volume of the artificial ventricles. The methods of perturbation were as follows:

(1) The temperature of the blood and the animal were changed by means of the blood heat exchanger which was placed between the left atrium and the input to the left artificial ventricle. This provided a means of changing the metabolic requirements of the animal and the oxygen-hemoglobin dissociation curve which in turn could affect the venous oxyhemoglobin concentration.

(2) It was also possible to change the content of the inspired air. Tanks were available which contained 10, 15, 38, and 100 per cent oxygen. The balance of the mixture in the first three tanks was nitrogen. The gases were administered through the anesthesia machine. The animal-machine system was perturbed by changing from one

gas mixture to another.

(3) Moving the limits or reference zone on the meter relay was another means of perturbing the system. This approach required the animal-machine system to increase or decrease the oxyhemoglobin concentration depending upon the direction the limits were moved.

With each of these methods of perturbation the theory was to necessitate activation of the control system. After a period of correction or control an attempt was made to reach a steady-state condition again and thus equilibrium of the animal-machine system.

A MODEL OF THE SYSTEM

Guyton et al. (22, 23, 24) have shown that the individual tissues have the ability to regulate the blood flow to meet metabolic requirements. The metabolite which they feel is responsible for this regulation of blood flow is oxygen. Grodins (21) has illustrated that the cardiovascular system might be under chemostatic control with oxygen and/or carbon dioxide being the important metabolites. An attempt has been made to utilize the findings of Guyton et al. and Grodins in the development of a model which incorporates reflection oximetry and the control system which has been developed by Swift et al. (51, 52, 53) and Cholvin et al. (8).

Various combinations of control with oxyhemoglobin concentration were incorporated into the study. The purpose of this was to determine the best method or combination of methods to control cardiac output.

Method one uses venous oxyhemoglobin concentration to control the output of the right ventricle and the left ventricle is controlled manually. Figure 39 is a block diagram of a cardiovascular control system for an artificial heart which uses venous oxyhemoglobin concentration to control ventricular output. Figure 39 is a modification of Grodins' circulatory chemostat shown in Figure 34. Venous oxyhemoglobin concentration has been chosen as the controlled variable rather than

tissue (mixed venous) P_{O_2} which Grodins used. Reflection oximetry has been incorporated into the block diagram of Figure 39 for continuous detection of the venous oxyhemoglobin concentration. $(O_2)_A$ and $(O_2)_V$ represent, respectively, the arterial and venous oxyhemoglobin concentrations. MR is the metabolic rate and Q the ventricular output of the artificial ventricles. The reflection oximeter detects the concentration of venous oxyhemoglobin and represents it as a current, I_V. I_{V_i} represents the reference level of venous oxyhemoglobin concentration.

The controller is a maximum effort controller. It uses an adjustable meter relay to perform the function of detecting the level of oxyhemoglobin concentration. In Figure 39, the y-axis of the controller represents the direction of rotation of the control motor and the control motor speed. The x-axis represents the error signal or deviation from the reference level of venous oxyhemoglobin concentration. The dead zone on the x-axis is the range of venous oxyhemoglobin concentration which we plan to maintain. It also allows for small variations in the venous oxyhemoglobin concentration without corrective changes by the control system. Any deviation outside these limits activates the control system which changes the stroke volume so that the venous oxyhemoglobin concentration might be brought back within the limits or reference zone.

Method two consists of control of the right ventricle with venous oxyhemoglobin concentration and control of the left ventricle with left atrial pressure. Figure 40 is a block diagram which represents this procedure.

Method three is very similar to method one, however rather than manual control of the left ventricle to synchronize the output of both ventricles, the control motors are paralleled. The block diagram of Figure 39 represents this procedure also, except that the controller box now represents control over both ventricles.

Method four consists of control of the right ventricle with the arteriovenous difference in oxyhemoglobin concentration. The left ventricle is controlled manually in an attempt to keep the output of both ventricles equal. Figure 41 is a block diagram which represents this procedure. The system utilizes two oximeters, one detects the arterial oxyhemoglobin concentration, the other the venous oxyhemoglobin concentration. A current or voltage represents the concentration of arterial and venous oxyhemoglobin concentration. A subtractor is used to obtain $I_d = I_A - I_V$ which represents the arteriovenous difference in oxyhemoglobin concentration. In this procedure, this parameter is used to control the output of the right ventricle. This mechanism functions on the assumption that the arterial oxyhemoglobin concentration remains relatively constant during changes in the venous oxyhemoglobin

concentration. Thus, again it is venous oxyhemoglobin concentration which is the actual controlling parameter. I_{d_i} represents the reference level of the arteriovenous difference in oxyhemoglobin concentration. The function of the controller is the same, except the x-axis now represents the arteriovenous difference in oxyhemoglobin concentration.

Method five utilizes the arteriovenous difference in oxyhemoglobin concentration to control the output of the right ventricle. Left atrial pressure is used to control the output of the left ventricle. Figure 42 illustrates this procedure. It is similar to method two except that the right ventricle is controlled by the arteriovenous difference in oxyhemoglobin concentration rather than the venous oxyhemoglobin concentration.

Method six is similar to method four, however the control motors are paralleled to permit the control of both ventricles with the arteriovenous difference in oxyhemoglobin concentration.

Grodins (21) indicates that cardiac output might be regulated by the mixed venous composition of O_2 indirectly through systemic arterial pressure. Figure 35 is a block diagram which shows the dependence of systemic arterial pressure, P_{AS}, on the amount of oxygen in the venous blood. This mechanism of control of cardiac output involves the arterial pressoreceptor control system. Figure 43 shows the dependence of systemic arterial pressure on the venous oxyhemoglobin concentration. The normal path of control might be through the

arterial pressoreceptor control system. However, this mechanism of control is weakened when the normal heart has been replaced with an artificial heart. Sympathetic fibers which innervate the peripheral blood vessels can still alter pressure, however autonomic regulation of the heart itself has been disrupted. Thus, normal pressoreceptor control of the heart rate and stroke volume is not present. Figure 43 illustrates how control of the ventricular output is possible by maintaining an optimum venous oxyhemoglobin concentration.

Other control systems and feedback mechanisms should also be considered which might affect the resistance of the blood vessels and ventricular output of an artificial heart. Rushmer (48) points out that the systemic arterial pressure serves as a pressure head to propel blood through the terminal branches of the arterial system into the capillary networks. The quantity of blood which flows into the various portions of tissues and organs is regulated by the variation in the caliber of the terminal arteries. Rushmer, like Guyton, believes that adjustments in the caliber of the arterioles and precapillary sphincters regulate the quantity of blood entering the capillary networks and individual capillary channels. Rushmer indicates that constriction of these sites of peripheral resistance may be considered in terms of three groups of mechanisms. These include the autonomic nerves, circulating hormones and local vasoactive chemicals.

It is therefore essential to incorporate these mechanisms into a model which shows the various methods of control of ventricular output. Figure 44 shows several different mechanisms which might affect vascular resistance and ventricular output of the artificial ventricles.

Sympathetic stimulation affects the system in two ways. When the venous oxyhemoglobin concentration decreases, sympathetic stimulation constricts the majority of the arteries of the circulation, especially the arterioles, which increase total peripheral resistance and consequently elevates the pressure. It also increases the vascular tone of all the veins of the body, which in turn increases the flow of blood into the heart and, therefore, increases the force of cardiac pumping.

Guyton (22) has indicated that the intensity of sympathetic activity of the vasomotor center increases almost directly in proportion to the concentration of carbon dioxide in the extracellular fluids. Therefore, he feels that carbon dioxide is one of the most powerful of all stimuli affecting the activity of the vasomotor center. A very high carbon dioxide concentration can increase the mean arterial pressure from a normal of 100 mm. Hg up to as high as 200 to 270 mm. Hg. The exact mechanism by which carbon dioxide affects the vasomotor center is not known. However, it is presumed that

carbon dioxide has a direct stimulatory effect on the neuronal cells.

Guyton explains that carbon dioxide is important as a regulator of arterial pressure because the amount of carbon dioxide produced by the tissues of the body increases in direct proportion to the rate of metabolism of the tissues. When the metabolism increases, the amount of blood flow required by the tissues to meet the metabolic needs is correspondingly increased. It is valuable, then, that the elevated carbon dioxide concentration increases the arterial pressure and that this in turn forces increased quantities of blood through the vascular system.

The arterial pressoreceptor control system should also be considered in a model of the cardiovascular system. In the wall of most of the large thoracic and neck arteries are many spider-like special nerve endings called pressoreceptors, or baroreceptors, that are stimulated when the arterial walls are stretched by pressure within the arteries.

The pressoreceptor impulses inhibit the sympathetic center of the medulla and excite the vagal center. Therefore, an increase in arterial pressure decreases the degree of sympathetic stimulation and increases the degree of parasympathetic stimulation; the net effects are vasodilatation throughout the peripheral circulatory system and decreased

cardiac rate and strength of contraction. The second effect is not observed with the artificial heart in operation.

Guyton (22) indicates that chemoreceptors located in the bifurcation of the carotid artery and along the arch of the aorta are sensitive to oxygen lack. Low oxygen concentration in the arterial blood excites the chemoreceptors and impulses are transmitted into the vasomotor center to excite sympathetic activity and inhibit parasympathetic activity, thus reflexly elevating the arterial pressure. This reflex, although not a powerful one, helps to increase the quantity of oxygen carried to the tissues whenever the arterial blood becomes deficient in oxygen.

The chemoreceptors are also stimulated by excess carbon dioxide in the arterial blood; however, the direct effect of carbon dioxide on the vasomotor center itself is about 10 to 20 times as strong as the chemoreceptor effect.

Figure 44 is thus a summary of various control mechanisms which might affect ventricular output of an artificial heart. It also incorporates the maximum effort controller which can use right atrial pressure and/or venous oxyhemoglobin concentration to control ventricular output.

RESULTS AND DISCUSSION

This study was designed to determine if venous or the arteriovenous difference in oxyhemoglobin concentration could be used as a parameter to control the stroke volume of an artificial heart. Twelve control studies were conducted in an effort to find the best method or combination of methods in which oxyhemoglobin concentration could be used as a controlling parameter.

Control Methods

The initial approach with each of the six methods was to equilibrate the animal-machine system, place the system on control and permit the system to correct for small changes in the circulatory system. The system was essentially operating under steady-state conditions.

Method one, which used venous oxyhemoglobin concentration to control the right heart and incorporated manual control of the left heart, provided a method whereby the animal-machine system could be easily equilibrated. Figure 45 illustrates control using this method. The arrows in the time channel represent activation of the control motors. An arrow pointing down represents an attempt to decrease the stroke volume and venous oxyhemoglobin concentration. An arrow pointing up represents an attempt to increase the stroke volume and venous oxyhemoglobin concentration. Small variations can be seen in

the venous oxyhemoglobin concentration and relative blood flow.

After the system was equilibrated, left atrial pressure was used to control the stroke volume of the left ventricle. In theory one might expect this approach to protect the respiratory system by preventing blood from pooling in the pulmonary circulation. Figure 32 illustrates control under steady state conditions with the right ventricle being controlled by the venous oxyhemoglobin concentration and the left ventricle by left atrial pressure. The venous oxyhemoglobin concentration is being sampled every 10 seconds and if an error is present corrections may be made for a duration of 5 seconds. The left ventricle is subject to continuous control by the left atrial pressure. In Figure 32, oscillations (overcorrections) are evident in relative blood flow, venous oxyhemoglobin concentration and the pressure recordings. The period of the cycle is approximately 4 minutes in the recording in Figure 32. The oscillations indicate that this method of control needs some type of damping. This method of control seemed to be quite successful after a satisfactory sampling rate was found.

The use of method 3 or control of both artificial ventricles with the venous oxyhemoglobin concentration also seemed to be quite successful. This approach provides simultaneous activation of the control motors in response to

changes in the venous oxyhemoglobin concentration. This method of control seemed to cause fewer oscillations (over-corrections) than the hybrid method previously described which used venous oxyhemoglobin concentration and left atrial pressure. Equal minute volume by the two ventricles is very important when this method is used. An unequal minute volume could lead to engorgement of either the systemic or pulmonary vascular beds.

The application of the arteriovenous difference in oxyhemoglobin concentration as a parameter to control the stroke volume of the artificial ventricles was not very successful. The assumption that the arterial oxyhemoglobin concentration would remain constant was not always true. In many of the studies pulmonary function was impaired and this seemed to affect the efficiency with which the venous blood was oxygenated. Many of the attempts at control with this parameter resulted in positive feedback. For example, the system tried to decrease ventricular output to correct for a low arteriovenous difference in oxyhemoglobin concentration when in effect, it should have tried to increase ventricular output. This occurred because the changes in the arterial oxyhemoglobin concentration were often much greater than changes in the venous oxyhemoglobin concentration. Control was then attempted by assuming that changes in the arterial oxyhemoglobin concentration would be greater than changes in the venous

oxyhemoglobin concentration. This approach was successful in some of the studies; however, there were also cases of positive feedback with this method. Some type of logic system is probably necessary in the event that this parameter is used for control. The experimental work indicated there were at least three different situations which a logic system might handle, each one requiring a different type of control. In case one there is an increase in the arteriovenous difference in oxyhemoglobin concentration due to a decrease in venous oxyhemoglobin concentration with the arterial oxyhemoglobin concentration remaining essentially constant. Correction of this situation requires an increase in the ventricular output. In case two the arteriovenous difference in oxyhemoglobin concentration is constant, however there is a gradual decline in both the arterial and venous oxyhemoglobin concentrations. In this case it is necessary to return to some other parameter for control, since we need to increase the ventricular output and oxygenation of the blood. In case three we have a decrease in the arteriovenous difference in oxyhemoglobin concentration resulting from a decrease in the arterial oxyhemoglobin concentration with the venous oxyhemoglobin concentration remaining essentially constant. This situation also requires an increase in ventricular output and oxygenation of the blood. A logic system might be an appropriate method for handling these three situations.

Although the venous and arteriovenous difference in oxyhemoglobin concentrations did lend themselves to control they also had their limitations. The experimental work indicated that a logic system incorporating right atrial pressure and venous oxyhemoglobin concentration might help to optimize the animal-machine system. There should also be some means of protecting the pulmonary circulation when venous oxyhemoglobin concentration is being used to control the stroke volume of both ventricles. Thus, it seems that a complex control system which incorporates both right and left atrial pressures and the venous and arteriovenous difference in oxyhemoglobin concentrations would be a definite advantage. The oxyhemoglobin concentrations would insure adequate tissue perfusion and pulmonary function. The left and right atrial pressures would insure adequate filling pressures and prevent collapse of the veins or engorgement of the pulmonary and systemic vascular beds.

The Effects of Perturbations on the System

After each method of control had been initiated and studied under steady-state conditions, the system was then subjected to various perturbations. The perturbations were used to vary the oxyhemoglobin concentration in order to initiate activation of the control motors with equilibrium of the system being the desired result.

Changing the temperature of the animal by means of the heat exchanger was an effective means of perturbing the system. This approach provided a means of changing the metabolic requirements of the animal by increasing or decreasing its temperature one or two degrees centigrade. The body temperature changes thus caused respective decreases or increases in the venous oxyhemoglobin concentration. The temperature changes also had an effect on the oxygen-hemoglobin dissociation curve and there was probably a direct temperature effect on the vascular resistance as well. As the venous oxyhemoglobin concentration changed with body temperature changes, one of the limits was reached. This activated the control motor which attempted to bring it back within the reference zone. Figure 46 illustrates the effect of perturbing the system with hyperthermia while the arterial oxyhemoglobin concentration was decreasing.

Perturbing the animal-machine system with various gas mixtures was not quite as successful as the above method. The change from 100 to 38 per cent oxygen was not adequate to perturb the system, since oxygen-hemoglobin dissociation is affected very little until the alveolar P_{O_2} drops below 100 mm. Hg (22). The change to 15 per cent oxygen caused changes in both the arterial and venous oxyhemoglobin concentrations; however, the change was more than the system could compensate for and therefore equilibrium was seldom reached. It was much

easier for the system to compensate for a change from 15 to 38 per cent or 100 per cent oxygen. Figures 47 and 48 illustrate the effect of perturbing the system by changing from one gas mixture to another. Figure 30 illustrates an attempt by the control system to compensate for pulmonary failure.

Moving the limits on the meter relay also provided an effective means of perturbing the system. This approach shifted the reference zone which thus increased or decreased the desired mean oxyhemoglobin concentration. Figure 49 illustrates the effect of changing the reference zone or limits controlling the right ventricle in an attempt to change the arteriovenous difference in oxyhemoglobin concentration.

The Effect of Sampling

The successful use of the venous and arteriovenous difference in oxyhemoglobin concentrations as controlling parameters of ventricular output depended on an appropriate sampling rate and/or control motor speed. With continuous measurement of these parameters the animal-machine system functioned as a closed loop system. Some of the first control studies which did not use sampling resulted in oscillations and gross overcorrections. Sampling allows the system to be open loop part of the time and closed loop part of the time. In essence it gives the system some damping, reduces the oscillations and the system approaches equilibrium or a steady-state condition much more rapidly. Various sampling methods were tried.

Periodic sampling at 10, 15, 20 or 30 second intervals was used. The maximum correction period with each was 5 seconds. Sampling the venous oxyhemoglobin concentration every 30 seconds seemed to be the most effective interval of these four. This seemed to most closely approximate the response time of the animal and it caused fewer oscillations and small over-corrections. Further study of sampling rates and control motor speeds may optimize control of the artificial ventricles.

Other factors also affected the control studies which should be mentioned at this time. Throughout many of the studies the systemic arterial pressure was very low and there was poor venous return to the artificial ventricles. Circulatory shock can lead to diminished blood flow to the vasomotor center which thus depresses the center often resulting in vasomotor and vascular failure (22). Vasomotor failure, loss or depression of the circulatory reflexes, probably caused dilatation of the venous reservoirs. This caused pooling of the blood in the various organs and peripheral circulation and prevented adequate filling of the ventricles. Vascular failure may also be associated with the vasomotor failure. The hematocrit was quite low in many of the studies since the system was primed with dextrose. The venous oxyhemoglobin concentration was often quite low which might indicate poor tissue perfusion and inadequate oxygenation of the tissues. The hemodilution and poor tissue perfusion may have contributed

to vascular failure and arteriolar dilatation. Prevention of circulatory shock would assure more normal vasomotor and vascular reflexes and probably permit more latitude in the control studies. Control studies performed during the early part of the experimental procedure when systemic arterial pressure and ventricular filling were more normal seemed to provide more latitude in animal-machine compensation.

The experimental control studies support the proposed models in Figures 39, 40, 43 and 44 which incorporate the use of venous oxyhemoglobin concentration to control the artificial ventricles. Venous oxyhemoglobin concentration can be used as a parameter to control either the right ventricle or both ventricles simultaneously. It can also be used in conjunction with left atrial pressure. It was possible to maintain the animal-machine system in homeostasis and equilibrium by maintaining an optimum venous oxyhemoglobin concentration. Physiological and metabolic requirements were often met in that adequate flow rates and pressures were maintained and respiratory and other cerebral reflexes were present. The performance of the system supported the hypothesized models under steady state conditions or when perturbations were introduced which represented changing physiological and metabolic requirements. The control studies indicate that the use of the arteriovenous difference in oxyhemoglobin concentration to control the artificial ventricles requires a logic circuit.

The control studies supported the models in Figures 41 and 42 only in the event that the arterial oxyhemoglobin concentration remained relatively constant. The appropriate logic system would make the arteriovenous difference in oxyhemoglobin concentration a much more useful control parameter. It may even be more useful than venous oxyhemoglobin concentration, since it possesses information about both the arterial and venous oxyhemoglobin concentrations and its changes are more rapid.

An artificial heart control system can be very complex if it is to duplicate that of the natural heart. It should be sensitive to ventricular filling pressures, blood flow rates and the oxygen requirements of the tissues. It should have facilities to change the heart rate and stroke volume. It also must be free of oscillations (overcorrections) which lead to instability. To meet all these requirements simultaneously or at the proper time is a difficult problem. A multiple control system incorporating a logic system to select the proper parameter or parameters of control and the proper method of correction at the right time may be the most successful approach.

SUMMARY

Development of a successful control system for an artificial heart is a complex problem. It is difficult to simulate the neural, hormonal, and chemical control which the normal cardiovascular system uses.

The experimental control studies indicated that the venous and arteriovenous difference in oxyhemoglobin concentrations can successfully be used as parameters to control the stroke volume of the artificial ventricles. The flexible fiber optic transmission lines provided a practical method of transmitting the information from the blood to the oximeter and control system. An implantable artificial heart would require miniaturization of many of the components. This could be possible with the sites of measurement being in the wall of the artificial heart. The fiber optic transmission lines could be incorporated in the umbilicus which would contain other lead wires and tubes. In a totally implantable system radio telemetry could be used to transmit the information.

The two most successful methods of control were simultaneous control of both ventricles with venous oxyhemoglobin concentration and the hybrid control method using venous oxyhemoglobin concentration to control the right ventricle and left atrial pressure to control the left ventricle. Simultaneous control of both ventricles produced fewer oscillations (overcorrections) than the hybrid control system using left

atrial pressure and venous oxyhemoglobin concentration. Theoretically, control of the left ventricle with left atrial pressure is advantageous since it attempts to protect the pulmonary circulation and prevent edema of the lungs. It tries to assure equal minute volume from both ventricles and prevent pooling of blood in the pulmonary vascular bed. However, the oscillations associated with this approach are not good and actually probably result in more pooling of blood. For example, blood may first pool in the pulmonary circulation as a result of correction by the right heart and then in the systemic circulation as the left heart corrects for a rise in left atrial pressure. The system may continue to oscillate back and forth until it reaches a point of instability. Because of this oscillatory problem, simultaneous or near simultaneous control of both ventricles is preferred.

The use of the arteriovenous difference in oxyhemoglobin concentration as a control parameter requires further study. Preliminary studies indicate that it requires a logic system to prevent the system from going into positive feedback.

The methods for perturbing the system were very successful. The heat exchanger and gas mixtures produced the desired changes in the venous oxyhemoglobin concentration. The magnitude of the perturbations was sometimes too great and animal-machine compensation was not completely successful. A better and wider selection of gas mixtures would be helpful

as a means of perturbing the system. Circulatory shock, producing vasomotor and vascular failure, was probably an important factor limiting animal-machine compensation.

The effect of sampling was interesting. It permitted the system to operate under both open and closed loop conditions. It helped eliminate oscillations (overcorrections) and the response time of the control system could be matched to that of the animal through the use of sampling.

The preliminary modeling was helpful in planning the control studies. It was also an aid to understanding the cause-effect relationships concerned with cardiovascular control.

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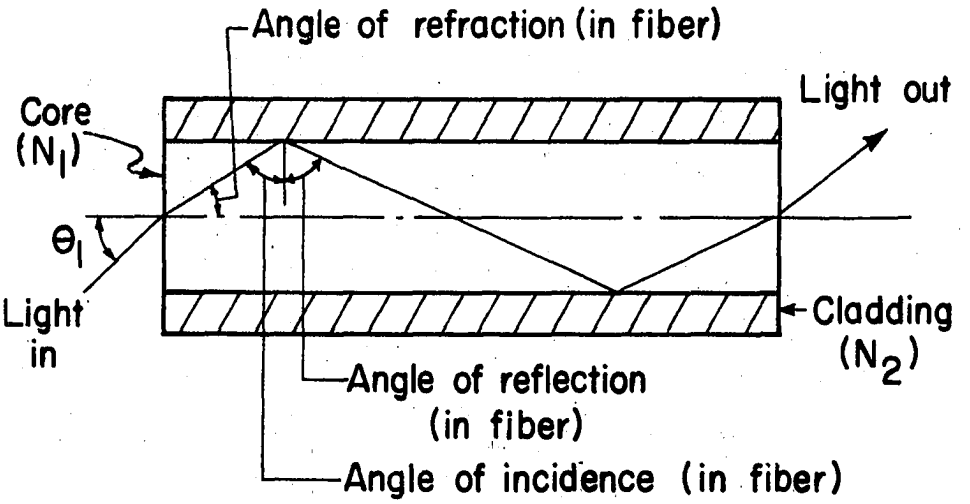
ILLUSTRATIONS

Figure 1. Light path in an individual optical fiber (Kahl 34, p. 27)



N_1 = Index of refraction for the core glass
N_2 = Index of refraction for the cladding
θ_1 = Angle of incidence in air (also half the total acceptance angle)

Figure 2. Block diagram of the optical portion of the reflection oximetry system

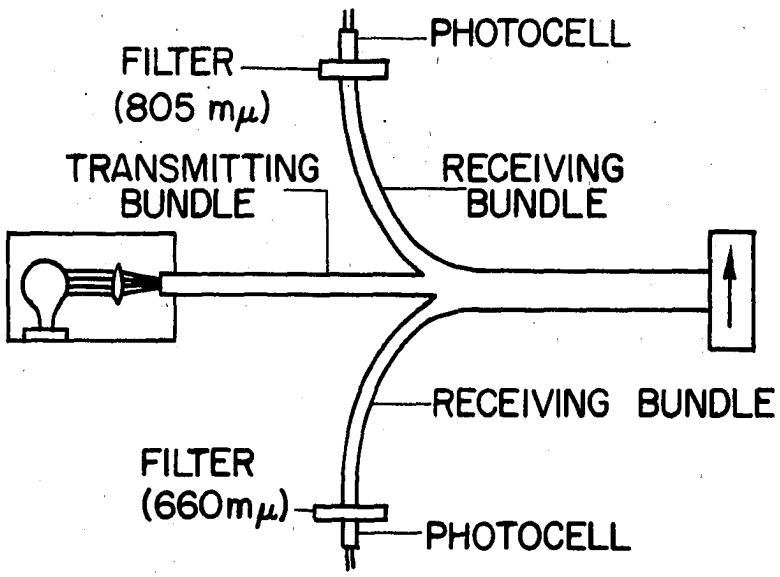

PHOTOCELL
FILTER
(805 mμ)
TRANSMITTING
BUNDLE
RECEIVING
BUNDLE
RECEIVING BUNDLE
FILTER
(660mμ)
PHOTOCELL

Figure 3. Circuit diagram of the power supply for the light source of the reflection oximetry system

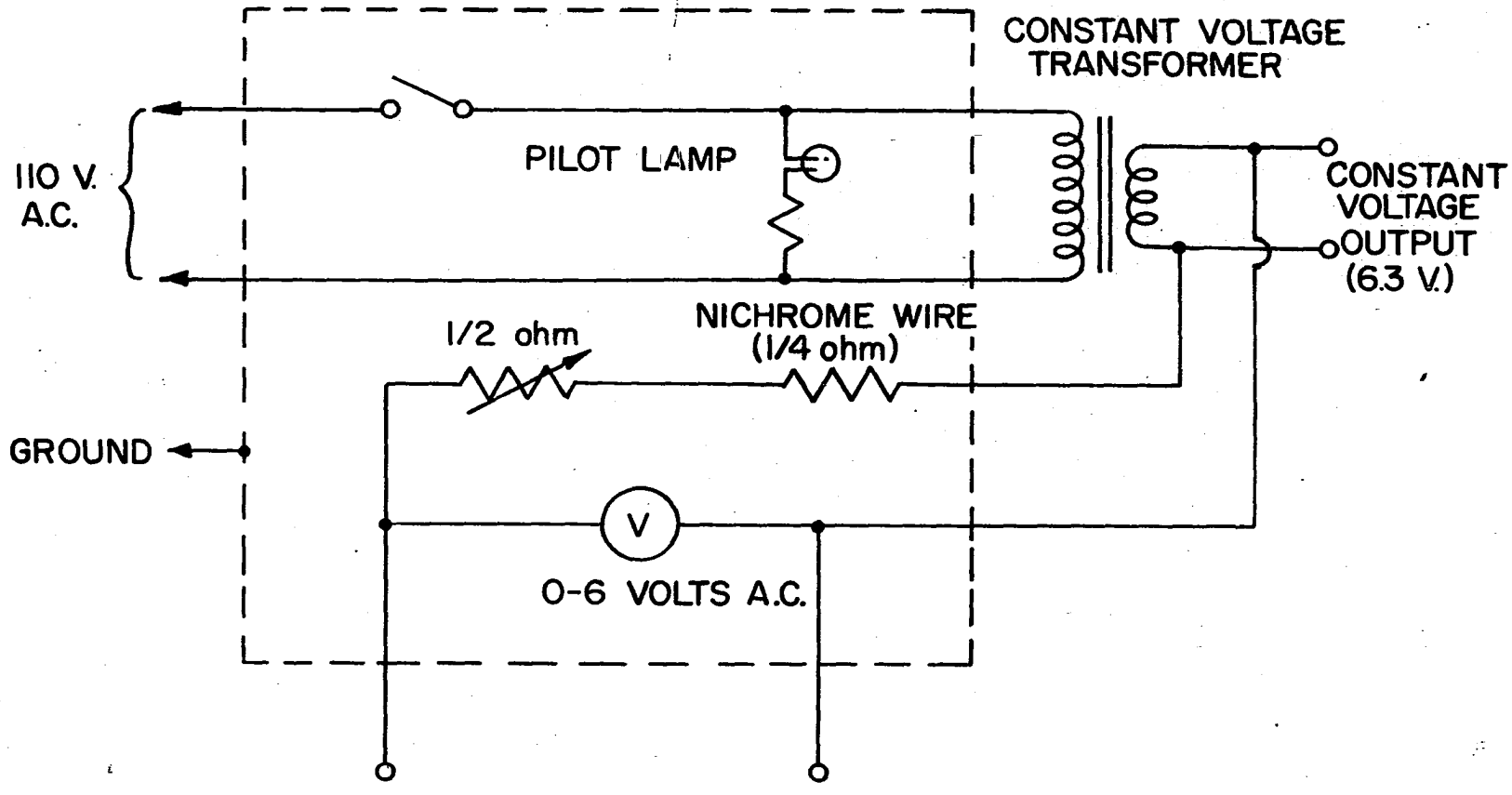
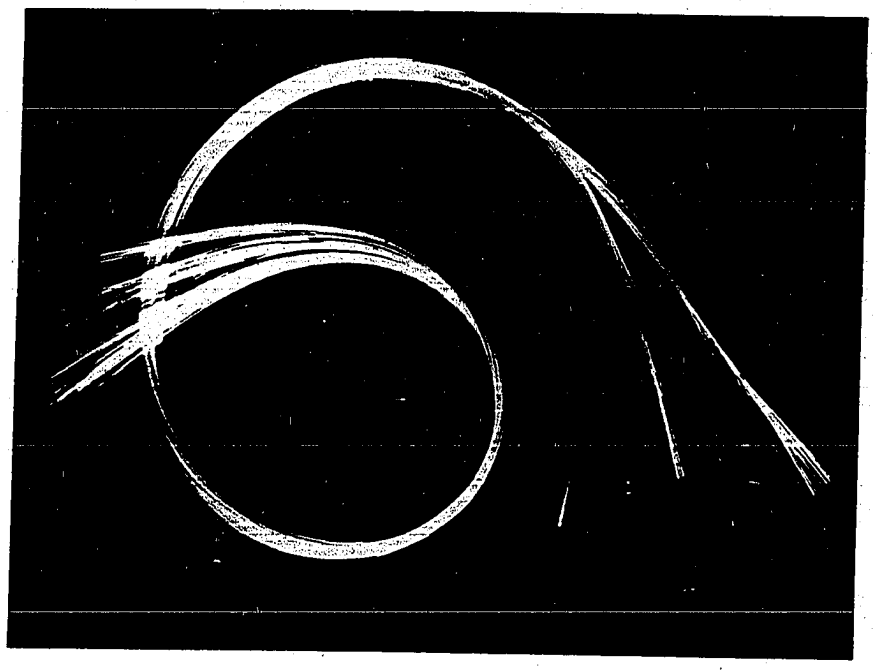

CONSTANT VOLTAGE
TRANSFORMER
110 V.
A.C.
PILOT LAMP
CONSTANT
VOLTAGE
OUTPUT
(6.3 V.)
1/2 ohm
NICHROME WIRE
(1/4 ohm)
GROUND
V
0-6 VOLTS A.C.

Figure 4. Glass fibers which make up the transmission lines

Figure 5. Fiber optic transmission line with connectors



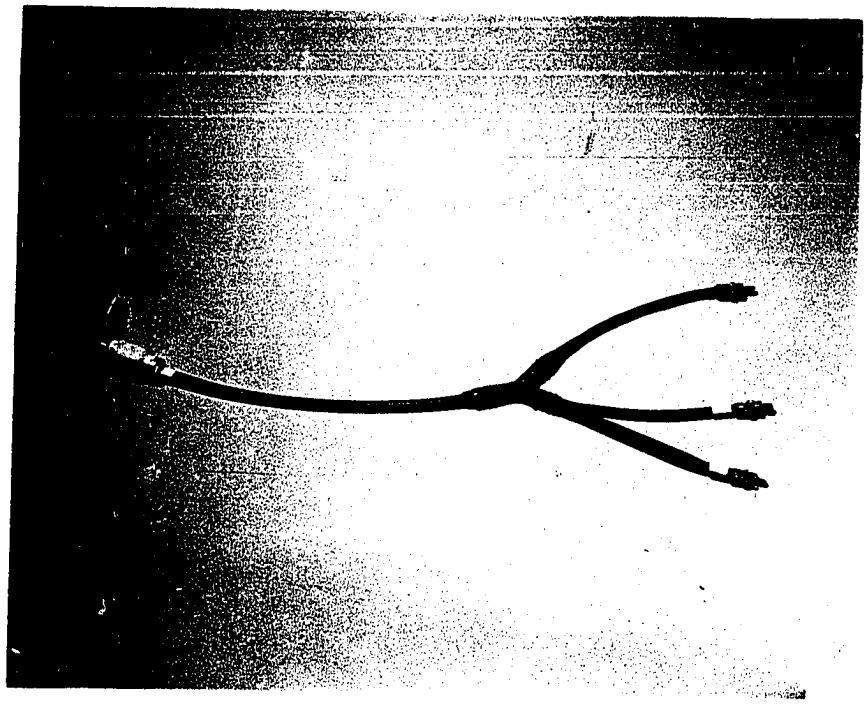


Figure 6. Commercial fiber optic transmission line and "T" connector

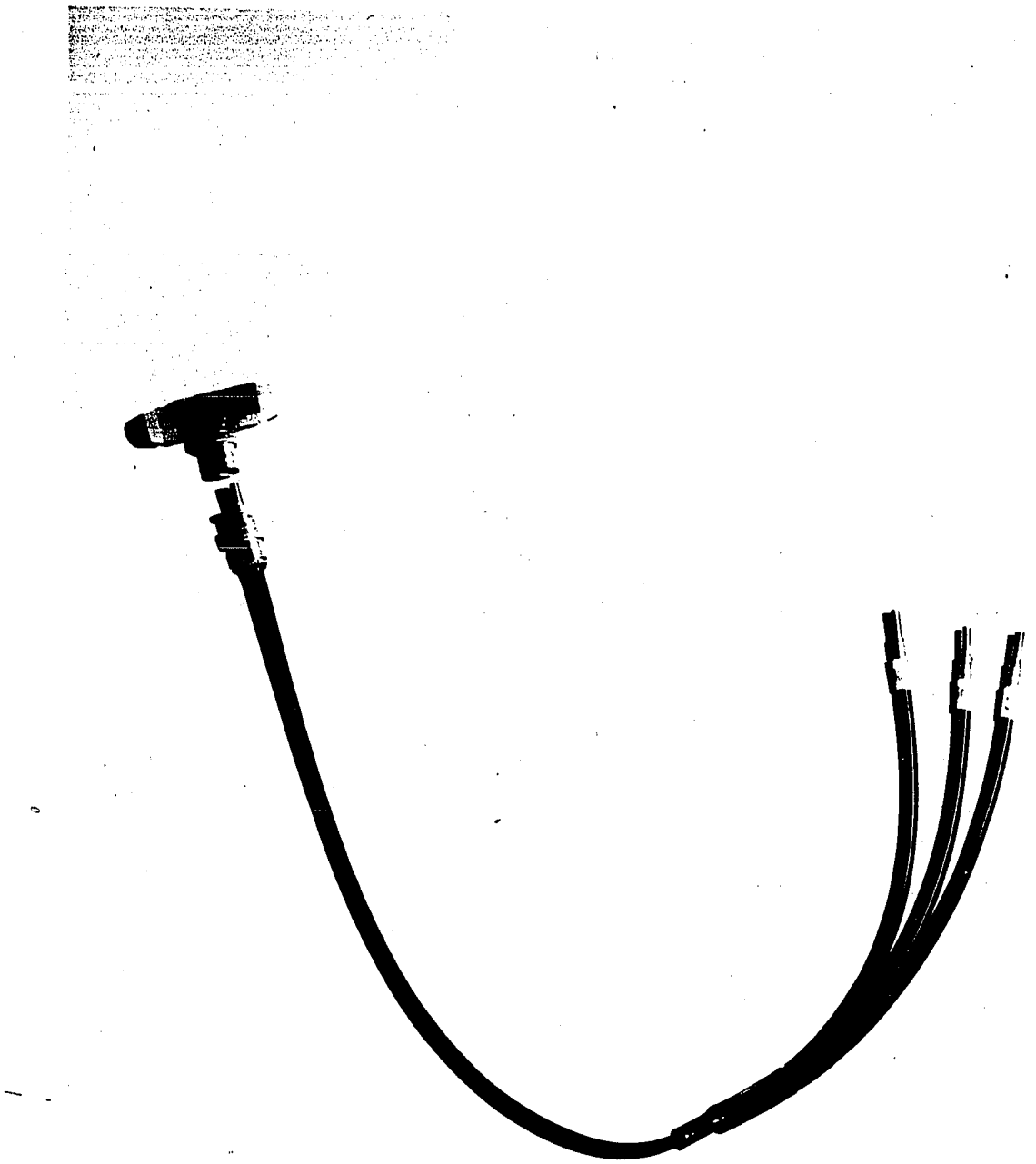


Figure 7. Spectral transmission of reduced and oxygenated hemoglobin (Wood 60, p. 665)

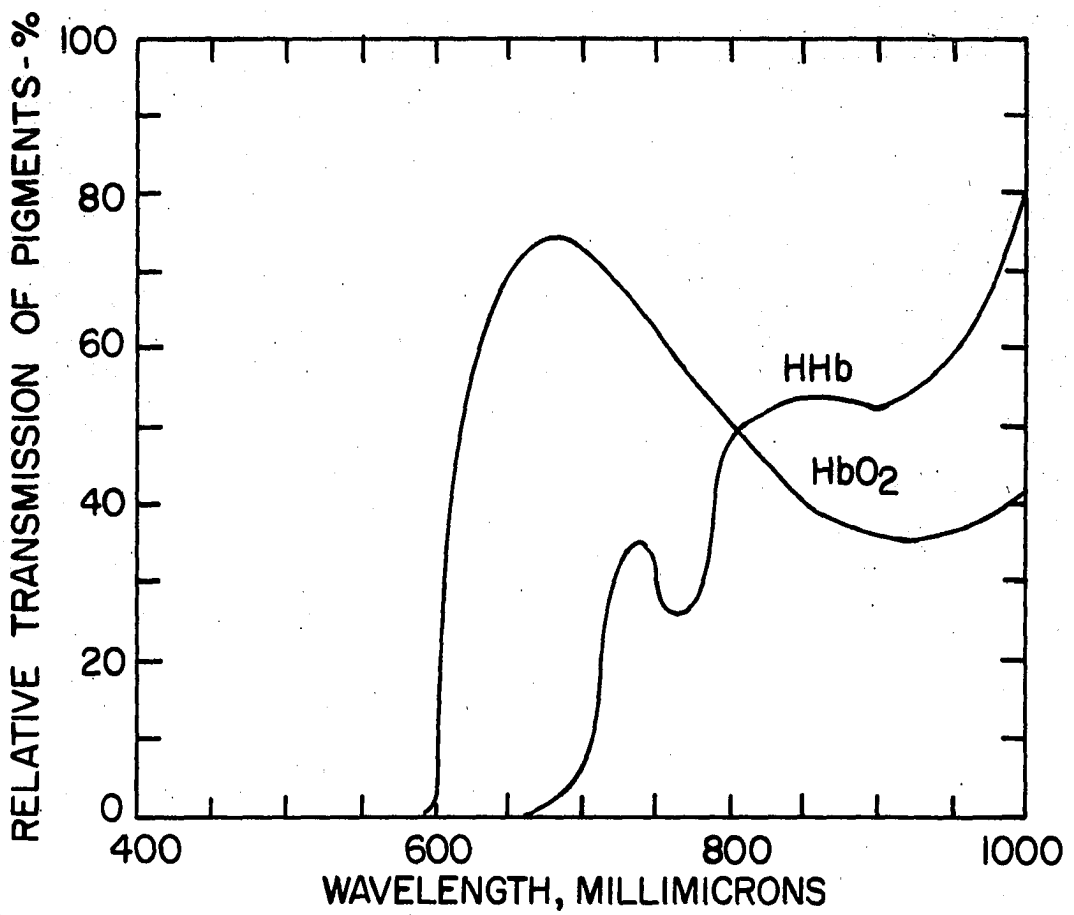

RELATIVE TRANSMISSION OF PIGMENTS - %
100
80
60
40
20
0
400
600
800
1000
WAVELENGTH, MILLIMICRONS
HHb
HbO2

Figure 8. Spectral sensitivity of photoconductive cells (Clairex Corp., New York, New York)

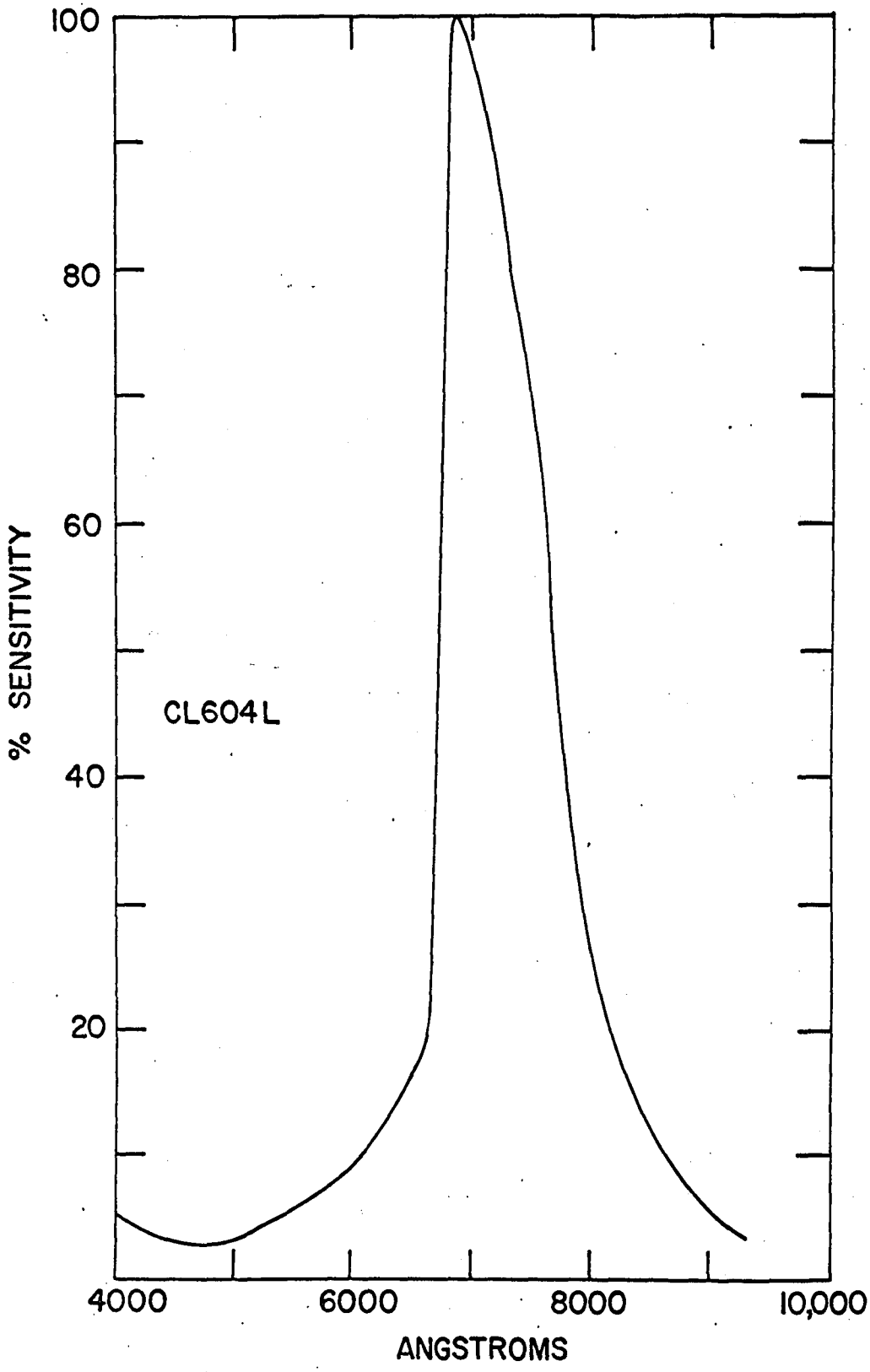
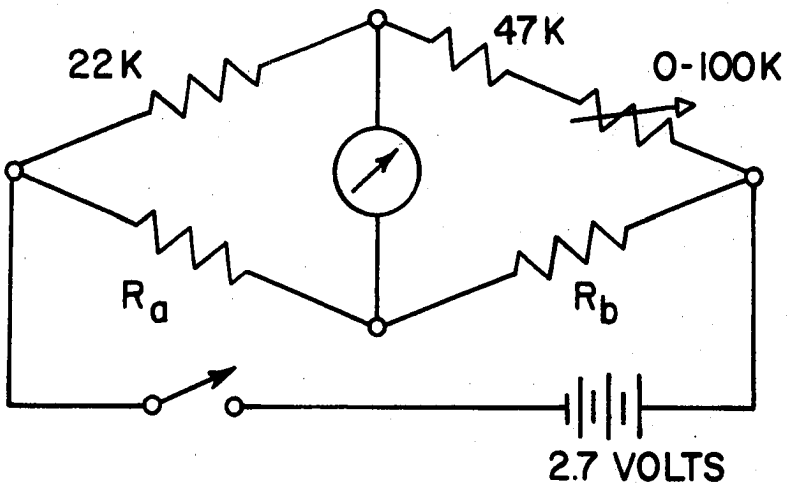

100
80
60
40
20
% SENSITIVITY
CL604L
4000
6000
8000
10,000
ANGSTROMS

Figure 9. Wheatstone bridge and power supply for the reflection oximetry system



R_a = RESISTANCE OF PHOTOCELL BEHIND 805 mμ FILTER

R_b = RESISTANCE OF PHOTOCELL BEHIND 660 mμ FILTER

Figure 10. The reflection oximetry system

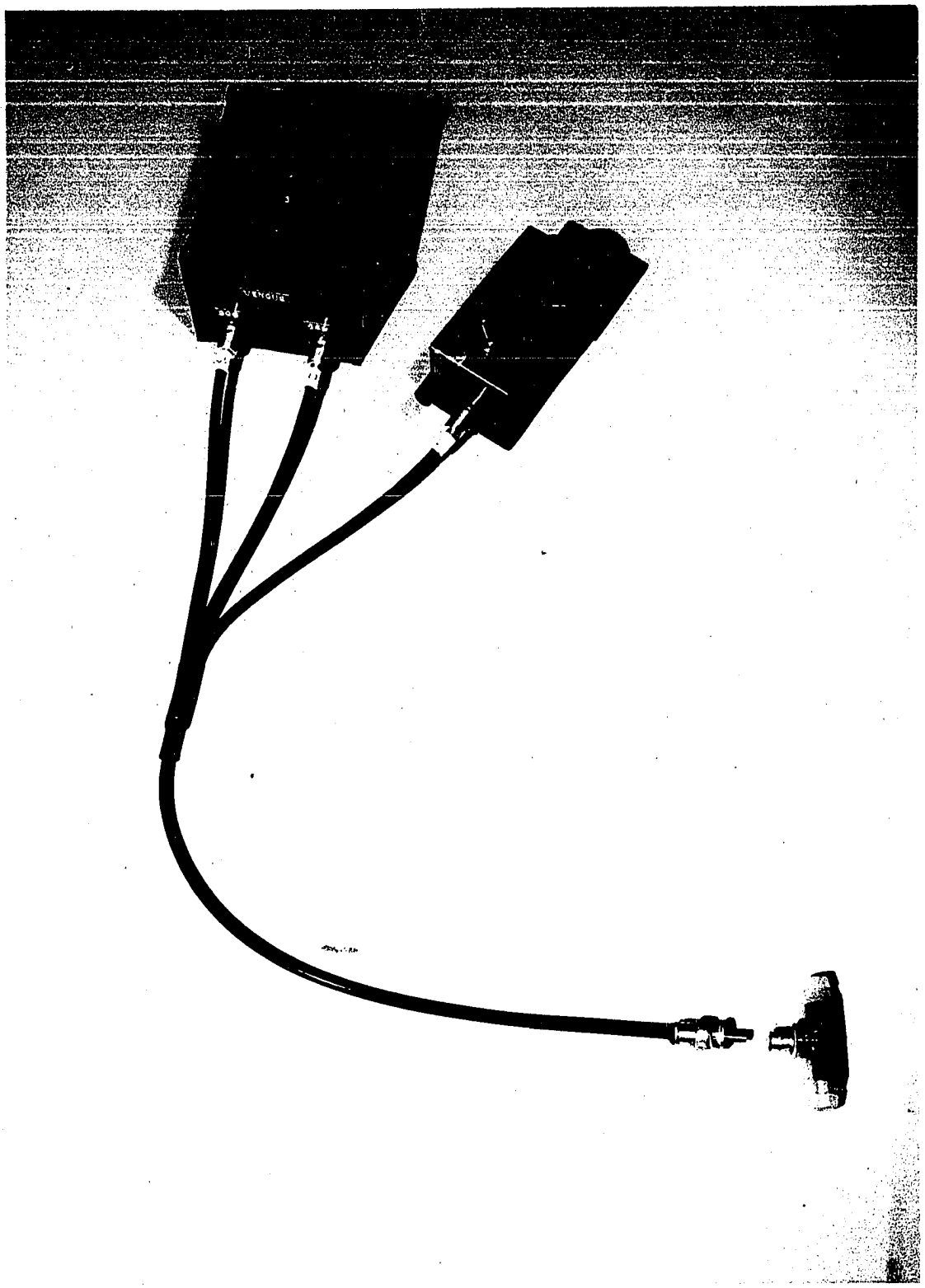


Figure 11. Switching circuit for the oximetry system

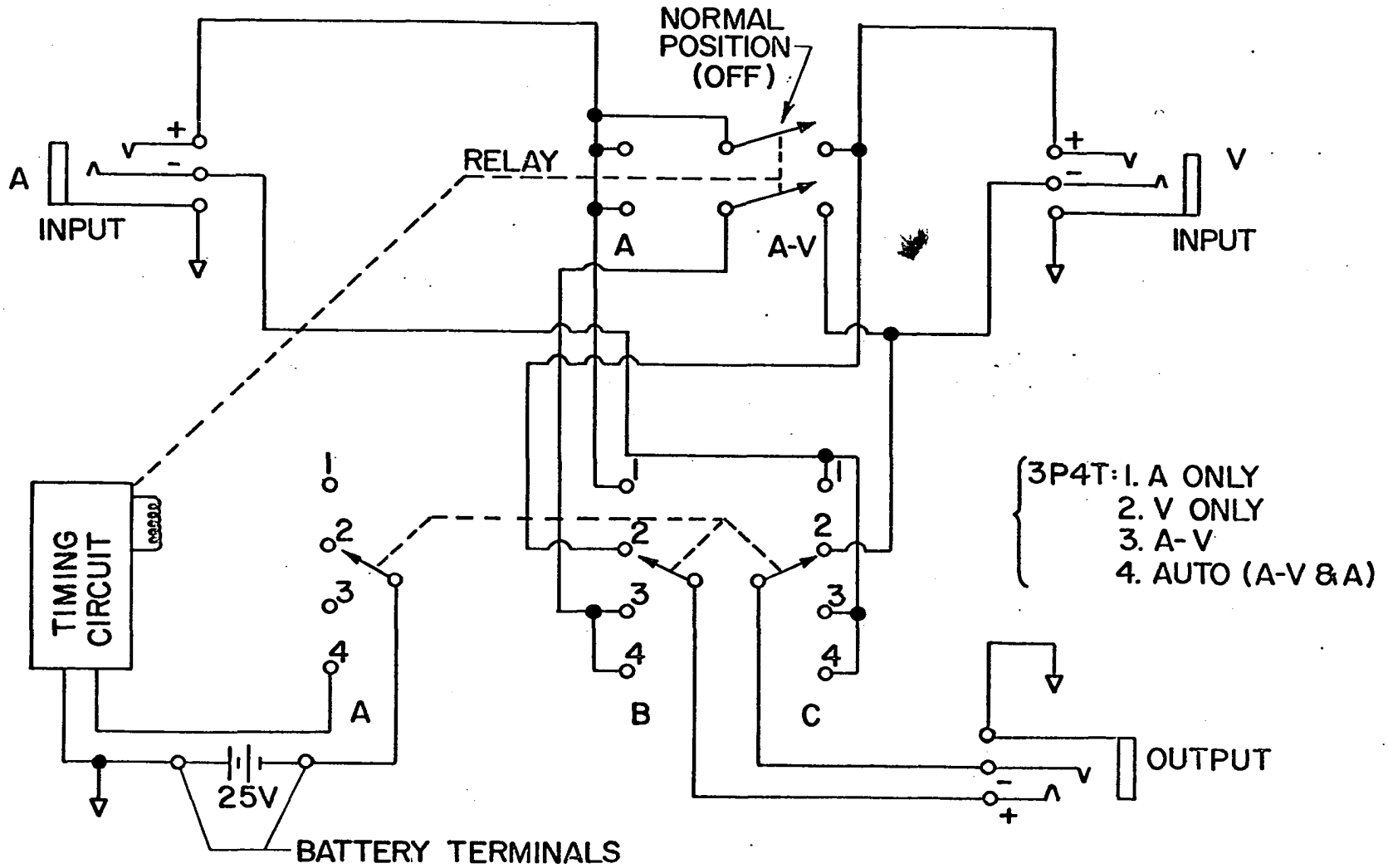

NORMAL
POSITION
(OFF)
RELAY
A
INPUT
+
-
V
A
A-V
V
INPUT
TIMING
CIRCUIT
1
2
3
4
A
B
C
3P4T: 1. A ONLY
2. V ONLY
3. A-V
4. AUTO (A-V & A)
OUTPUT
25V
BATTERY TERMINALS

Figure 12. Timing circuit for the oximetry system

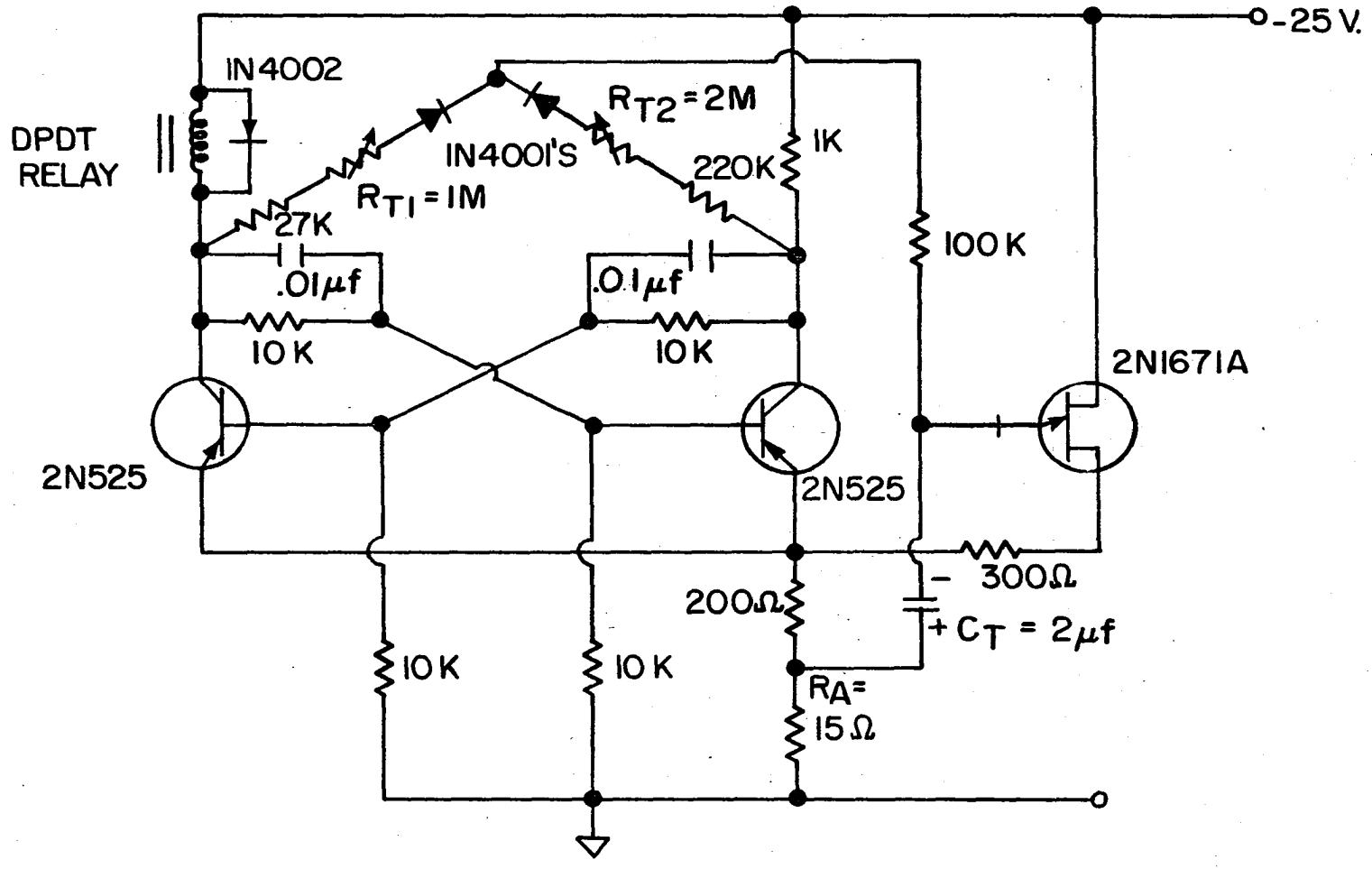

-25 V.
IN4002
DPDT
RELAY
IN4001'S
R_{T2} = 2M
R_{T1} = 1M
27K
220K
1K
100K
.01μf
.01μf
10K
10K
2N1671A
2N525
2N525
300Ω
200Ω
C_T = 2μf
10K
10K
R_A =
15Ω

Figure 13. Block diagram of pump system used for *in vitro* studies

W. B. - Wheatstone bridge

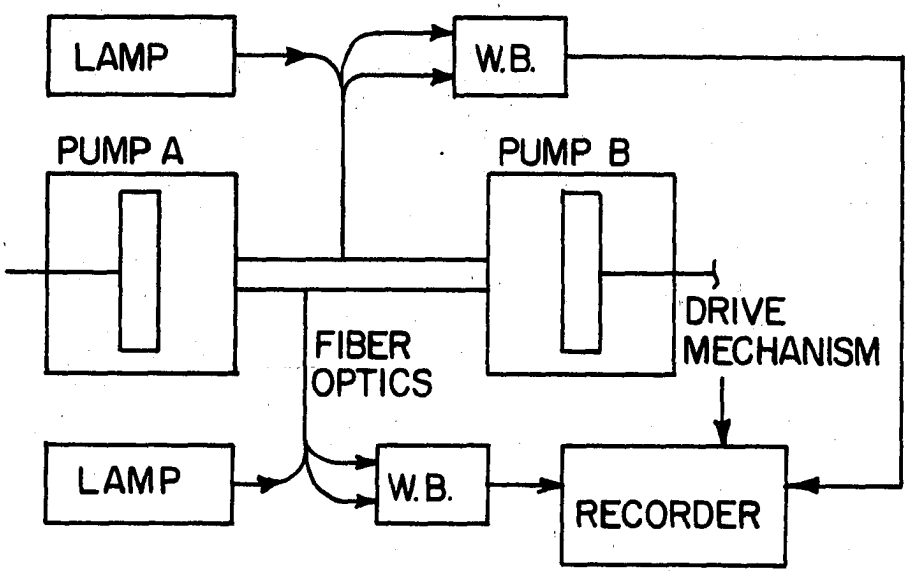

LAMP
W.B.
PUMP A
PUMP B
DRIVE
MECHANISM
FIBER
OPTICS
LAMP
W.B.
RECORDER

Figure 14. Block diagram to show location of the oximeters during extracorporeal cardiopulmonary bypass

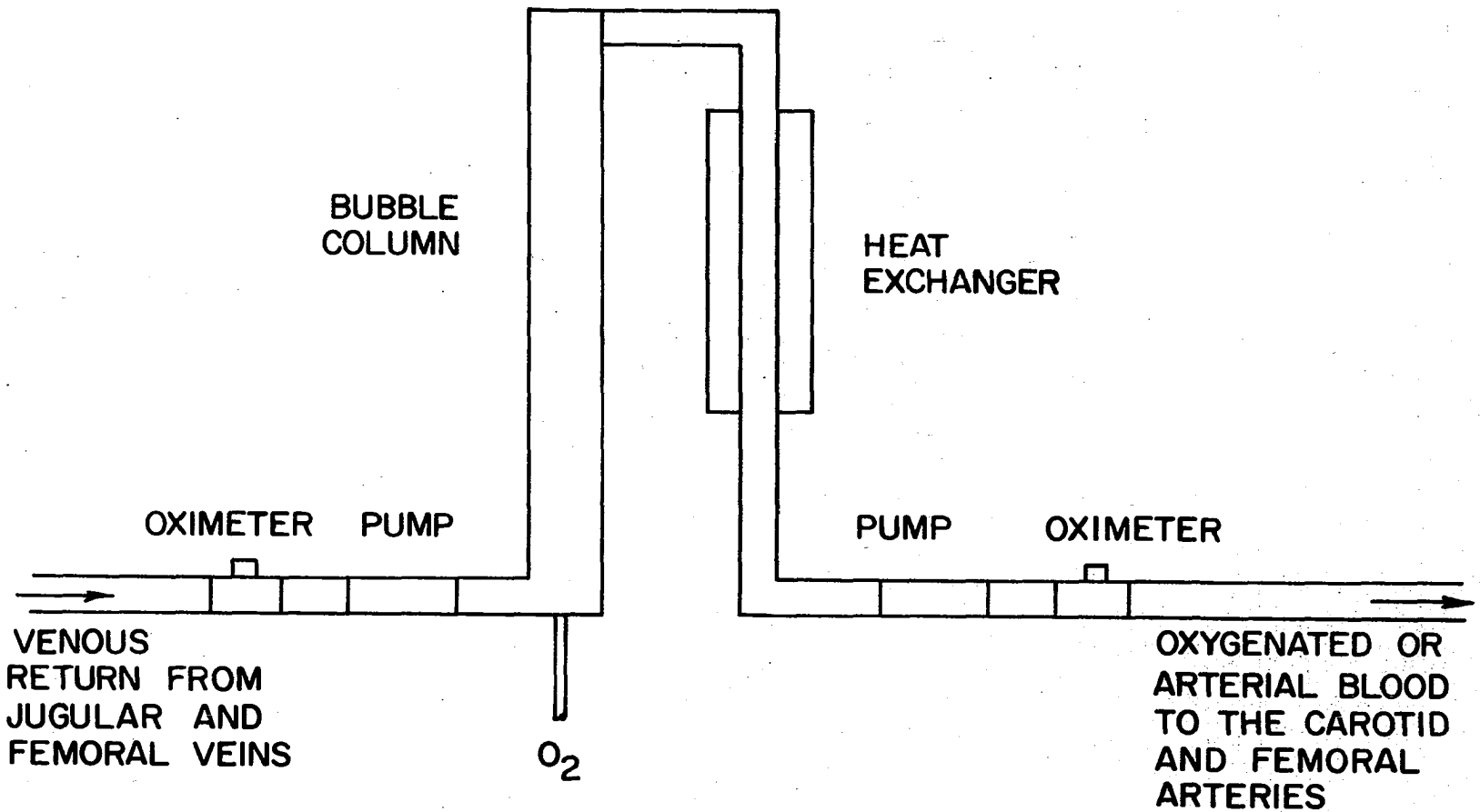

BUBBLE
COLUMN
HEAT
EXCHANGER
OXIMETER
PUMP
PUMP
OXIMETER
VENOUS
RETURN FROM
JUGULAR AND
FEMORAL VEINS
O_2
OXYGENATED OR
ARTERIAL BLOOD
TO THE CAROTID
AND FEMORAL
ARTERIES

Figure 15. Block diagram to show location of the oximeters during the artificial heart studies

B. C. - Buffer chamber

B. T. - Bubble trap

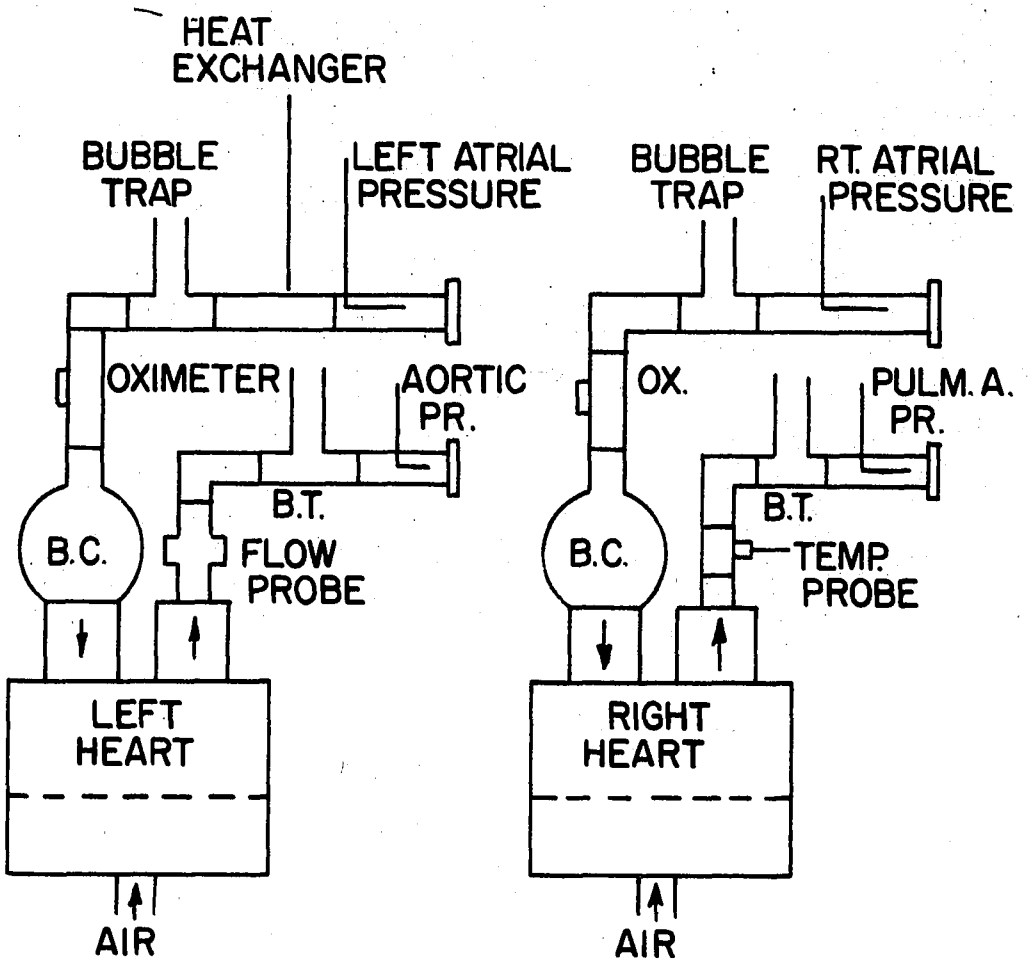

HEAT
EXCHANGER
BUBBLE
TRAP
LEFT ATRIAL
PRESSURE
OXIMETER
AORTIC
PR.
B.T.
B.C.
FLOW
PROBE
LEFT
HEART
AIR
BUBBLE
TRAP
RT. ATRIAL
PRESSURE
OX.
PULM. A.
PR.
B.T.
B.C.
TEMP.
PROBE
RIGHT
HEART
AIR

Figure 16. Bridge voltage vs. linear flow velocity for constant oxyhemoglobin concentrations

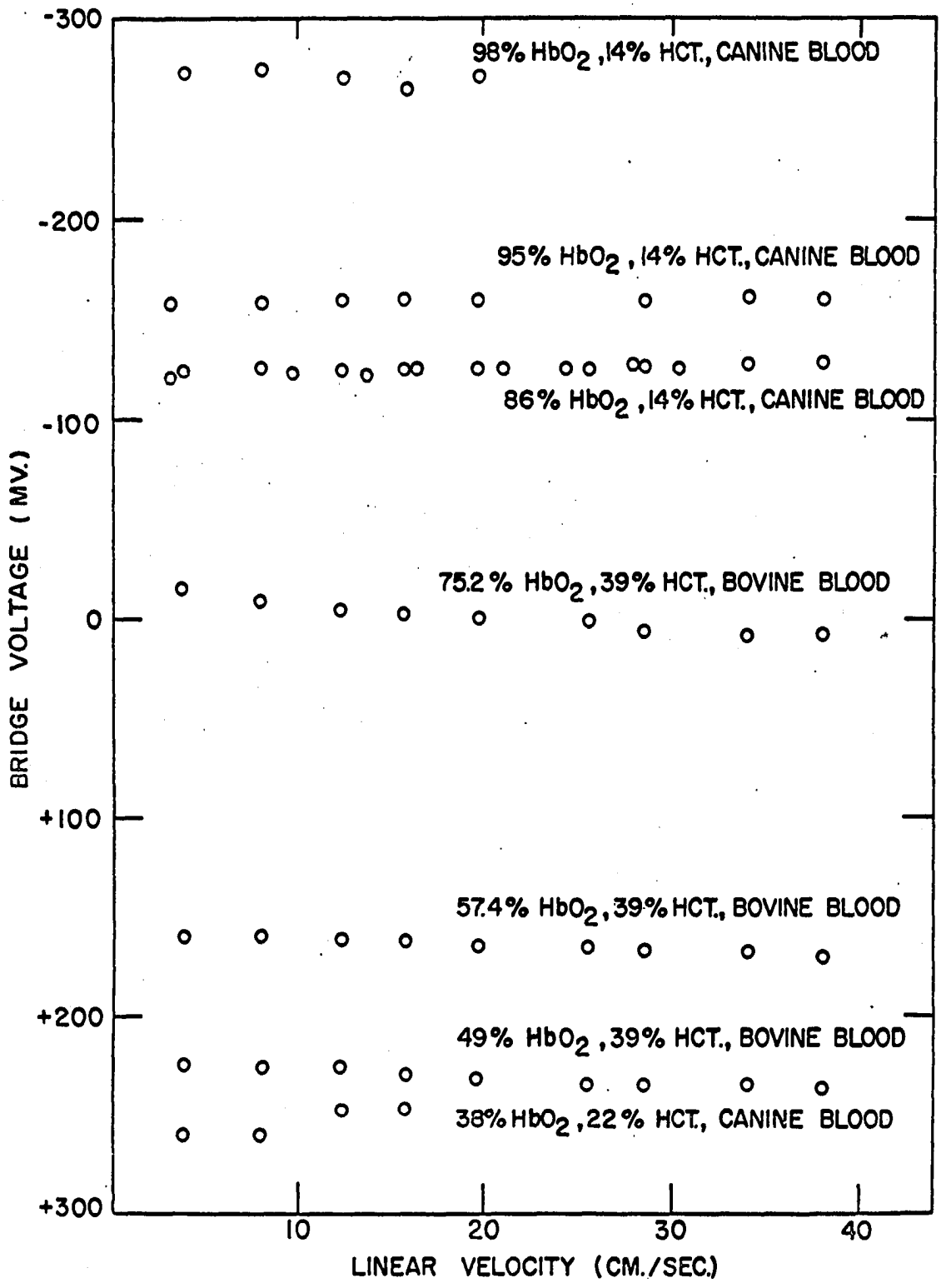

98% HbO2 ,14% HCT., CANINE BLOOD
95% HbO2 , 14% HCT., CANINE BLOOD
86% HbO2 , 14% HCT., CANINE BLOOD
75.2 % HbO2 , 39% HCT., BOVINE BLOOD
57.4% HbO2 , 39% HCT., BOVINE BLOOD
49% HbO2 , 39% HCT., BOVINE BLOOD
38% HbO2 , 22 % HCT., CANINE BLOOD
-300
-200
-100
0
+100
+200
+300
BRIDGE VOLTAGE (MV.)
10
20
30
40
LINEAR VELOCITY (CM./SEC.)

Figure 17. Bridge voltage vs. oxyhemoglobin concentration for constant hematocrits (canine blood)

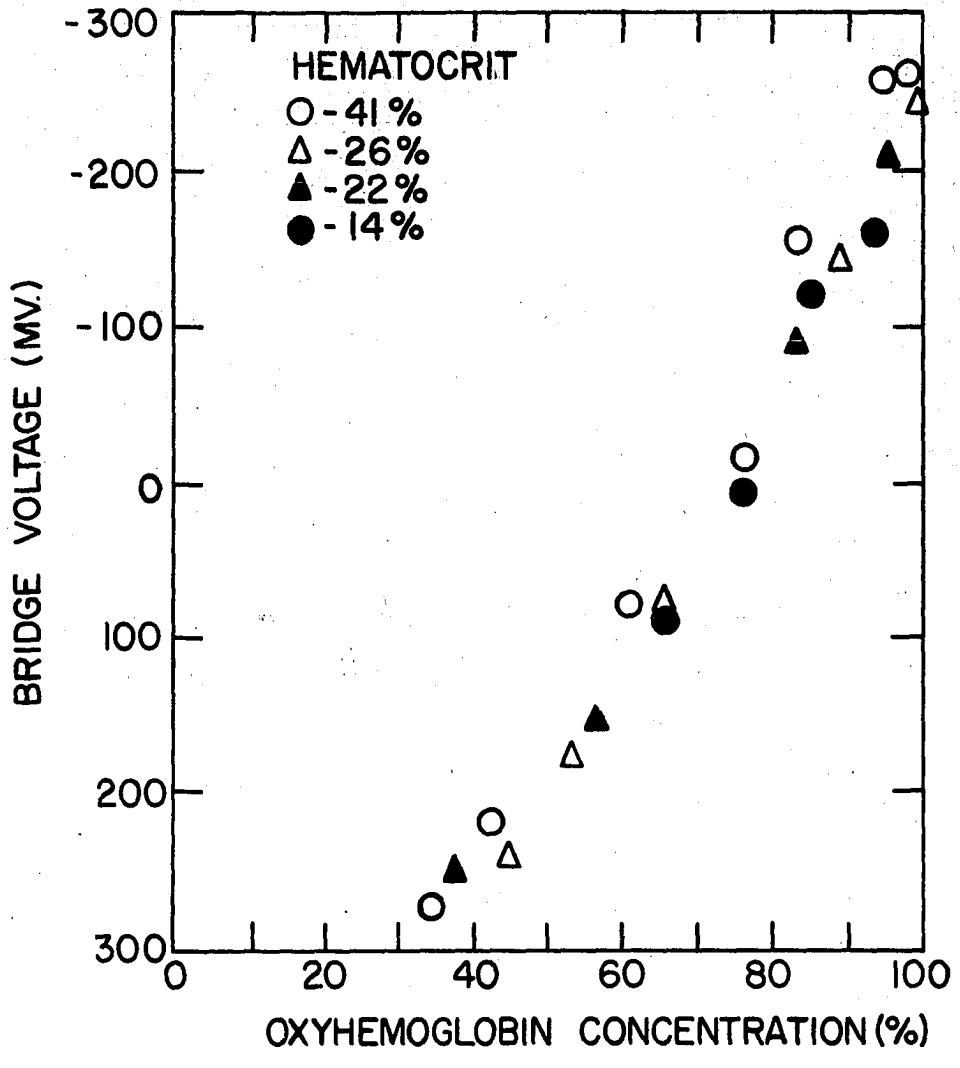

HEMATOCRIT
○ - 41%
△ - 26%
▲ - 22%
● - 14%
-300
-200
-100
0
100
200
300
BRIDGE VOLTAGE (MV.)
0
20
40
60
80
100
OXYHEMOGLOBIN CONCENTRATION (%)

Figure 18. Bridge voltage vs. oxyhemoglobin concentration for constant hematocrits (ovine blood)

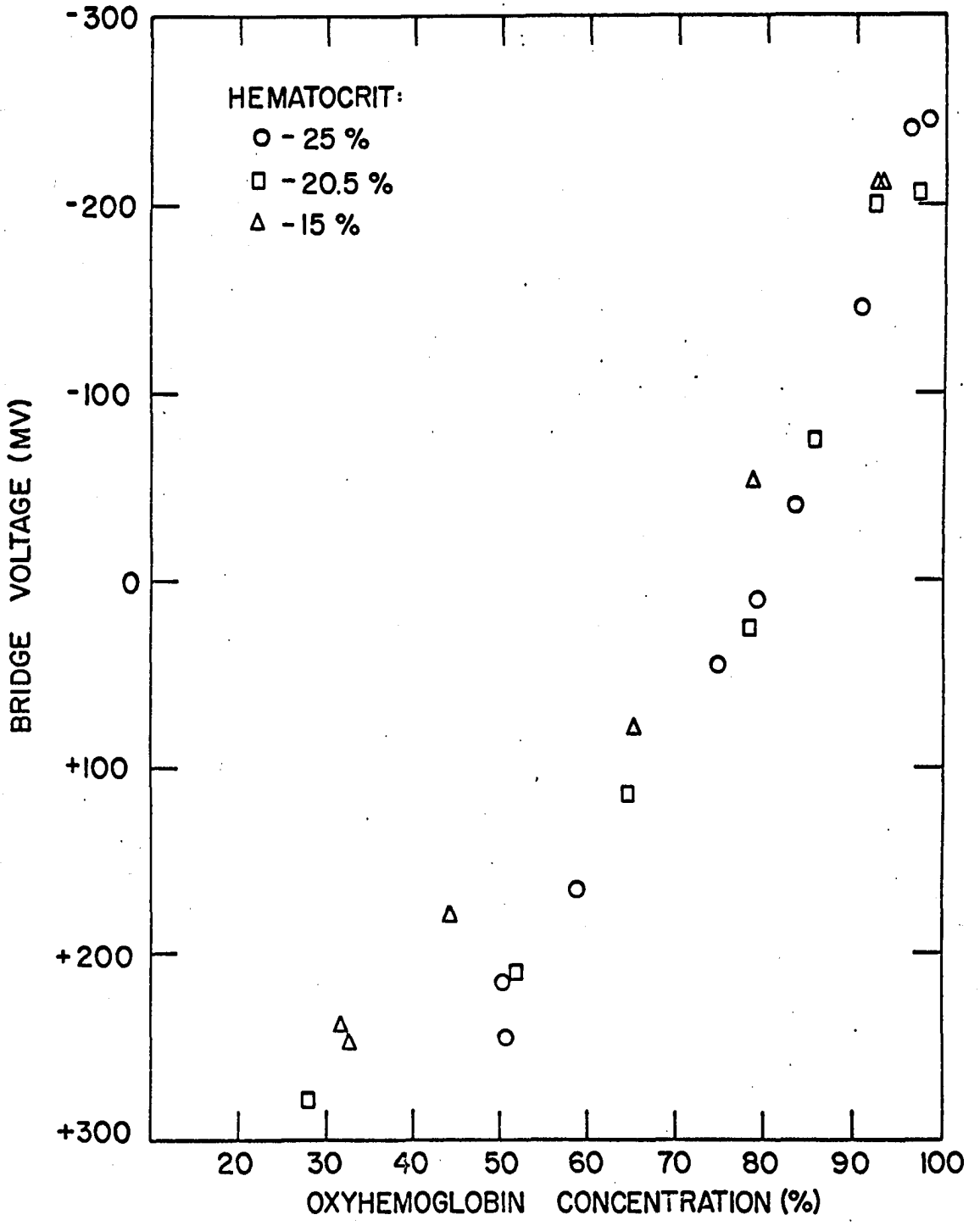

HEMATOCRIT:
○ - 25 %
□ - 20.5 %
△ - 15 %
-300
-200
-100
0
+100
+200
+300
BRIDGE VOLTAGE (MV)
20
30
40
50
60
70
80
90
100
OXYHEMOGLOBIN CONCENTRATION (%)

Figure 19. The effect of species difference on the bridge voltage for various oxyhemoglobin concentrations at a hematocrit of approximately 21.4 per cent

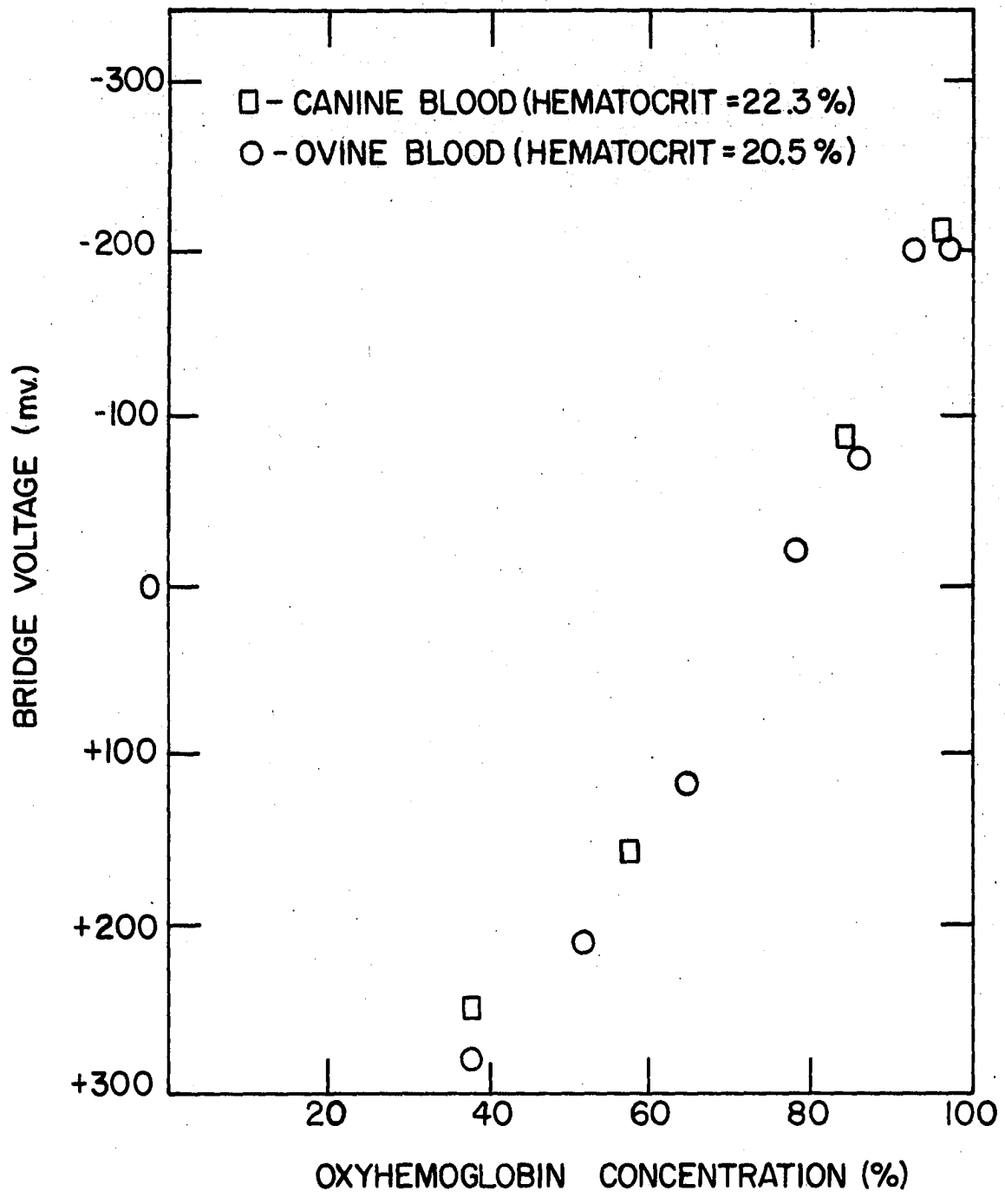

□ - CANINE BLOOD (HEMATOCRIT = 22.3 %)
○ - OVINE BLOOD (HEMATOCRIT = 20.5 %)
-300
-200
-100
0
+100
+200
+300
BRIDGE VOLTAGE (mv.)
20
40
60
80
100
OXYHEMOGLOBIN CONCENTRATION (%)

Figure 20. A recording during extracorporeal cardiopulmonary bypass in dog 29 which illustrates continuous monitoring of the venous oxyhemoglobin concentration. The paper speed is 25 mm. per second. Each mark in the time channel represents 1 second

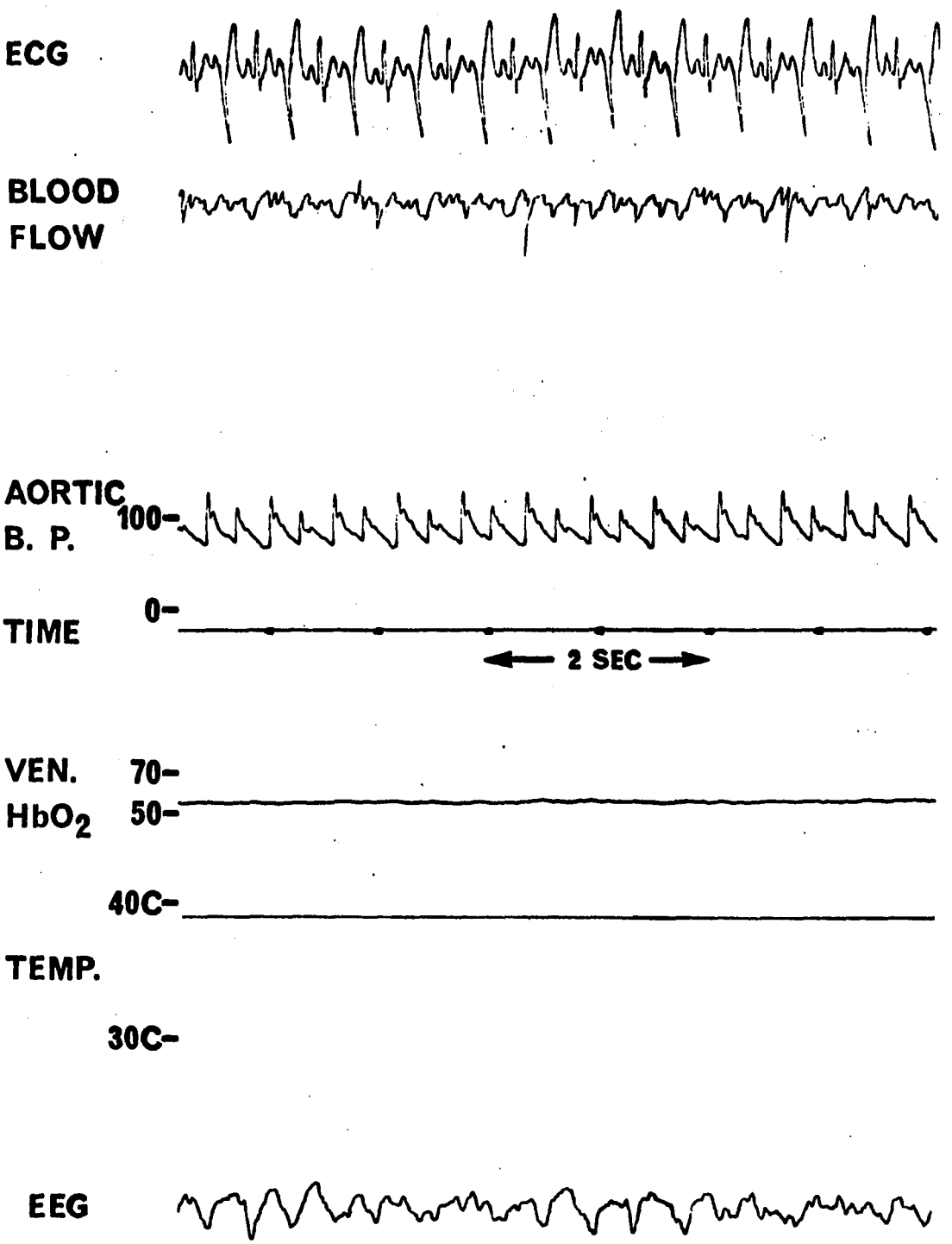

ECG
BLOOD FLOW
AORTIC B. P.
100-
0-
TIME
2 SEC
VEN. HbO2
70-
50-
40C-
TEMP.
30C-
EEG

Figure 21. A recording during extracorporeal cardio-pulmonary bypass in dog 43 which illustrates continuous monitoring of the arterial and venous oxyhemoglobin concentrations. The paper speed is 50 mm. per second

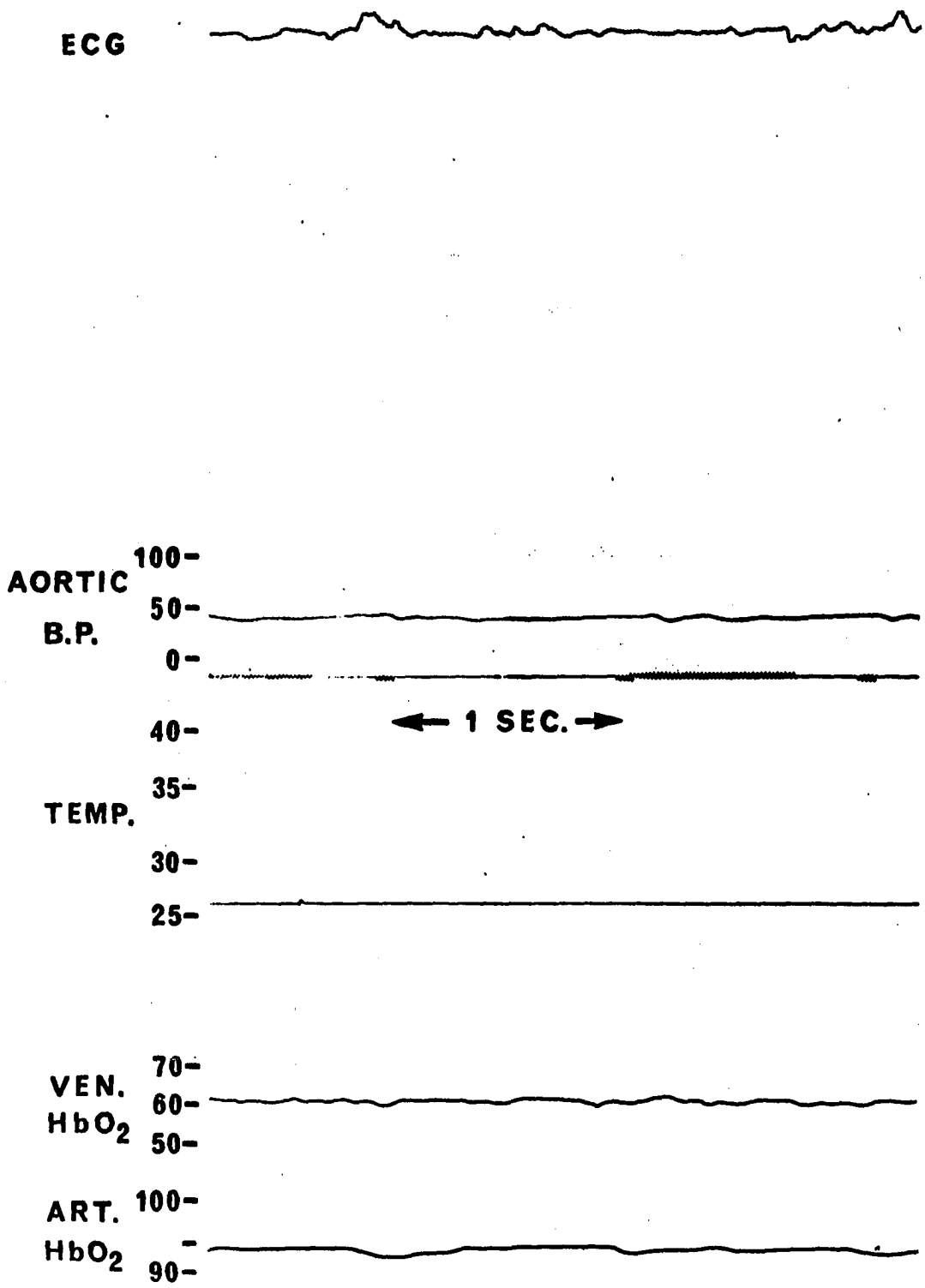

ECG
AORTIC B.P.
100-
50-
0-
1 SEC.
40-
TEMP.
35-
30-
25-
VEN. HbO2
70-
60-
50-
ART. HbO2
100-
90-

Figure 22. A recording during extracorporeal cardiopulmonary bypass in dog 17 which illustrates the effect of changes in the aortic blood pressure on the venous oxyhemoglobin concentration. Blood flow was not recorded. The paper speed is 1 mm. per second

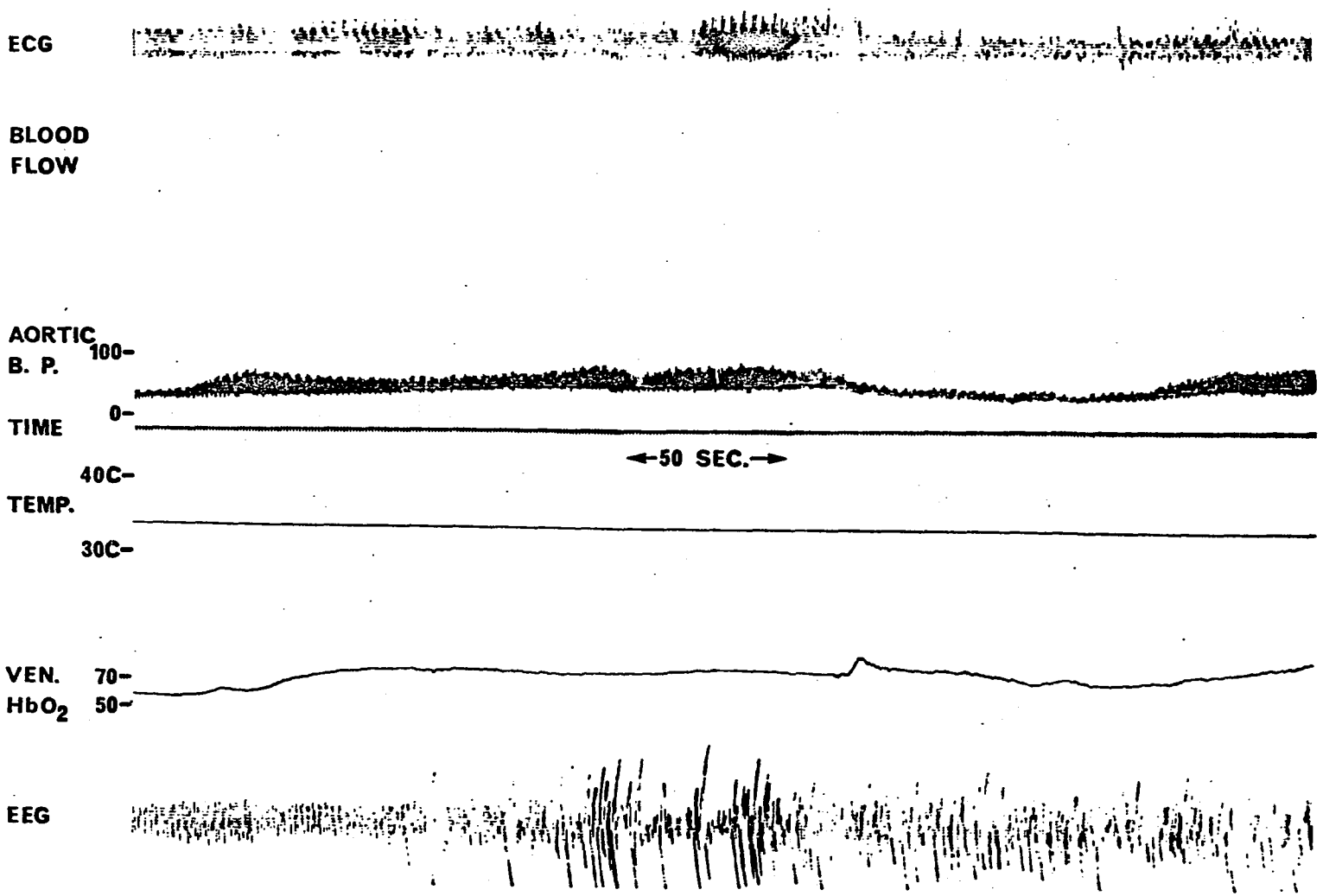

ECG
BLOOD
FLOW
AORTIC
B. P.
100–
0–
TIME
←50 SEC.→
40C–
TEMP.
30C–
VEN.
HbO2
70–
50–
EEG

Figure 23. A recording during extracorporeal cardiopulmonary bypass in dog 25 which illustrates the effect of hypothermia on the venous oxyhemoglobin concentration. The temperature recorded is the esophageal temperature. The arrow pointing down indicates the initial drop in the esophageal temperature. The arrow pointing up indicates the initial rise in the venous oxyhemoglobin concentration. The paper speed is 1 mm. per second

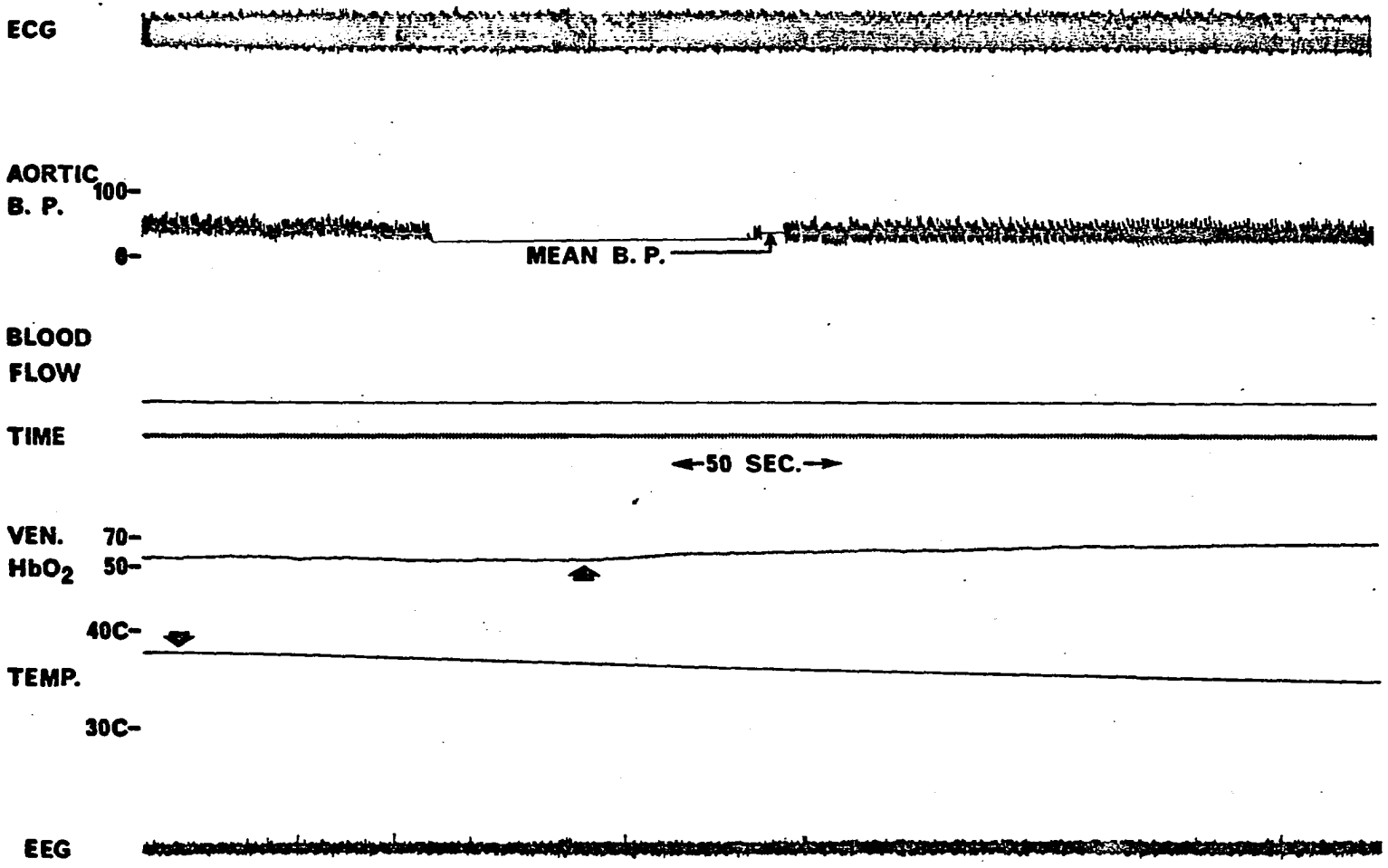

ECG
AORTIC B. P.
100–
0–
MEAN B. P.
BLOOD FLOW
TIME
50 SEC.
VEN. HbO2
70–
50–
40C–
TEMP.
30C–
EEG

Figure 24. A recording during extracorporeal cardiopulmonary bypass in dog 25 which illustrates the effect of hyperthermia on the venous oxyhemoglobin concentration. The small arrow pointing up indicates initiation of hyperthermia. The large arrow pointing up indicates a change from esophageal temperature to venous blood temperature. The paper speed is 1 mm. per second

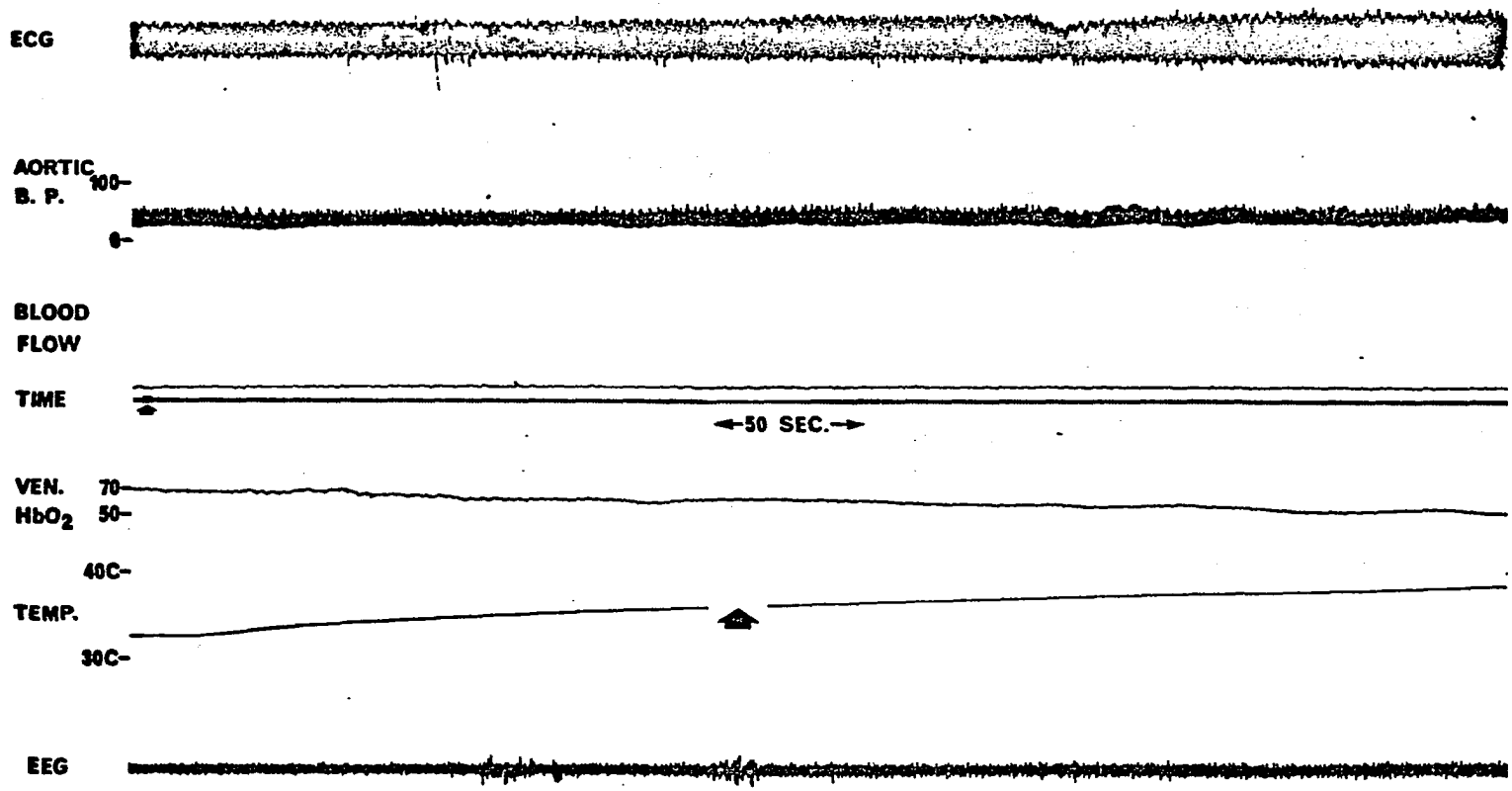

ECG
AORTIC
B. P.
100–
0–
BLOOD
FLOW
TIME
50 SEC.
VEN.
HbO2
70
50–
40C–
TEMP.
30C–
EEG

Figure 25. A recording during an artificial heart study in dog 40 which illustrates continuous monitoring of the arterial and venous oxyhemoglobin concentrations. The points of measurement were in the input cannulae to the artificial ventricles. Small pulsatile changes can be seen in the arterial oxyhemoglobin concentration. The paper speed is 50 mm. per second

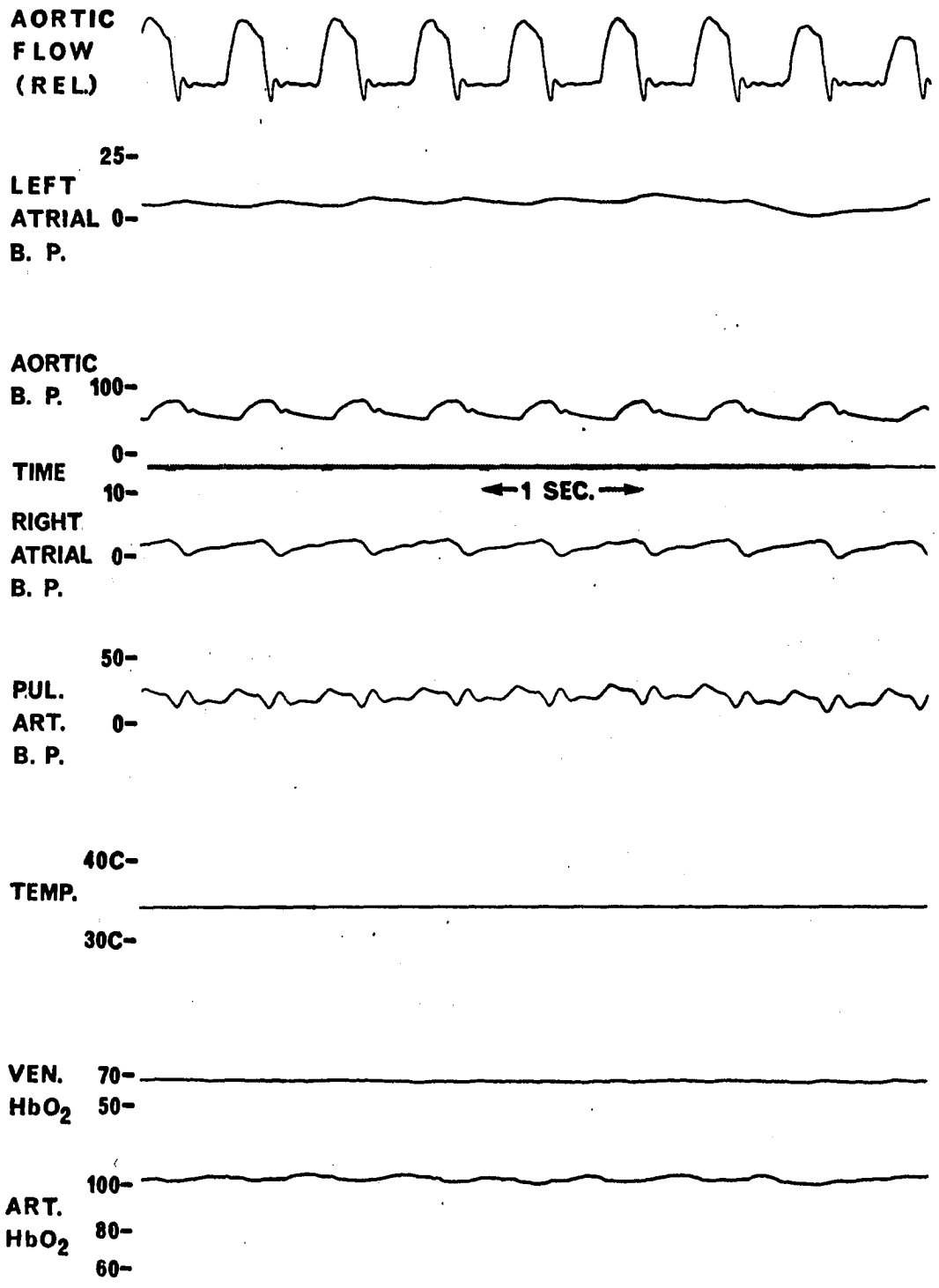

AORTIC FLOW (REL.)
25-
LEFT ATRIAL 0-
B. P.
AORTIC B. P. 100-
0-
TIME
10-
←1 SEC.→
RIGHT ATRIAL 0-
B. P.
50-
PUL. ART. 0-
B. P.
40C-
TEMP.
30C-
VEN. 70-
HbO2 50-
100-
ART. 80-
HbO2 60-

Figure 26. A recording during an artificial heart study in dog 38 which illustrates the effect of monitoring the arterial oxyhemoglobin concentration at the output of the left ventricle (in the aortic cannula). Pulsatile effects can be seen in the arterial oxyhemoglobin concentration. The paper speed is 25 mm. per second

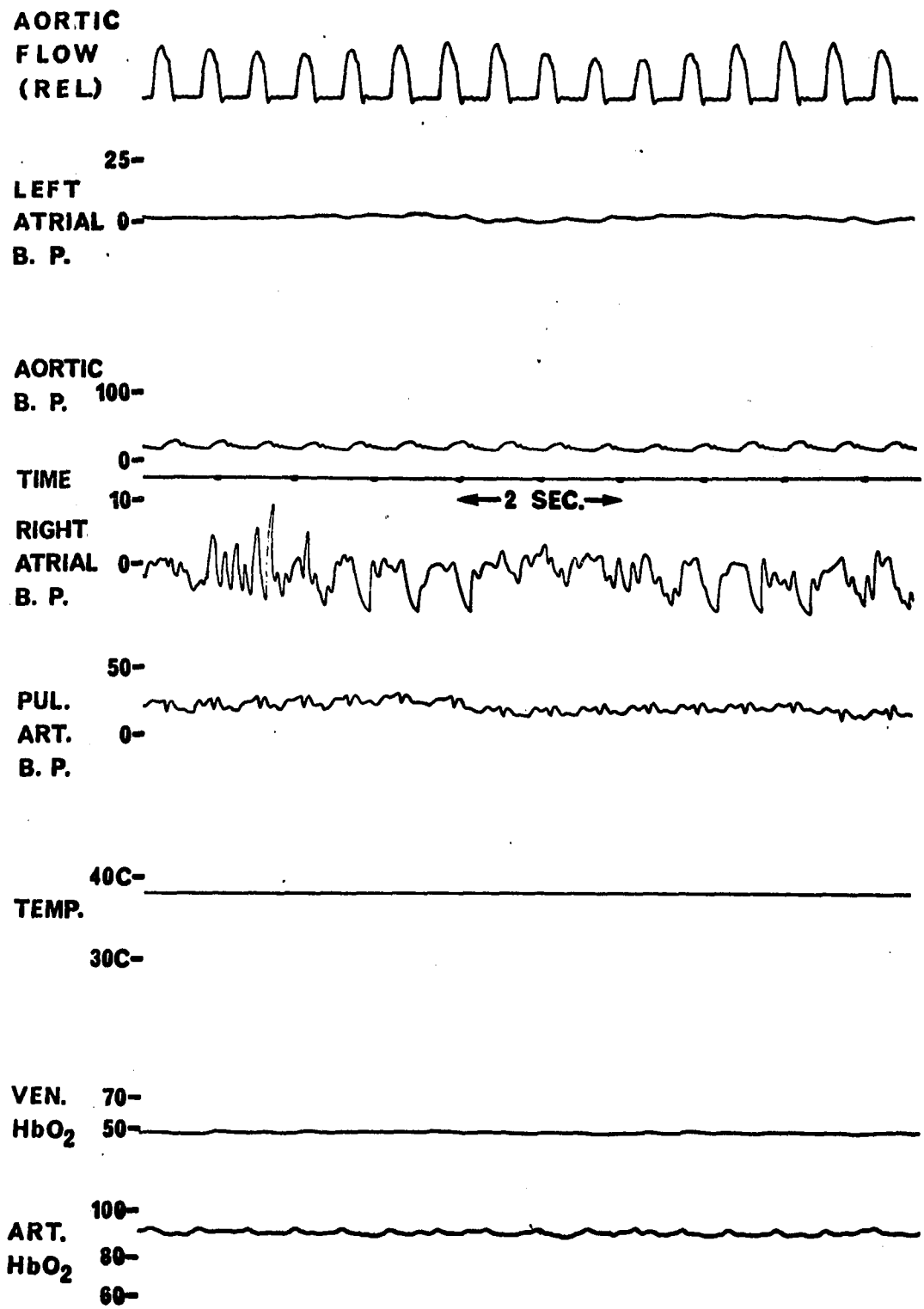

AORTIC
FLOW
(REL.)
25-
LEFT
ATRIAL 0-
B. P.
AORTIC
B. P. 100-
0-
TIME
10-
2 SEC.
RIGHT
ATRIAL 0-
B. P.
50-
PUL.
ART. 0-
B. P.
40C-
TEMP.
30C-
VEN. 70-
HbO2 50-
100-
ART.
HbO2 80-
60-

Figure 27. A recording during an artificial heart study in sheep 18 which illustrates operation of the manual and automatic switching system for recording the arterial, venous and arteriovenous difference in oxyhemoglobin concentrations. The paper speed is 2-1/2 mm. per second

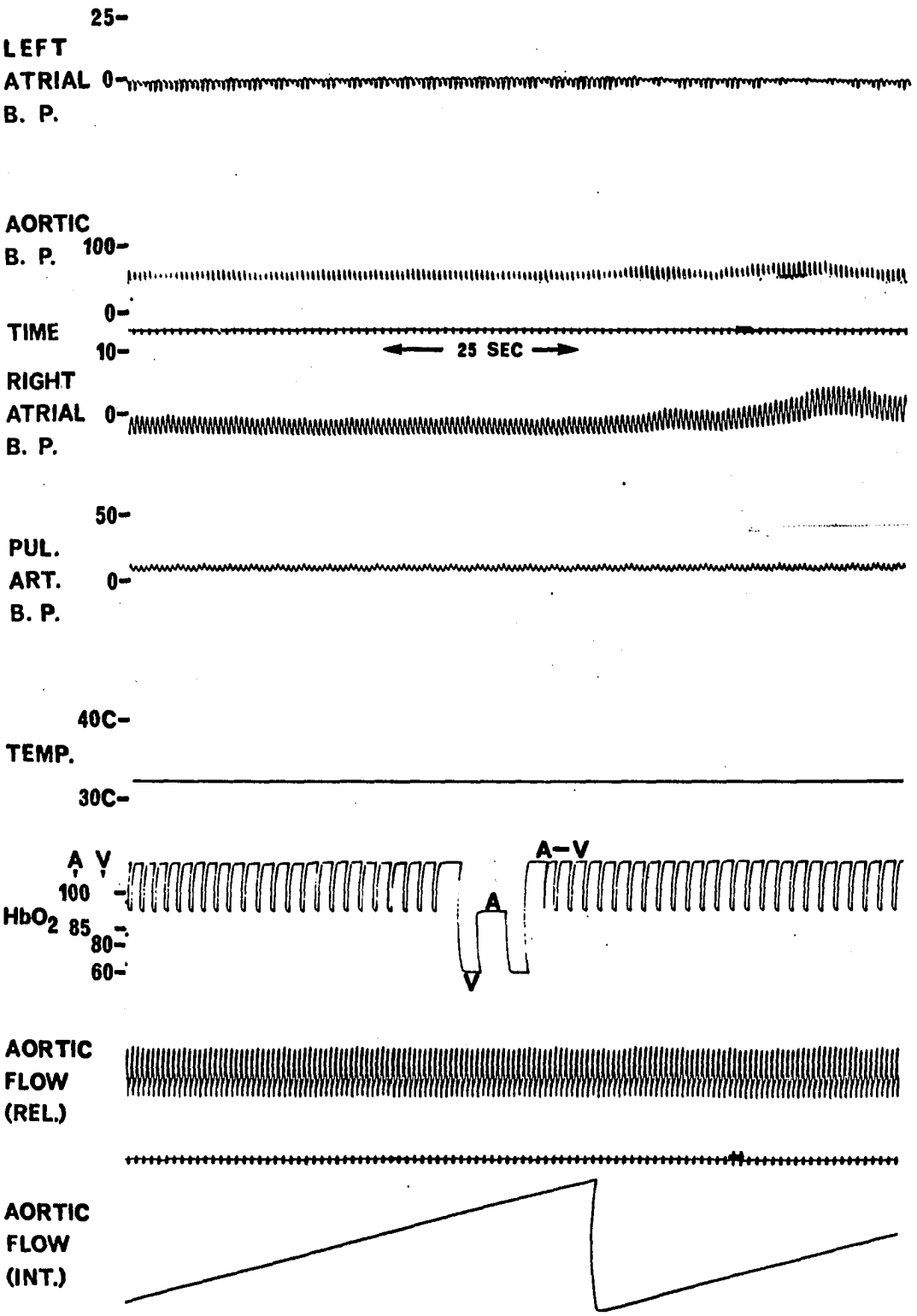

25-
LEFT
ATRIAL 0-
B. P.
AORTIC
B. P. 100-
0-
TIME
10-
25 SEC
RIGHT
ATRIAL 0-
B. P.
50-
PUL.
ART. 0-
B. P.
40C-
TEMP.
30C-
A V
100
HbO2 85
80-
60-
A-V
A
V
AORTIC
FLOW
(REL.)
AORTIC
FLOW
(INT.)

Figure 28. A recording during an artificial heart control study in dog 37 which illustrates the effect of changing the content of inspired air from 100 per cent oxygen to a mixture to 15 per cent oxygen and 85 per cent nitrogen (large arrow pointing up). A gradual decline can be seen in the arterial and venous oxyhemoglobin concentrations. The small arrows pointing down indicate the 50 second time lag between changes in the arterial and venous oxyhemoglobin concentrations. The paper speed is 1 mm. per second

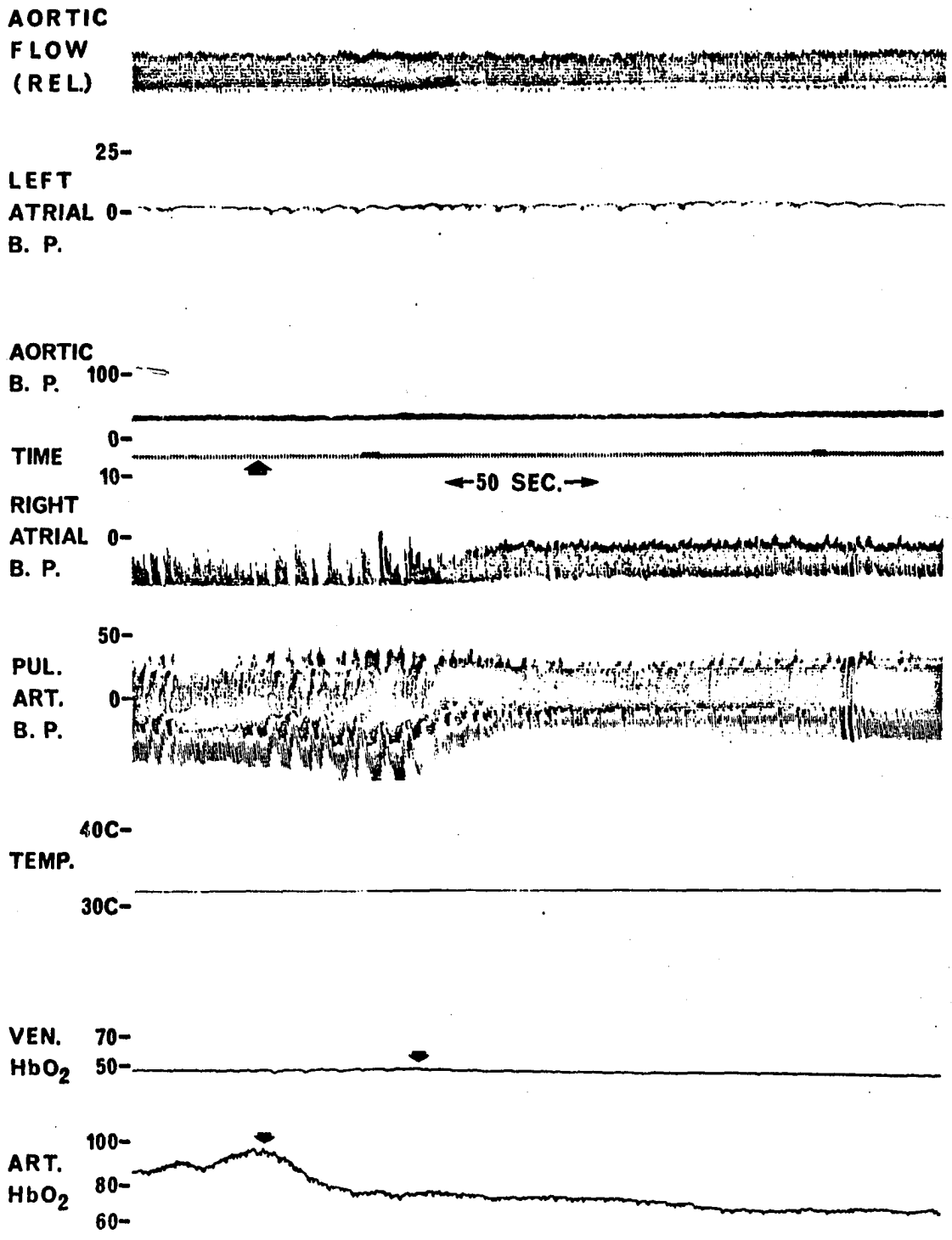

AORTIC
FLOW
(REL.)
25-
LEFT
ATRIAL 0-
B. P.
AORTIC
B. P. 100-
0-
TIME
10-
←50 SEC.→
RIGHT
ATRIAL 0-
B. P.
50-
PUL.
ART. 0-
B. P.
40C-
TEMP.
30C-
VEN. 70-
HbO2 50-
100-
ART.
HbO2 80-
60-

Figure 29. A recording during an artificial heart control study in dog 37 which illustrates the effect of changing the content of inspired air from 15 per cent oxygen to 100 per cent oxygen (large arrow pointing up). A gradual increase can be seen in the arterial and venous oxyhemoglobin concentrations. The small arrows pointing up indicate the 50 second time lag between changes in the arterial and venous oxyhemoglobin concentrations. The paper speed is 1 mm. per second

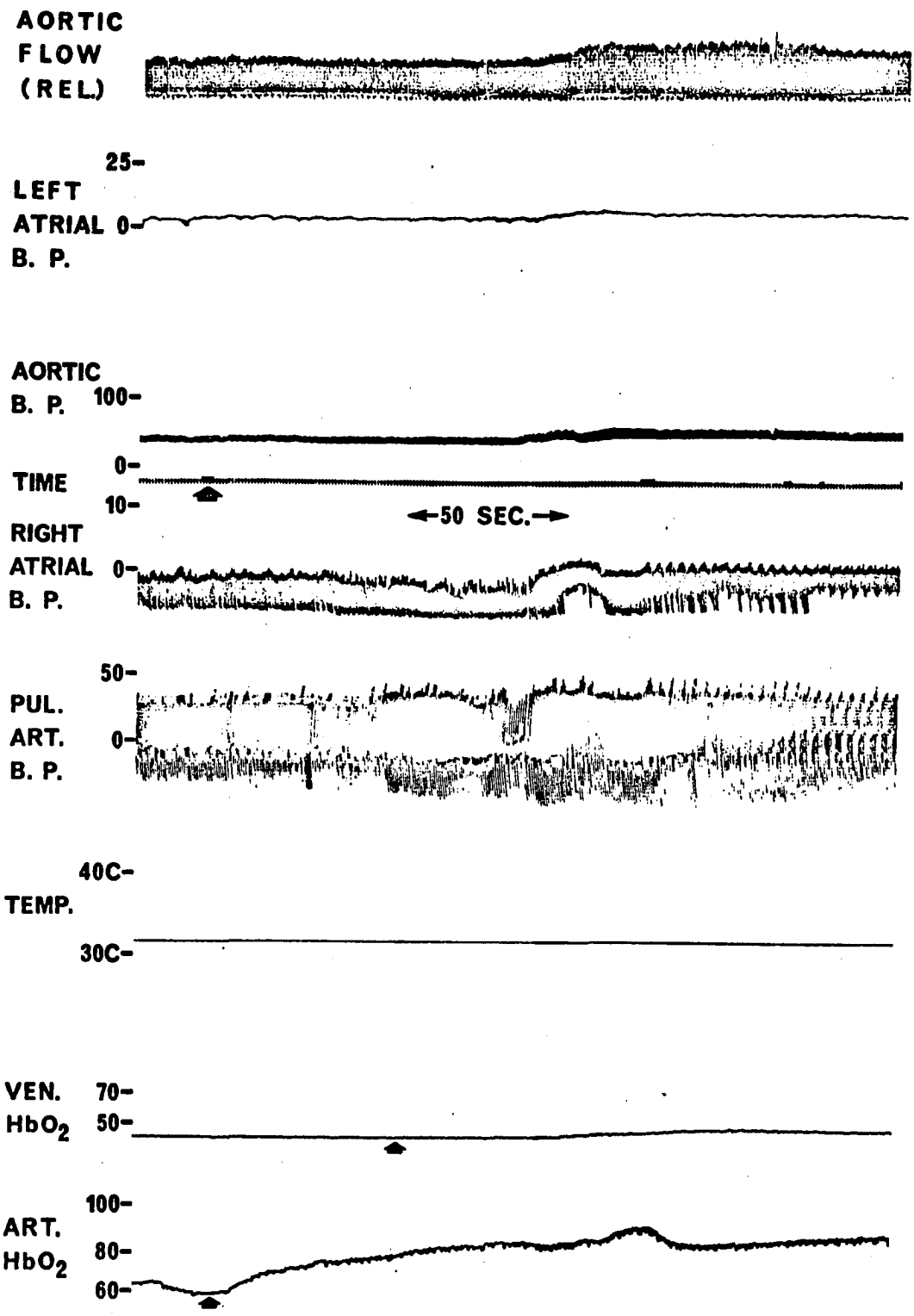

AORTIC
FLOW
(REL.)
25-
LEFT
ATRIAL 0-
B. P.
AORTIC
B. P. 100-
0-
TIME
10-
←50 SEC.→
RIGHT
ATRIAL 0-
B. P.
50-
PUL.
ART. 0-
B. P.
40C-
TEMP.
30C-
VEN. 70-
HbO2 50-
100-
ART.
HbO2 80-
60-

Figure 30. A recording during an artificial heart control study in dog 42 which illustrates the effects of pulmonary failure and an attempt by the animal-machine system to compensate for it. The right heart is being controlled by the venous oxyhemoglobin concentration, the left heart by left atrial pressure. The sampling rate for the right ventricle is 30-5; it is permitted to correct every 30 seconds with a maximum correction period of 5 seconds. The sampling rate for the left ventricle is 15-5. Note the delay in correction by the right ventricle due to the time lag between the changes in arterial and venous oxyhemoglobin concentrations. The paper speed is 1 mm. per second

IR - An increase in stroke volume by the right ventricle

DR - A decrease in stroke volume by the right ventricle

DL - A decrease in stroke volume by the left ventricle

IL - An increase in stroke volume by the left ventricle

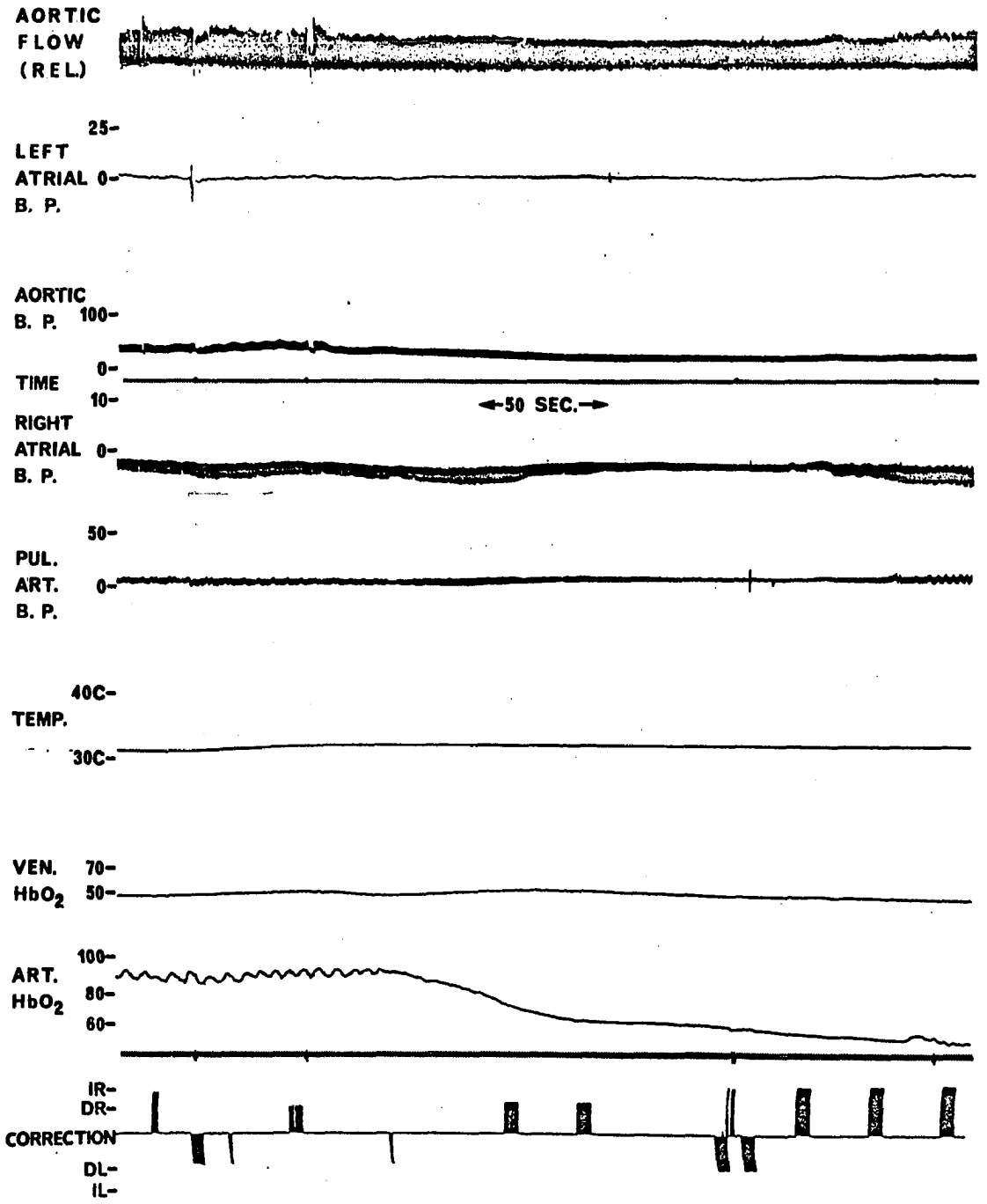

AORTIC
FLOW
(REL.)
25-
LEFT
ATRIAL 0-
B. P.
AORTIC
B. P. 100-
0-
TIME
10-
←50 SEC.→
RIGHT
ATRIAL 0-
B. P.
50-
PUL.
ART. 0-
B. P.
40C-
TEMP.
30C-
VEN. 70-
HbO2 50-
100-
ART.
HbO2 80-
60-
IR-
DR-
CORRECTION
DL-
IL-

Figure 31. A recording during an artificial heart control study in dog 42 which illustrates some marked oscillations in the arterial oxyhemoglobin concentration which are associated with the respirator and shunting of blood. The marked decreases in the arterial oxyhemoglobin concentration indicated by the arrows are associated with manual increases in the inspiratory pressure to 25 or 30 centimeters of water. The paper speed is 1 mm. per second

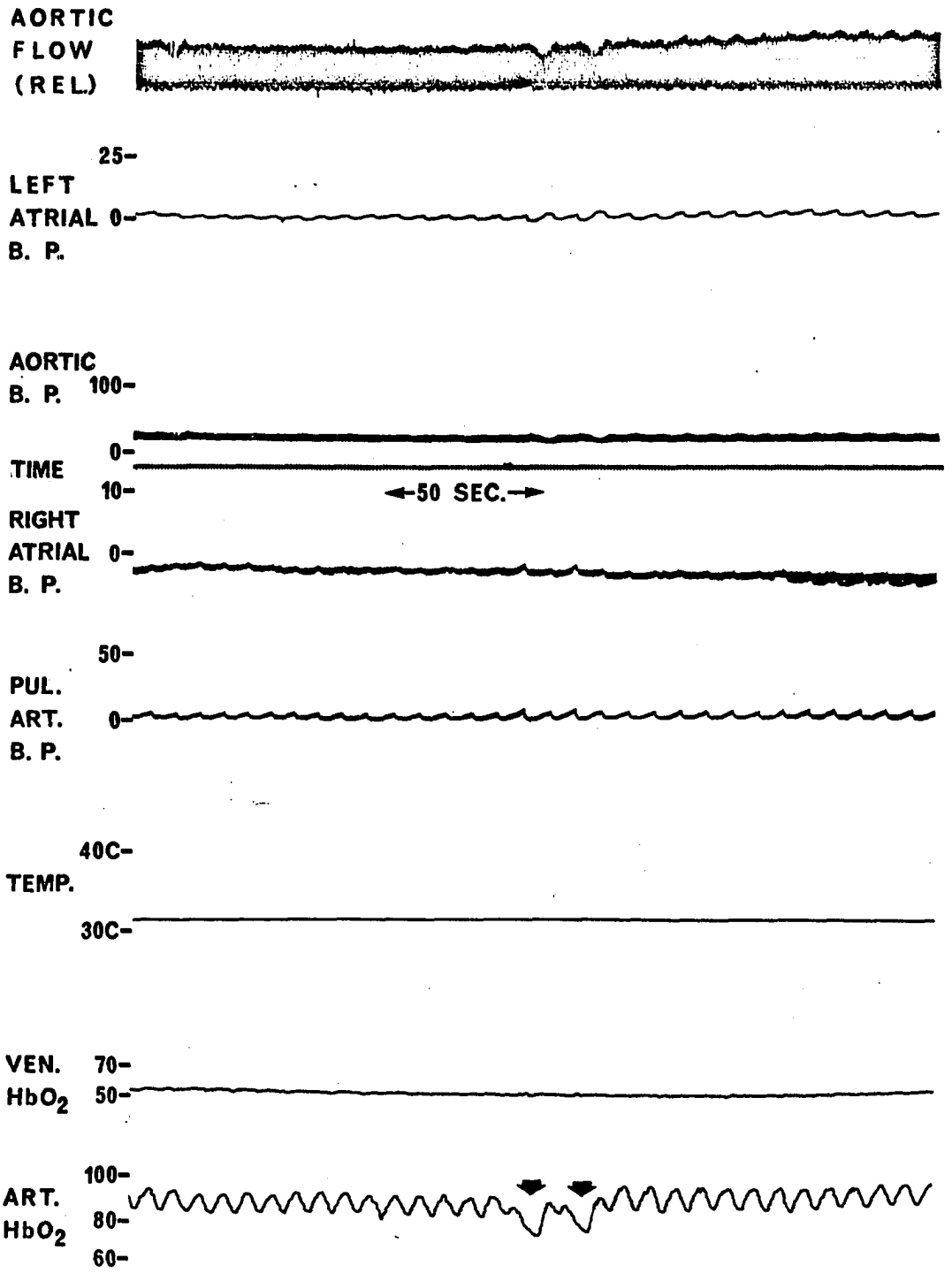

AORTIC
FLOW
(REL.)
25-
LEFT
ATRIAL 0-
B. P.
AORTIC
B. P. 100-
0-
TIME
10-
←50 SEC.→
RIGHT
ATRIAL 0-
B. P.
50-
PUL.
ART. 0-
B. P.
40C-
TEMP.
30C-
VEN. 70-
HbO2 50-
100-
ART.
HbO2 80-
60-

Figure 32. A recording during an artificial heart control study in dog 35 which illustrates control during steady state conditions and the effect of relative blood flow on the venous oxyhemoglobin concentration. The right ventricle is being controlled by venous oxyhemoglobin concentration, the left by atrial pressure. The sampling rate for the right ventricle is 10-5, the left ventricle is permitted to correct continuously. The arrows above and below the time channel represent corrections, respectively, by the right and left ventricles. An arrow pointing up represents an increase in stroke volume. An arrow pointing down represents a decrease in stroke volume. The paper speed is 1 mm. per second

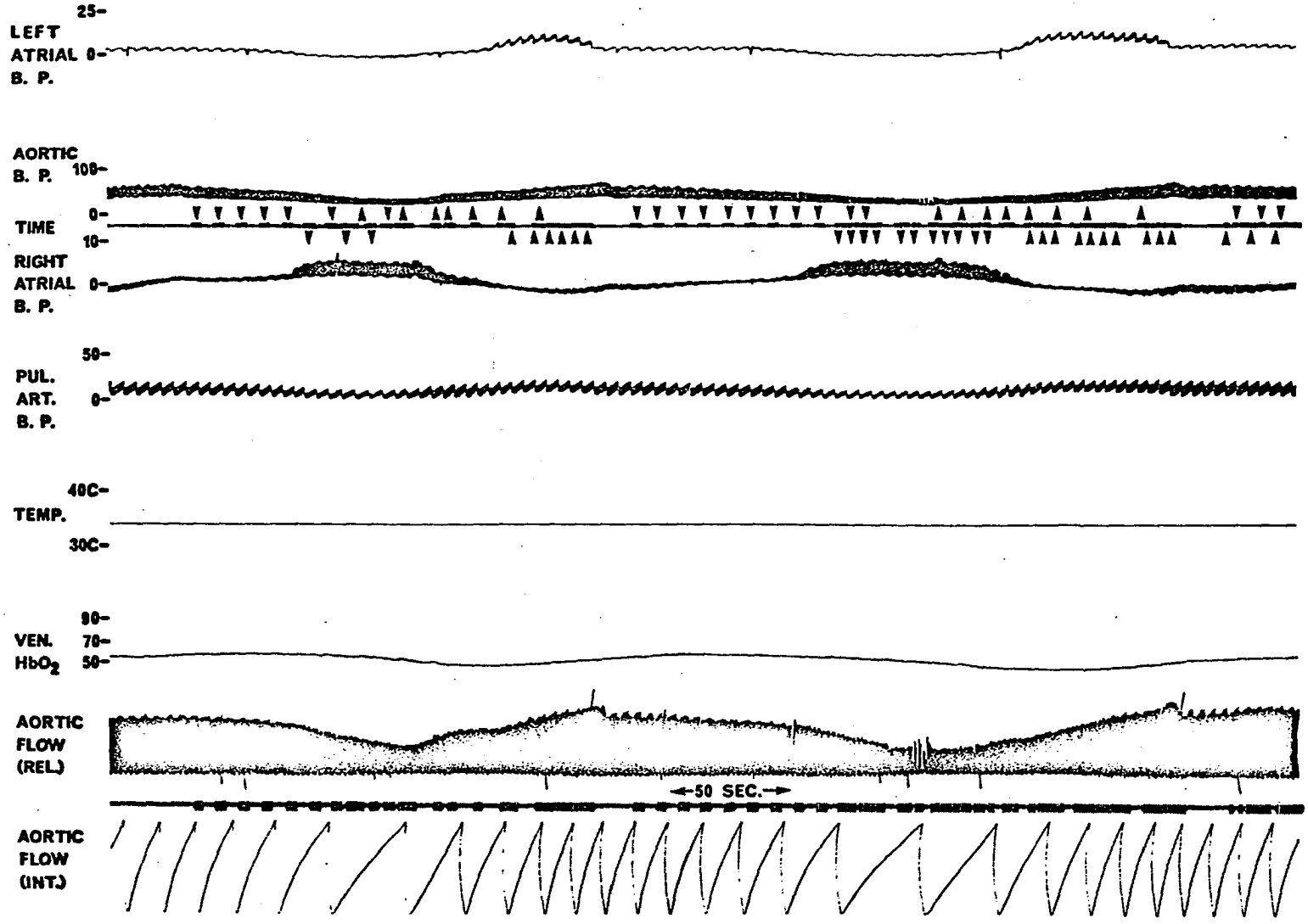

25-
LEFT ATRIAL B. P.
0-
AORTIC B. P.
100-
0-
TIME
10-
RIGHT ATRIAL B. P.
0-
50-
PUL. ART. B. P.
0-
40C-
TEMP.
30C-
90-
VEN. HbO2
70-
50-
AORTIC FLOW (REL)
50 SEC.
AORTIC FLOW (INT.)

Figure 33. A recording during an artificial heart control study in dog 27 which illustrates some oscillations or large fluctuations in the venous oxyhemoglobin concentration which are associated with abrupt decreases in relative blood flow and variable venous mixing. The paper speed is 1 mm. per second

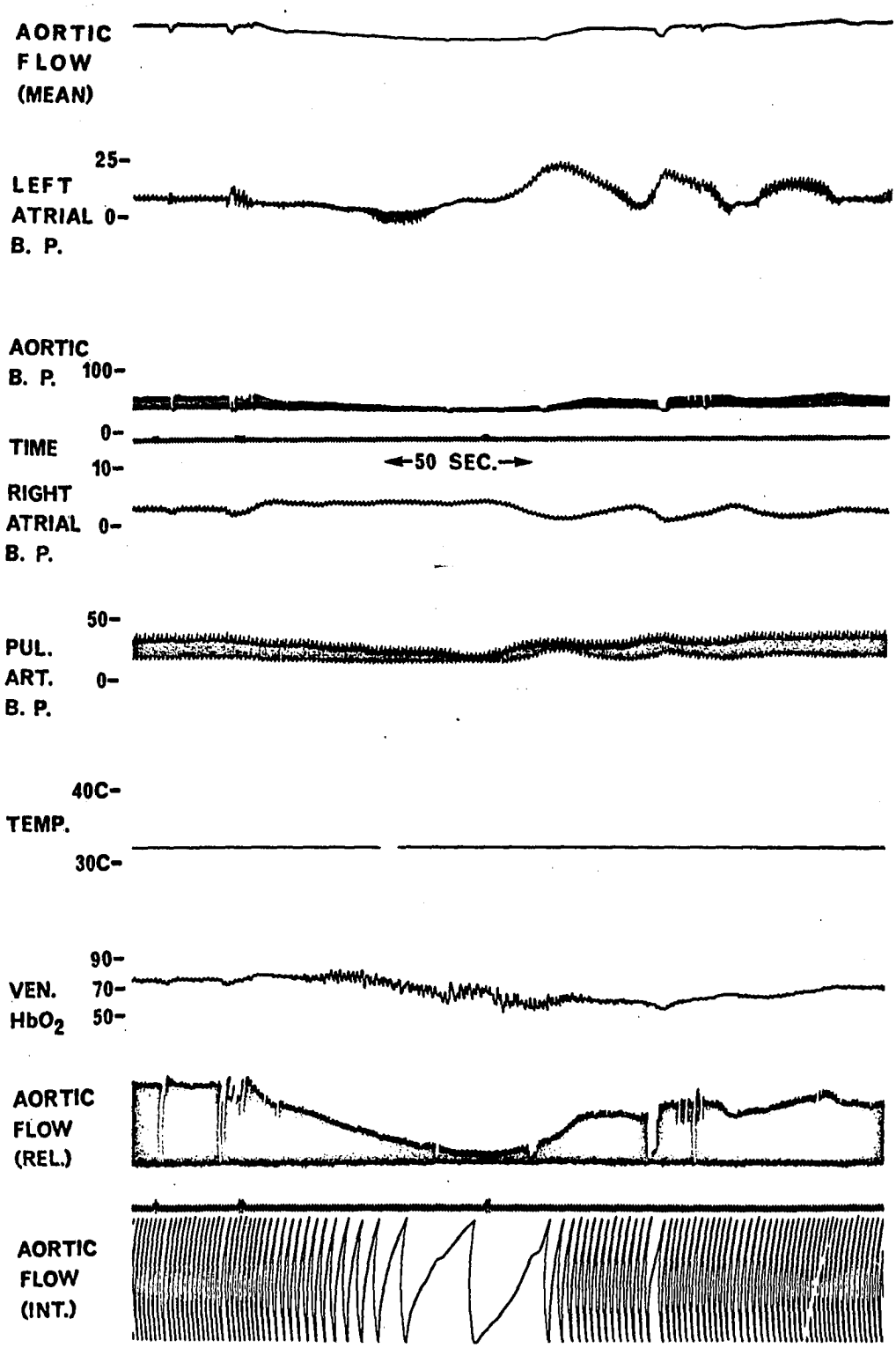

AORTIC FLOW (MEAN)
25-
LEFT ATRIAL 0-
B. P.
AORTIC B. P. 100-
0-
TIME
10-
RIGHT ATRIAL 0-
B. P.
←50 SEC.→
50-
PUL. ART. 0-
B. P.
40C-
TEMP.
30C-
90-
VEN. 70-
HbO_2 50-
AORTIC FLOW (REL.)
AORTIC FLOW (INT.)

Figure 34. Block diagram of a circulatory chemostat (Grodins 21, p. 144)

$(O_2)_A$ - Arterial P_{O_2}

$(O_2)_V$ - Tissue (mixed venous) P_{O_2}

$(CO_2)_A$ - Arterial P_{CO_2}

$(CO_2)_V$ - Tissue (mixed venous) P_{CO_2}

MR - Metabolic rate

Q - Cardiac output

$(O_2)_{V_i}$ - Reference level of tissue (mixed venous) P_{O_2}

$(CO_2)_{V_i}$ - Reference level of tissue (mixed venous) P_{CO_2}

$(O_2)_{V_e}$ - Error level of tissue (mixed venous) P_{O_2}

$(CO_2)_{V_e}$ - Error level of tissue (mixed venous) P_{CO_2}

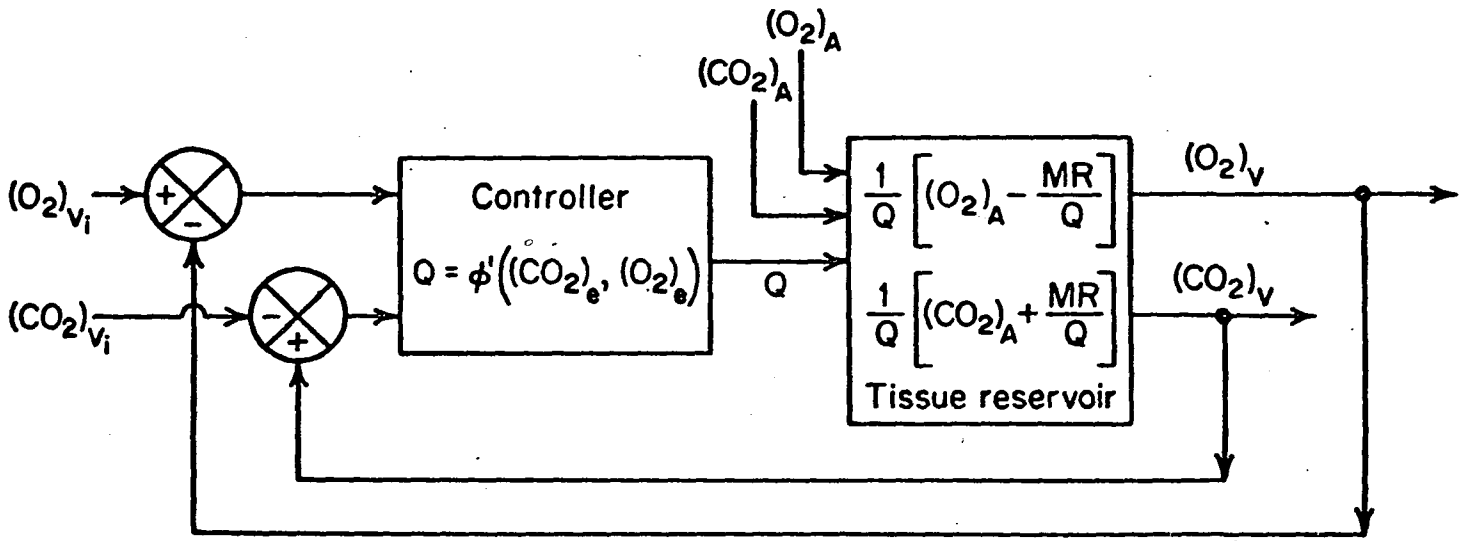

$(O_2)_A$
$(CO_2)_A$
$(O_2)_{V_i}$
$(CO_2)_{V_i}$
Controller
$Q = \phi'\left((CO_2)_e, (O_2)_e\right)$
Q
$\frac{1}{Q}\left[(O_2)_A - \frac{MR}{Q}\right]$
$\frac{1}{Q}\left[(CO_2)_A + \frac{MR}{Q}\right]$
Tissue reservoir
$(O_2)_V$
$(CO_2)_V$

Figure 35. Block diagram to show dependence of P_{AS} on venous composition (Grodins 21, p. 146)

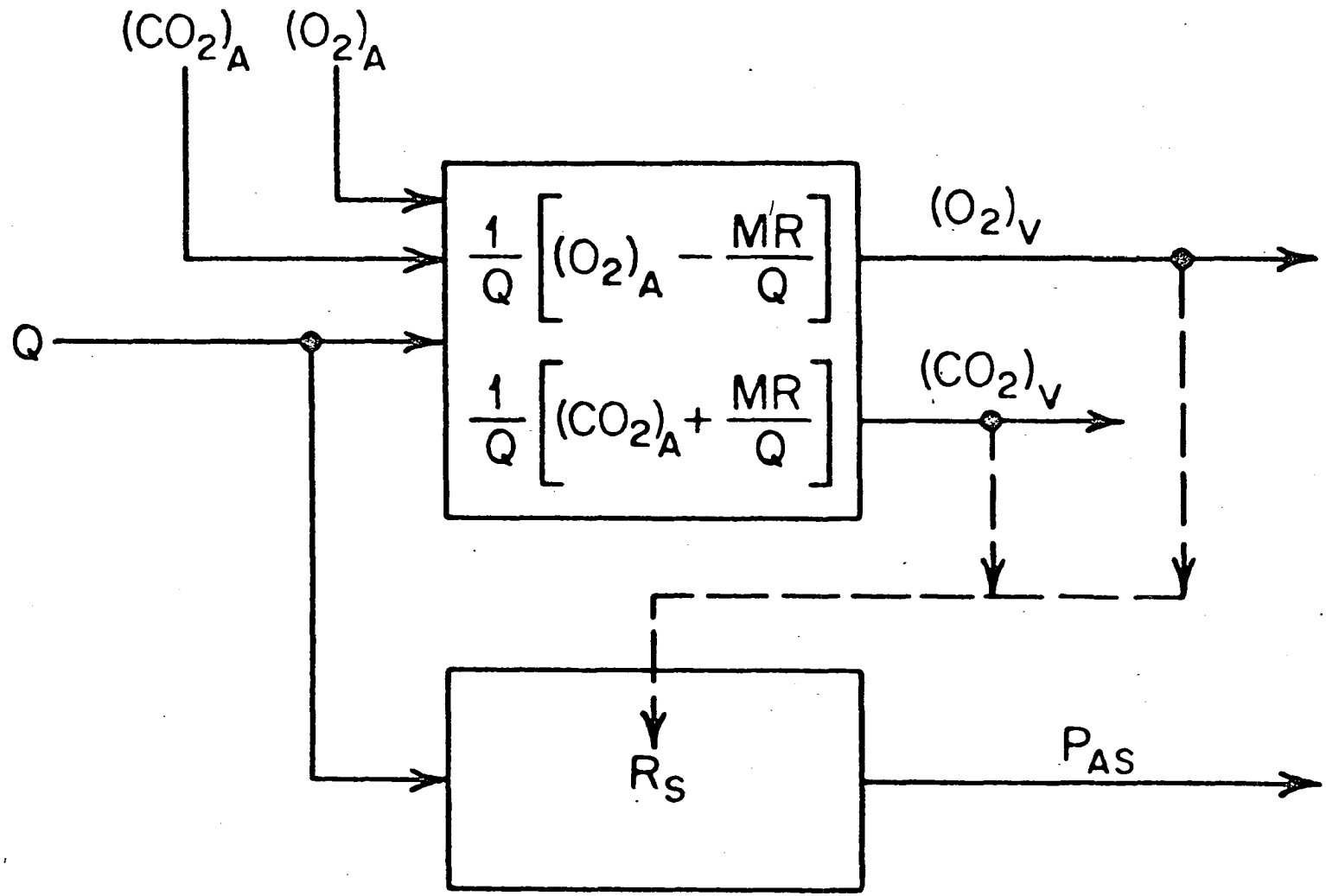

$(CO_2)_A$
$(O_2)_A$
$\frac{1}{Q}\left[(O_2)_A - \frac{MR}{Q}\right]$
$(O_2)_V$
Q
$\frac{1}{Q}\left[(CO_2)_A + \frac{MR}{Q}\right]$
$(CO_2)_V$
R_S
P_{AS}

Figure 36. Isolated controlled system of steady-state cardiovascular chemostat (Grodins 21, p. 148)

F - Blood flow through a particular parallel circuit

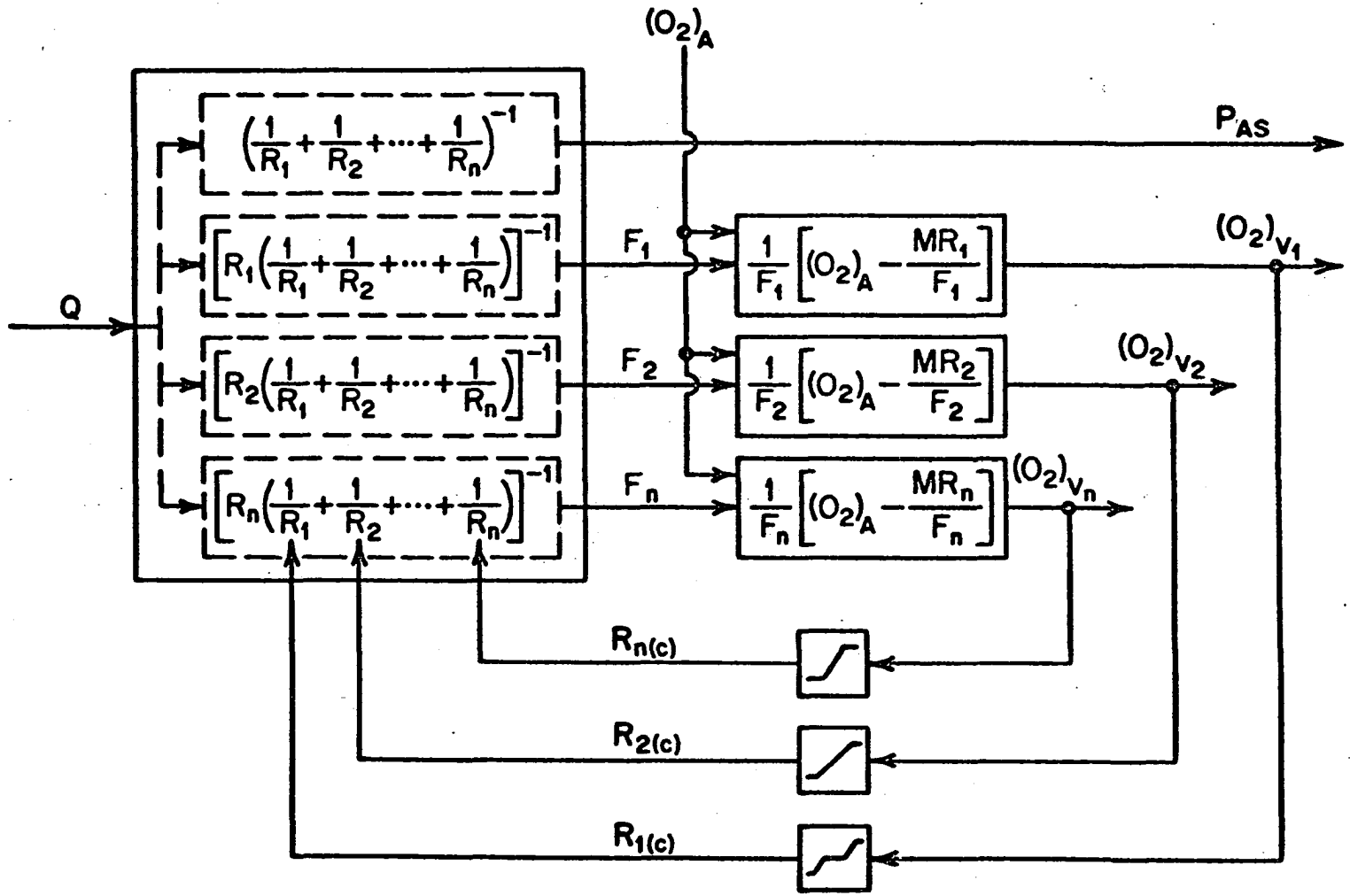

$(O_2)_A$
P_{AS}
$(O_2)_{V_1}$
$(O_2)_{V_2}$
$(O_2)_{V_n}$
Q
F_1
F_2
F_n
$\left(\frac{1}{R_1}+\frac{1}{R_2}+\cdots+\frac{1}{R_n}\right)^{-1}$
$\left[R_1\left(\frac{1}{R_1}+\frac{1}{R_2}+\cdots+\frac{1}{R_n}\right)\right]^{-1}$
$\left[R_2\left(\frac{1}{R_1}+\frac{1}{R_2}+\cdots+\frac{1}{R_n}\right)\right]^{-1}$
$\left[R_n\left(\frac{1}{R_1}+\frac{1}{R_2}+\cdots+\frac{1}{R_n}\right)\right]^{-1}$
$\frac{1}{F_1}\left[(O_2)_A-\frac{MR_1}{F_1}\right]$
$\frac{1}{F_2}\left[(O_2)_A-\frac{MR_2}{F_2}\right]$
$\frac{1}{F_n}\left[(O_2)_A-\frac{MR_n}{F_n}\right]$
$R_{n(c)}$
$R_{2(c)}$
$R_{1(c)}$

Figure 37. Block diagram of the steady-state cardiovascular chemostat (Grodins 21, p. 150)

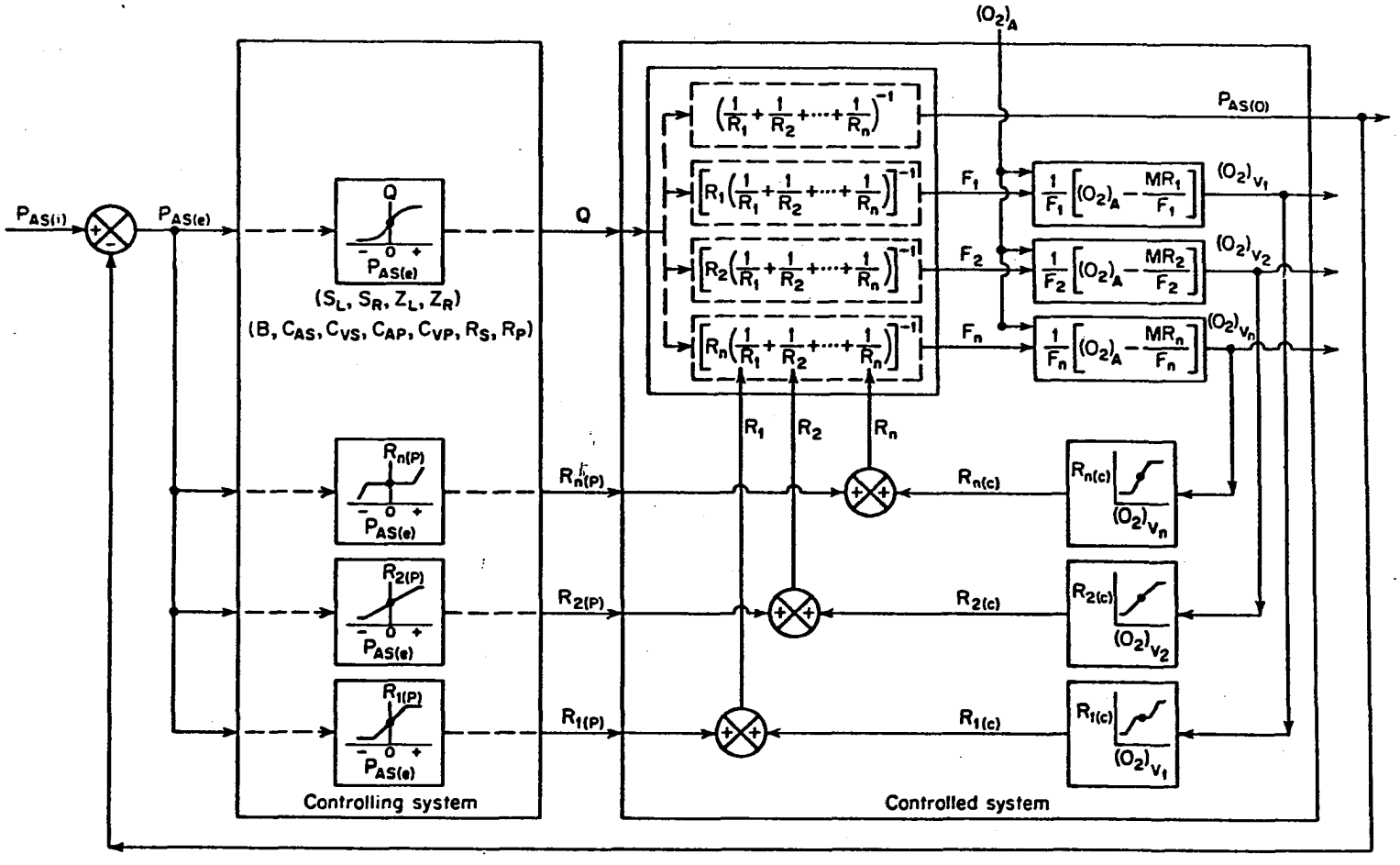

$P_{AS(i)}$
$P_{AS(e)}$
Q
$P_{AS(e)}$
(S_L, S_R, Z_L, Z_R)
$(B, C_{AS}, C_{VS}, C_{AP}, C_{VP}, R_S, R_P)$
$R_{n(P)}$
$R_{2(P)}$
$R_{1(P)}$
Controlling system
$(O_2)_A$
$P_{AS(O)}$
$\left(\frac{1}{R_1}+\frac{1}{R_2}+\cdots+\frac{1}{R_n}\right)^{-1}$
$\left[R_1\left(\frac{1}{R_1}+\frac{1}{R_2}+\cdots+\frac{1}{R_n}\right)\right]^{-1}$
$\left[R_2\left(\frac{1}{R_1}+\frac{1}{R_2}+\cdots+\frac{1}{R_n}\right)\right]^{-1}$
$\left[R_n\left(\frac{1}{R_1}+\frac{1}{R_2}+\cdots+\frac{1}{R_n}\right)\right]^{-1}$
F_1
F_2
F_n
$\frac{1}{F_1}\left[(O_2)_A-\frac{MR_1}{F_1}\right]$
$\frac{1}{F_2}\left[(O_2)_A-\frac{MR_2}{F_2}\right]$
$\frac{1}{F_n}\left[(O_2)_A-\frac{MR_n}{F_n}\right]$
$(O_2)_{V_1}$
$(O_2)_{V_2}$
$(O_2)_{V_n}$
R_1
R_2
R_n
$R_{n(c)}$
$R_{2(c)}$
$R_{1(c)}$
Controlled system

Figure 38. Circuit design for amplification of the signal from the reflection oximetry system

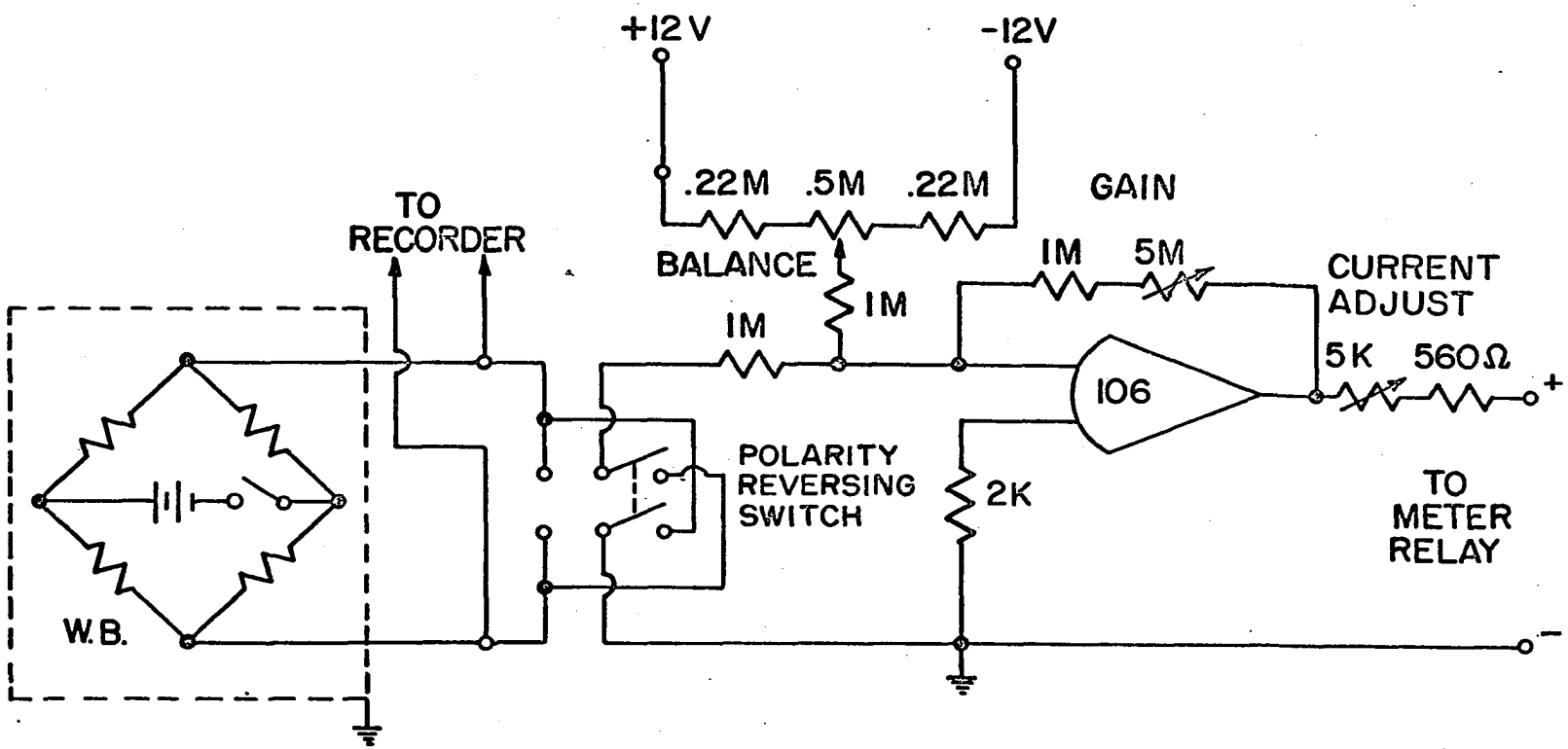

+12V
-12V
.22M
.5M
.22M
GAIN
TO
RECORDER
BALANCE
IM
IM
IM
5M
CURRENT
ADJUST
5K
560Ω
106
+
POLARITY
REVERSING
SWITCH
2K
TO
METER
RELAY
W.B.
-

Figure 39. Block diagram of a cardiovascular control system for an artificial heart which uses venous oxyhemoglobin concentration to control ventricular output

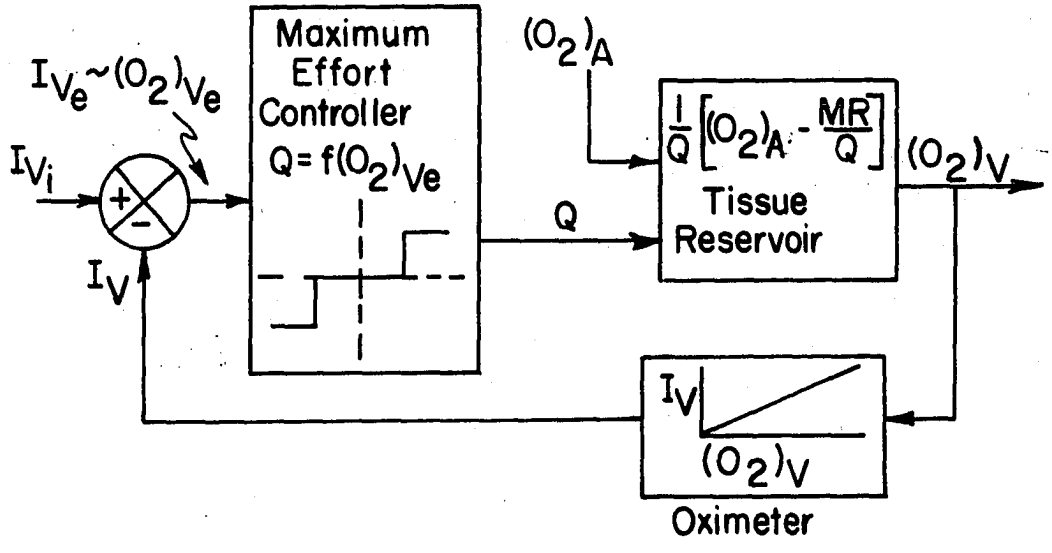

Maximum
Effort
Controller
$Q = f(O_2)_{Ve}$
$I_{Ve} \sim (O_2)_{Ve}$
I_{Vi}
I_V
+
−
$(O_2)_A$
$\frac{I}{Q}\left[(O_2)_A - \frac{MR}{Q}\right]$
Tissue
Reservoir
Q
$(O_2)_V$
I_V
$(O_2)_V$
Oximeter

Figure 40. Block diagram of a cardiovascular control system which uses venous oxyhemoglobin concentration to control the output of the right ventricle and left atrial pressure to control the output of the left ventricle

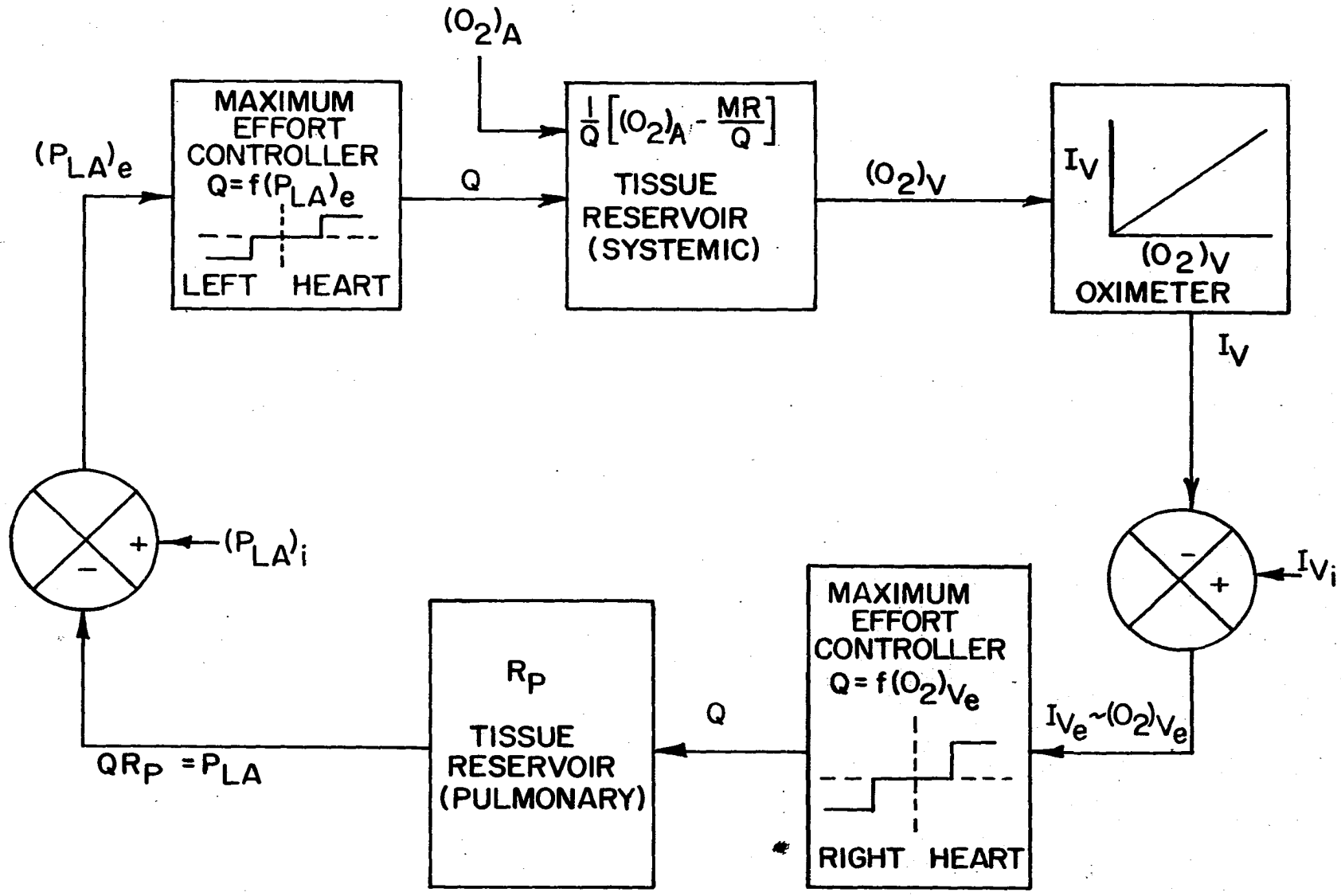

$(O_2)_A$
MAXIMUM EFFORT CONTROLLER $Q = f(P_{LA})_e$
LEFT HEART
$(P_{LA})_e$
Q
$\frac{1}{Q}\left[(O_2)_A - \frac{MR}{Q}\right]$
TISSUE RESERVOIR (SYSTEMIC)
$(O_2)_V$
I_V
$(O_2)_V$
OXIMETER
I_V
I_{V_i}
$(P_{LA})_i$
R_P
TISSUE RESERVOIR (PULMONARY)
$QR_P = P_{LA}$
Q
MAXIMUM EFFORT CONTROLLER $Q = f(O_2)_{V_e}$
RIGHT HEART
$I_{V_e} \sim (O_2)_{V_e}$

Figure 41. Block diagram of a cardiovascular control system for an artificial heart which uses the arterio-venous difference in oxyhemoglobin concentration to control ventricular output

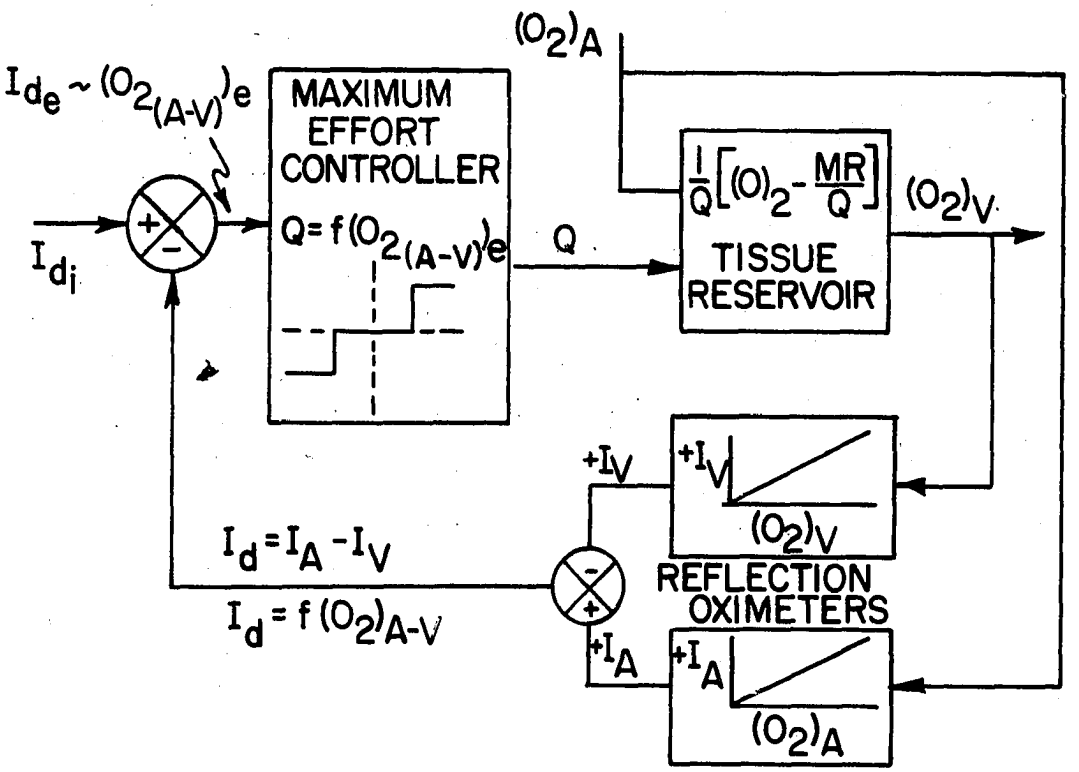

$(O_2)_A$
$I_{d_e} \sim (O_{2(A-V)})_e$
MAXIMUM EFFORT CONTROLLER
$Q = f(O_{2(A-V)})_e$
I_{d_i}
Q
$\frac{1}{Q}\left[(O)_2 - \frac{MR}{Q}\right]$
TISSUE RESERVOIR
$(O_2)_V$
$+I_V$
$+I_V$
$(O_2)_V$
$I_d = I_A - I_V$
$I_d = f(O_2)_{A-V}$
REFLECTION OXIMETERS
$+I_A$
$+I_A$
$(O_2)_A$

Figure 42. Block diagram of a cardiovascular control system for an artificial heart which uses the arteriovenous difference in oxyhemoglobin concentration to control the output of the right ventricle and left atrial pressure to control the output of the left ventricle

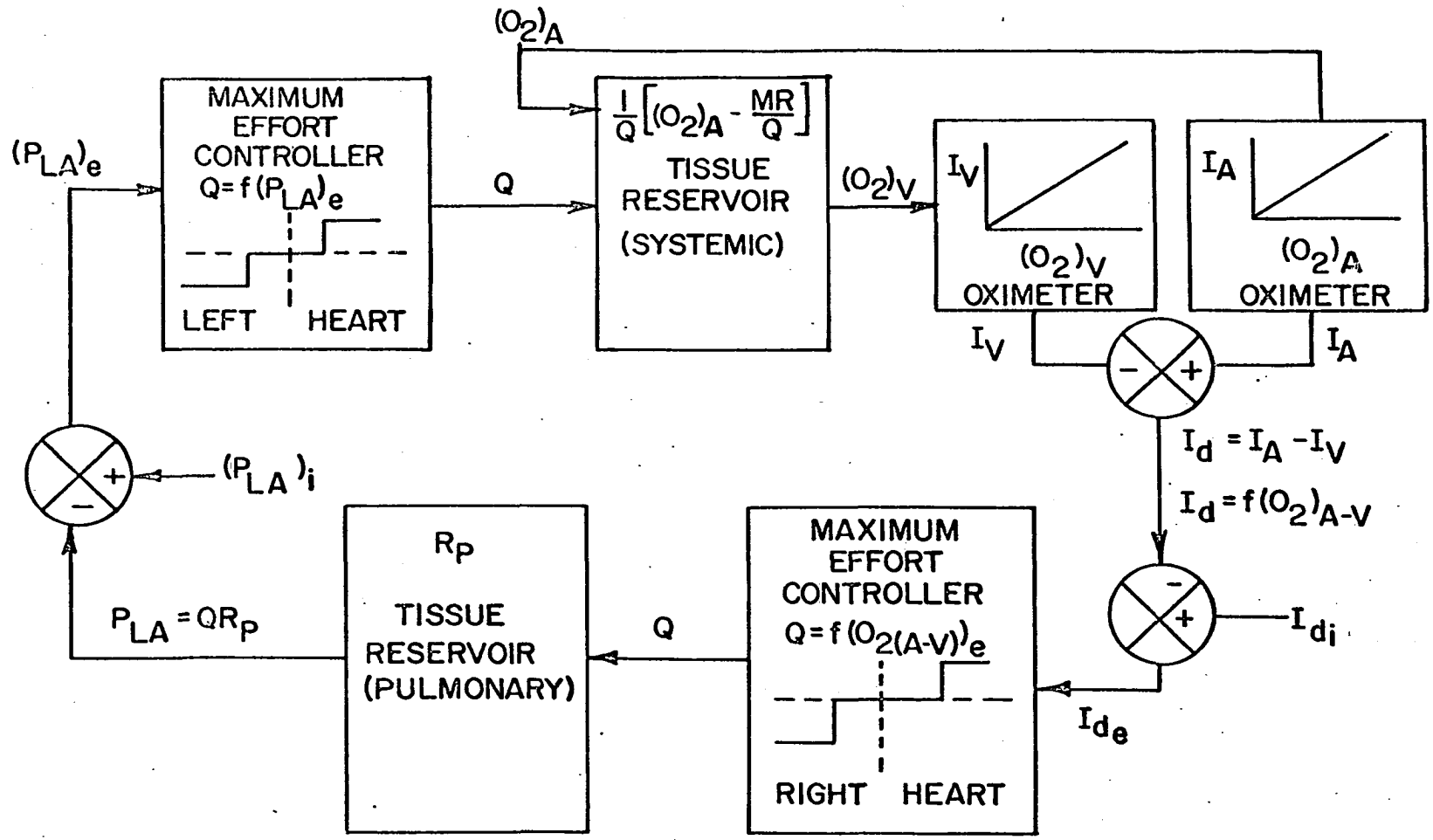

$(O_2)_A$
MAXIMUM EFFORT CONTROLLER
$Q = f(P_{LA})_e$
LEFT HEART
$(P_{LA})_e$
Q
$\frac{1}{Q}\left[(O_2)_A - \frac{MR}{Q}\right]$
TISSUE RESERVOIR (SYSTEMIC)
$(O_2)_V$
I_V
$(O_2)_V$ OXIMETER
I_A
$(O_2)_A$ OXIMETER
I_V
I_A
$I_d = I_A - I_V$
$I_d = f(O_2)_{A-V}$
I_{di}
I_{de}
MAXIMUM EFFORT CONTROLLER
$Q = f(O_{2(A-V)})_e$
RIGHT HEART
Q
R_P
TISSUE RESERVOIR (PULMONARY)
$P_{LA} = QR_P$
$(P_{LA})_i$

Figure 43. Block diagram to show the dependence of P_{AS} on venous composition and how venous oxyhemoglobin concentration provides this control for an artificial heart

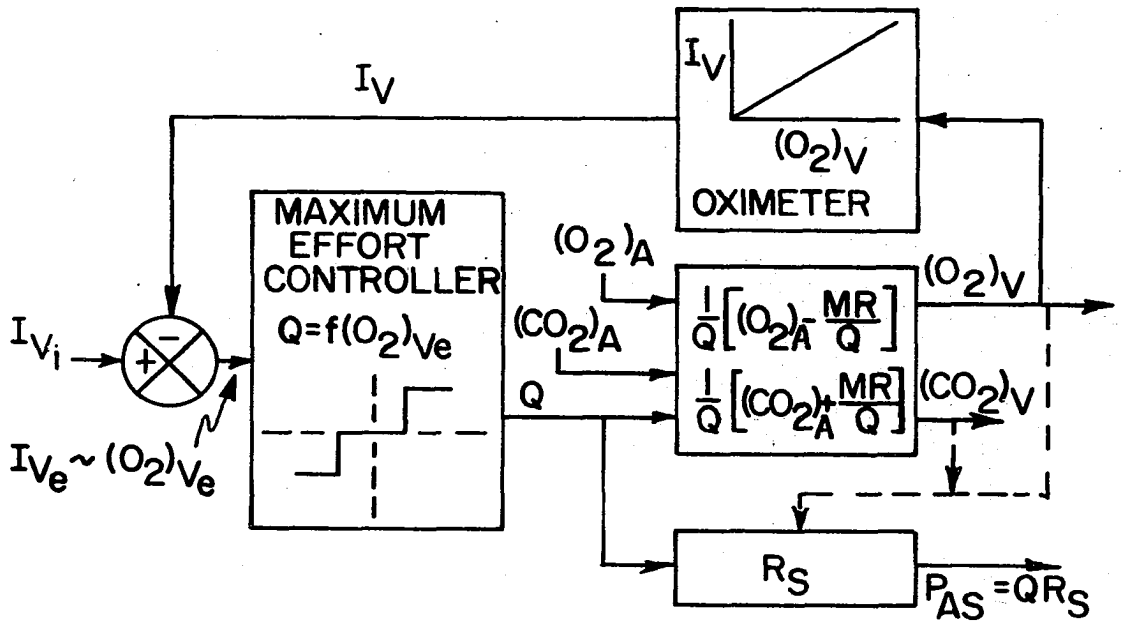
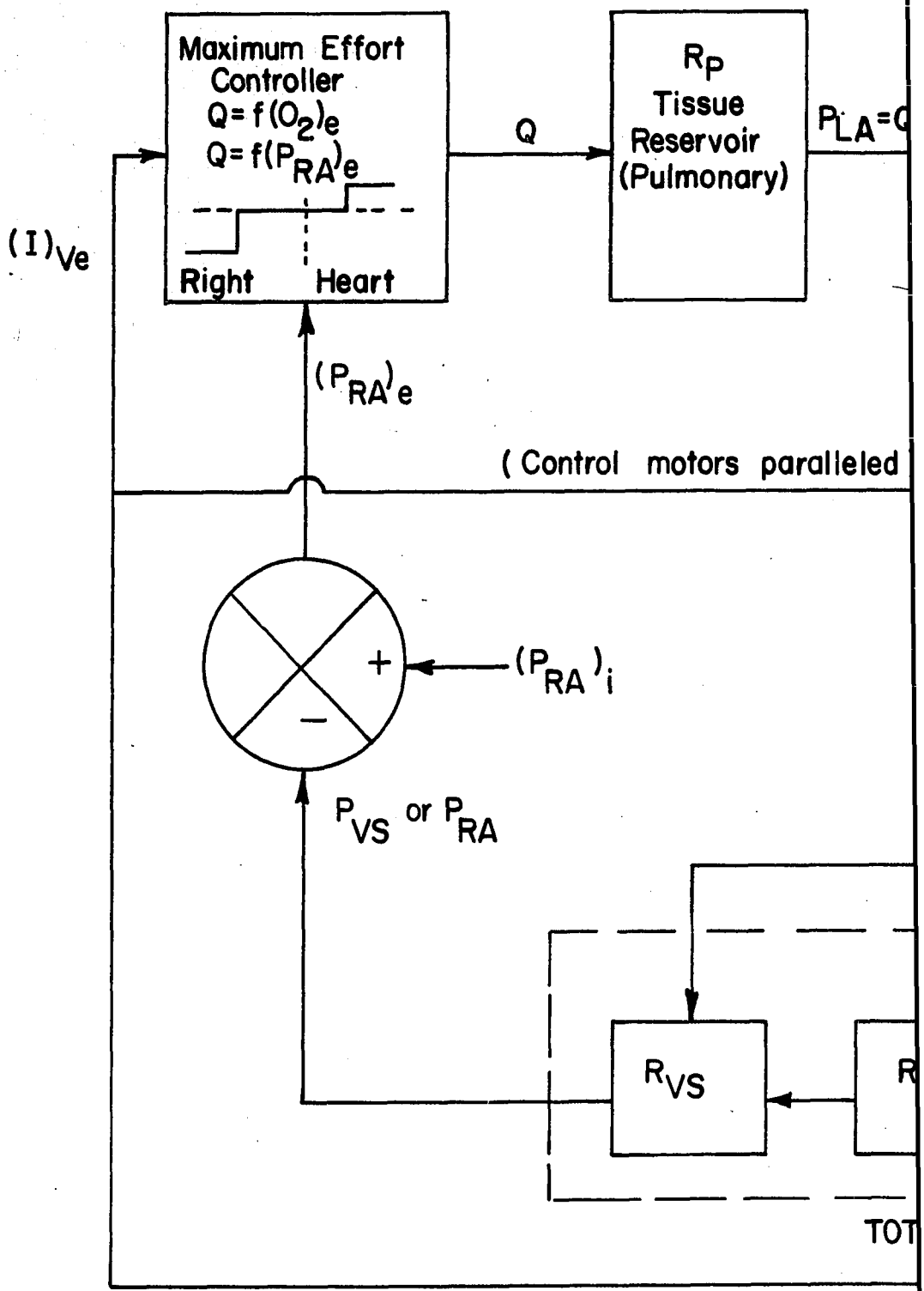
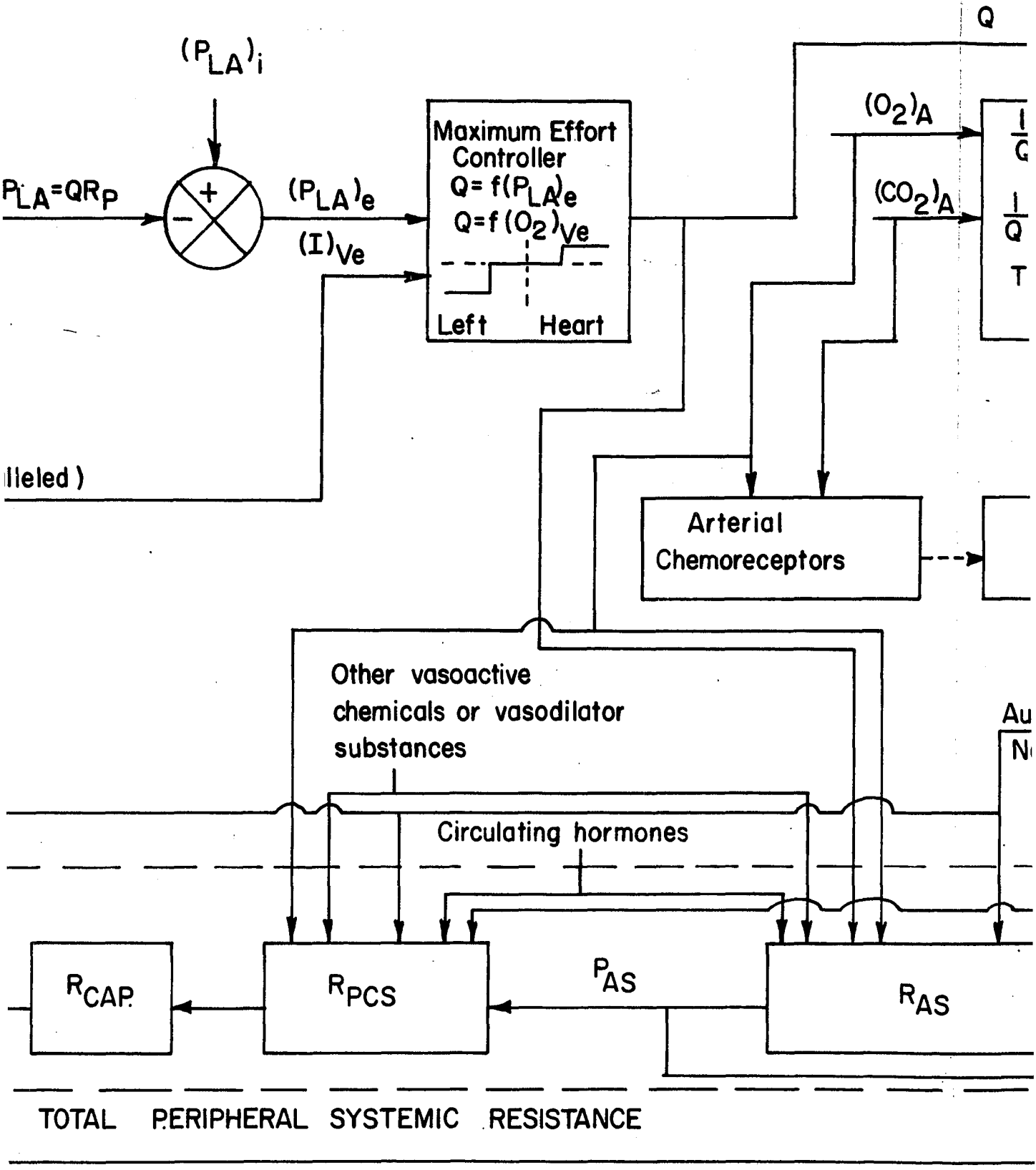

I_V
I_V
$(O_2)_V$
OXIMETER
MAXIMUM
EFFORT
CONTROLLER
$Q=f(O_2)_{Ve}$
$(O_2)_A$
$(CO_2)_A$
Q
$\frac{1}{Q}\left[(O_2)_A-\frac{MR}{Q}\right]$
$\frac{1}{Q}\left[(CO_2)_A+\frac{MR}{Q}\right]$
$(O_2)_V$
$(CO_2)_V$
I_{V_i}
$I_{V_e}\sim(O_2)_{V_e}$
R_S
$P_{AS}=QR_S$

Figure 44. Block diagram which shows the mechanisms which may affect the ventricular output of an artificial heart

P_{RA} - Right atrial pressure

P_{LA} - Left atrial pressure


Maximum Effort Controller
$Q = f(O_2)_e$
$Q = f(P_{RA})_e$
Right Heart
Q
R_P Tissue Reservoir (Pulmonary)
P_{LA}=Q
$(I)_{Ve}$
$(P_{RA})_e$
(Control motors paralleled
+
−
$(P_{RA})_i$
P_{VS} or P_{RA}
R_{VS}
R
TOT


Q
$(P_{LA})_i$
$P_{LA}=QR_P$
+
−
$(P_{LA})_e$
$(I)_{Ve}$
Maximum Effort Controller
$Q= f(P_{LA})_e$
$Q=f(O_2)_{Ve}$
Left Heart
$(O_2)_A$
$(CO_2)_A$
I/Q
I/Q
T
lleled)
Arterial Chemoreceptors
Other vasoactive chemicals or vasodilator substances
Au
N
Circulating hormones
$R_{CAP.}$
R_{PCS}
P_{AS}
R_{AS}
TOTAL PERIPHERAL SYSTEMIC RESISTANCE

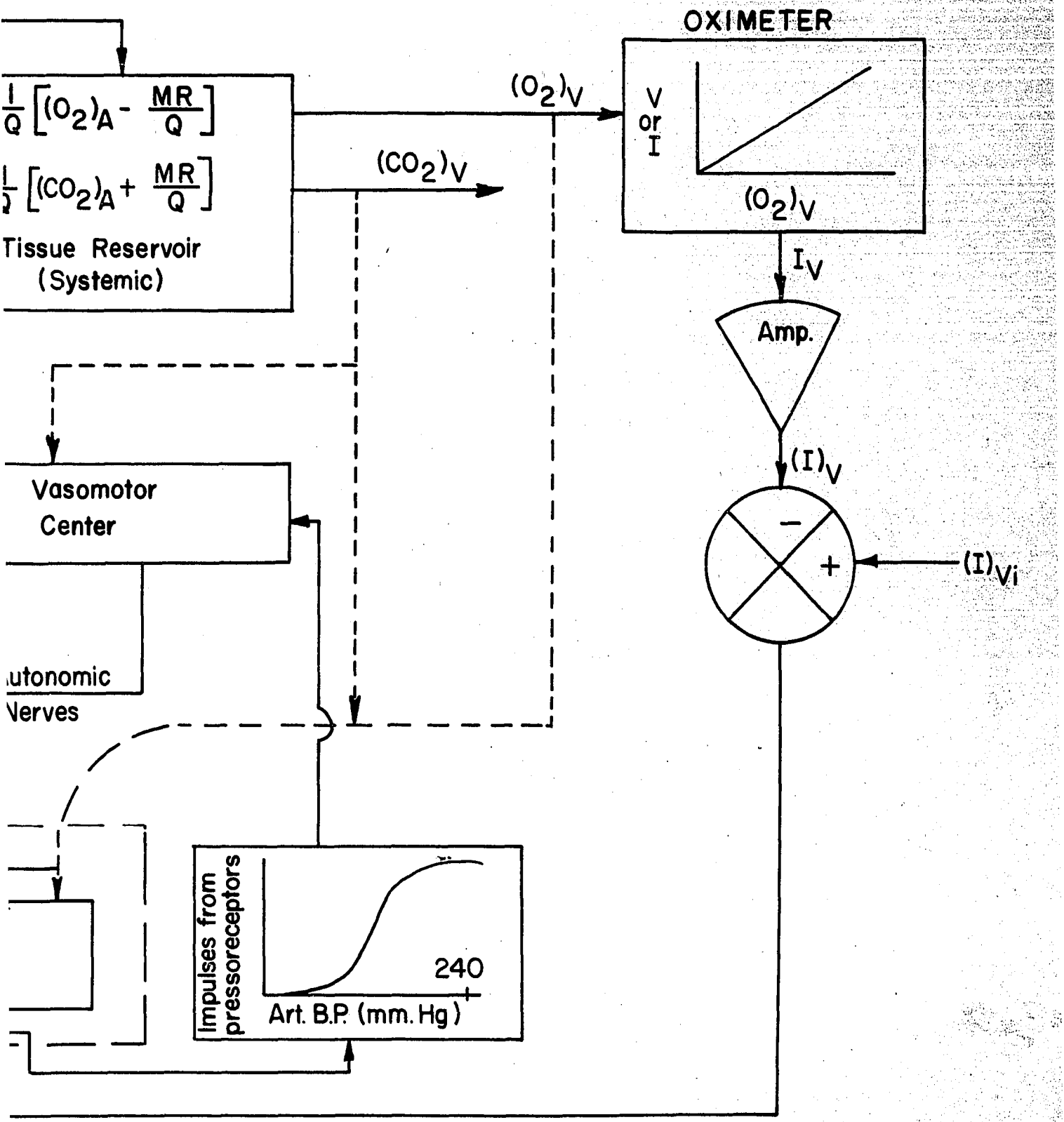

OXIMETER
$\frac{1}{Q}\left[(O_2)_A - \frac{MR}{Q}\right]$
$\frac{1}{Q}\left[(CO_2)_A + \frac{MR}{Q}\right]$
Tissue Reservoir
(Systemic)
$(O_2)_V$
$(CO_2)_V$
V
or
I
$(O_2)_V$
I_V
Amp.
$(I)_V$
Vasomotor
Center
−
+
$(I)_{Vi}$
utonomic
Nerves
Impulses from
pressoreceptors
240
Art. B.P. (mm. Hg)

Figure 45. A recording during an artificial heart control study in dog 28 which illustrates control under steady state conditions. The right ventricle is being controlled by the venous oxyhemoglobin concentration. The left ventricle is being operated manually. The sampling rate for the right ventricle is 15-5; it is permitted to correct every 15 seconds with a maximum correction period of 5 seconds. The arrows above the time channel which point up and down represent, respectively, increases and decreases in stroke volume by the right ventricle. The paper speed is 1 mm. per second

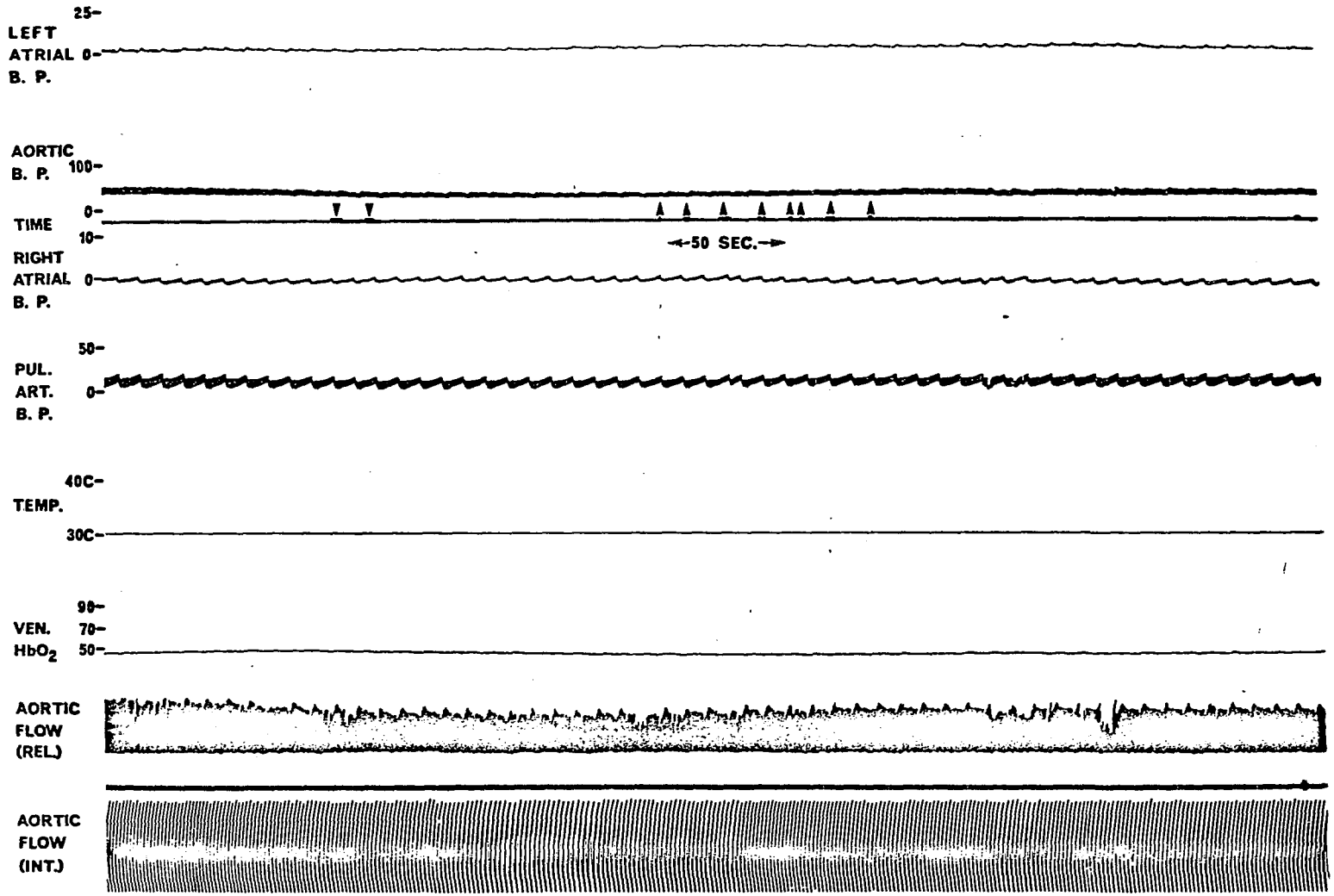

25-
LEFT
ATRIAL 0-
B. P.
AORTIC
B. P. 100-
0-
TIME
10-
RIGHT
ATRIAL 0
B. P.
50-
PUL.
ART. 0-
B. P.
40C-
TEMP.
30C-
90-
VEN. 70-
HbO2 50-
AORTIC
FLOW
(REL.)
AORTIC
FLOW
(INT.)
-50 SEC.-

Figure 46. A recording during an artificial heart control study in dog 41 which illustrates the effect of perturbing the system by hyperthermia while the arterial oxyhemoglobin concentration is decreasing. The right ventricle is being controlled by venous oxyhemoglobin concentration, the left ventricle by left atrial pressure. The sampling rate is 30-5 for the right, 10-5 for the left. The arrows pointing up represent initiation and termination of hyperthermia. The paper speed is 1 mm. per second

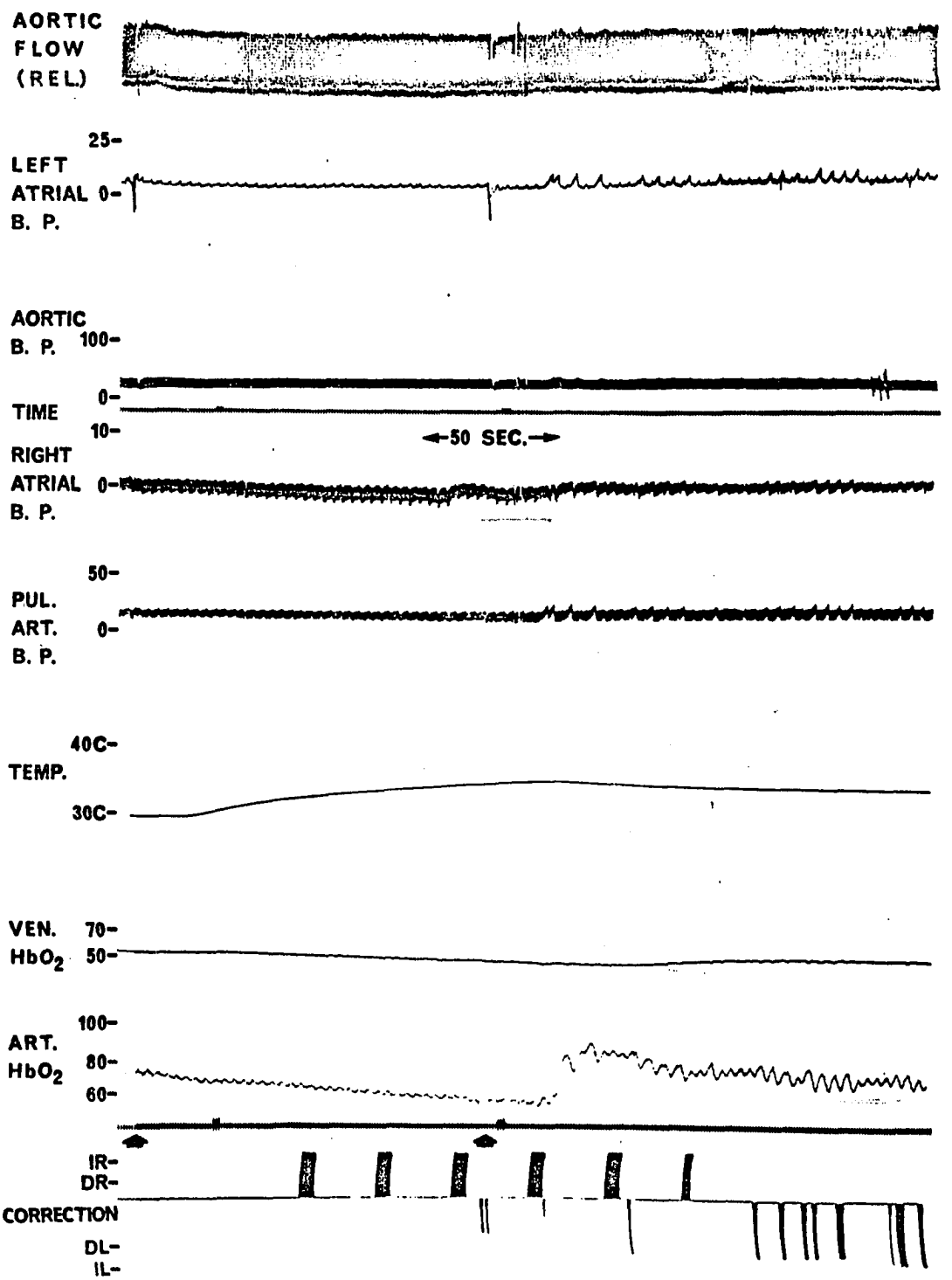

AORTIC FLOW (REL.)
25-
LEFT ATRIAL 0-
B. P.
AORTIC B. P. 100-
0-
TIME
10-
RIGHT ATRIAL 0-
B. P.
←50 SEC.→
50-
PUL. ART. 0-
B. P.
40C-
TEMP.
30C-
VEN. 70-
HbO_2 50-
100-
ART. 80-
HbO_2 60-
IR-
DR-
CORRECTION
DL-
IL-

Figure 47. A recording during an artificial heart control study in dog 36 which illustrates the effect of perturbing the system by changing the inspired gas mixture from 100 per cent to 15 per cent oxygen (large arrow pointing up). The right ventricle is being controlled by venous oxyhemoglobin concentration, the left by left atrial pressure. The sampling rate is 30-5 for the right, 10-5 for the left. The paper speed is 1 mm. per second

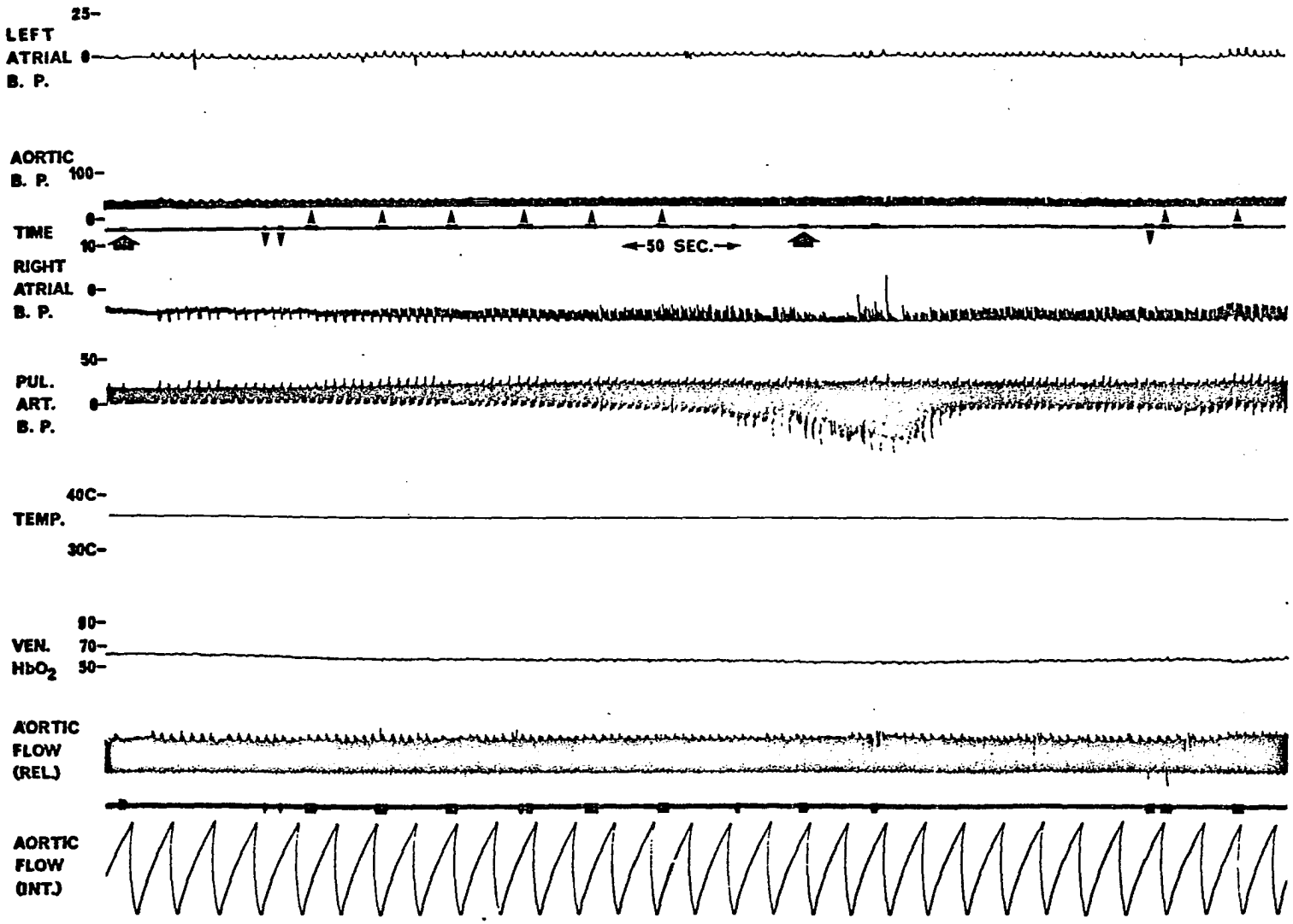

25–
LEFT
ATRIAL 0–
B. P.
AORTIC
B. P. 100–
0–
TIME
10–
50 SEC.
RIGHT
ATRIAL 0–
B. P.
50–
PUL.
ART. 0–
B. P.
40C–
TEMP.
30C–
90–
VEN. 70–
HbO2 50–
AORTIC
FLOW
(REL.)
AORTIC
FLOW
(INT.)

Figure 48. A recording during an artificial heart control study in dog 36 which illustrates the effect of perturbing the system by changing the inspired gas mixture from 15 per cent oxygen to 100 per cent oxygen (large arrow pointing up). The right ventricle is being controlled by venous oxyhemoglobin concentration, the left by left atrial pressure. The sampling rate is 30-5 for the right, 10-5 for the left. The paper speed is 1 mm. per second

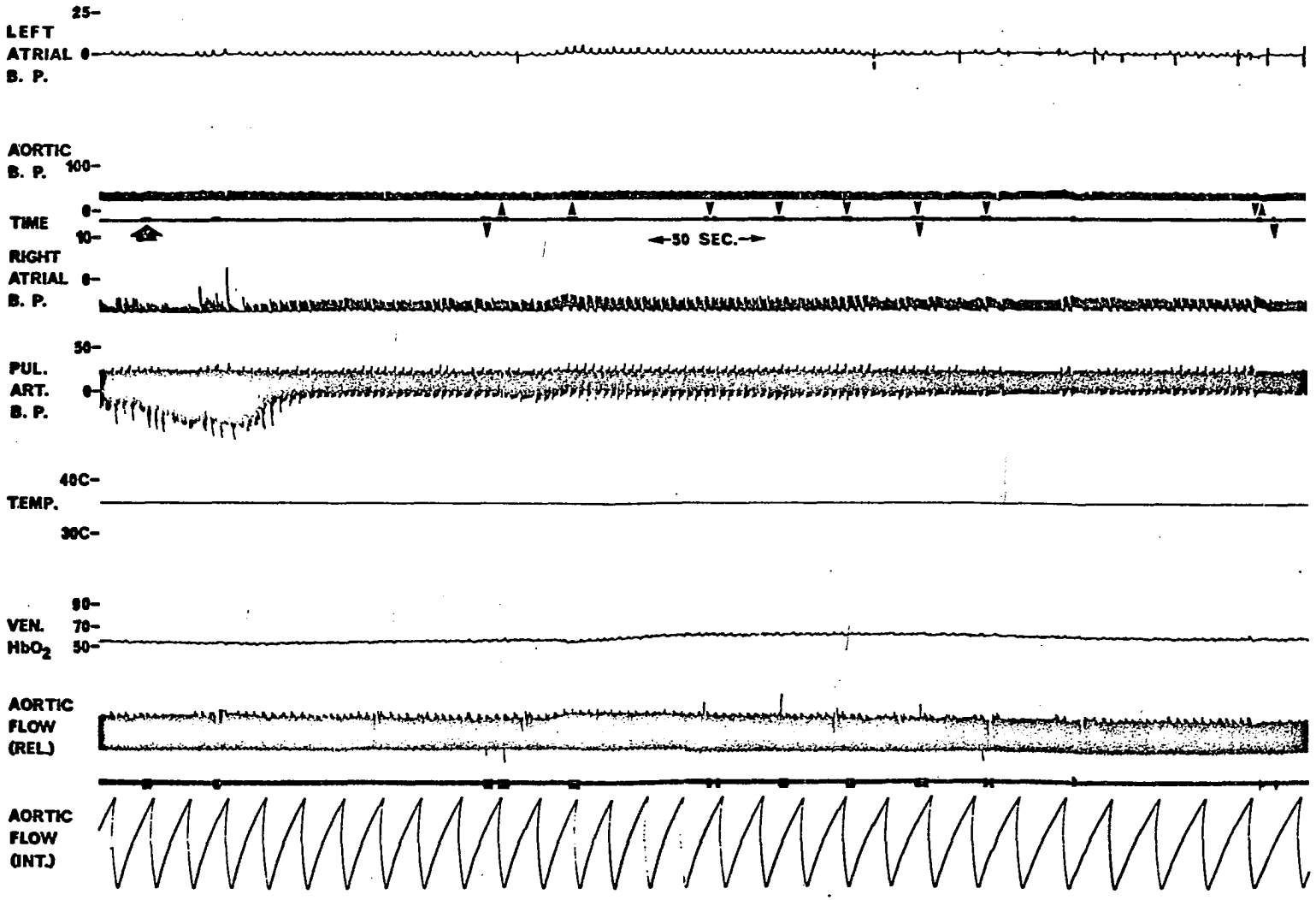
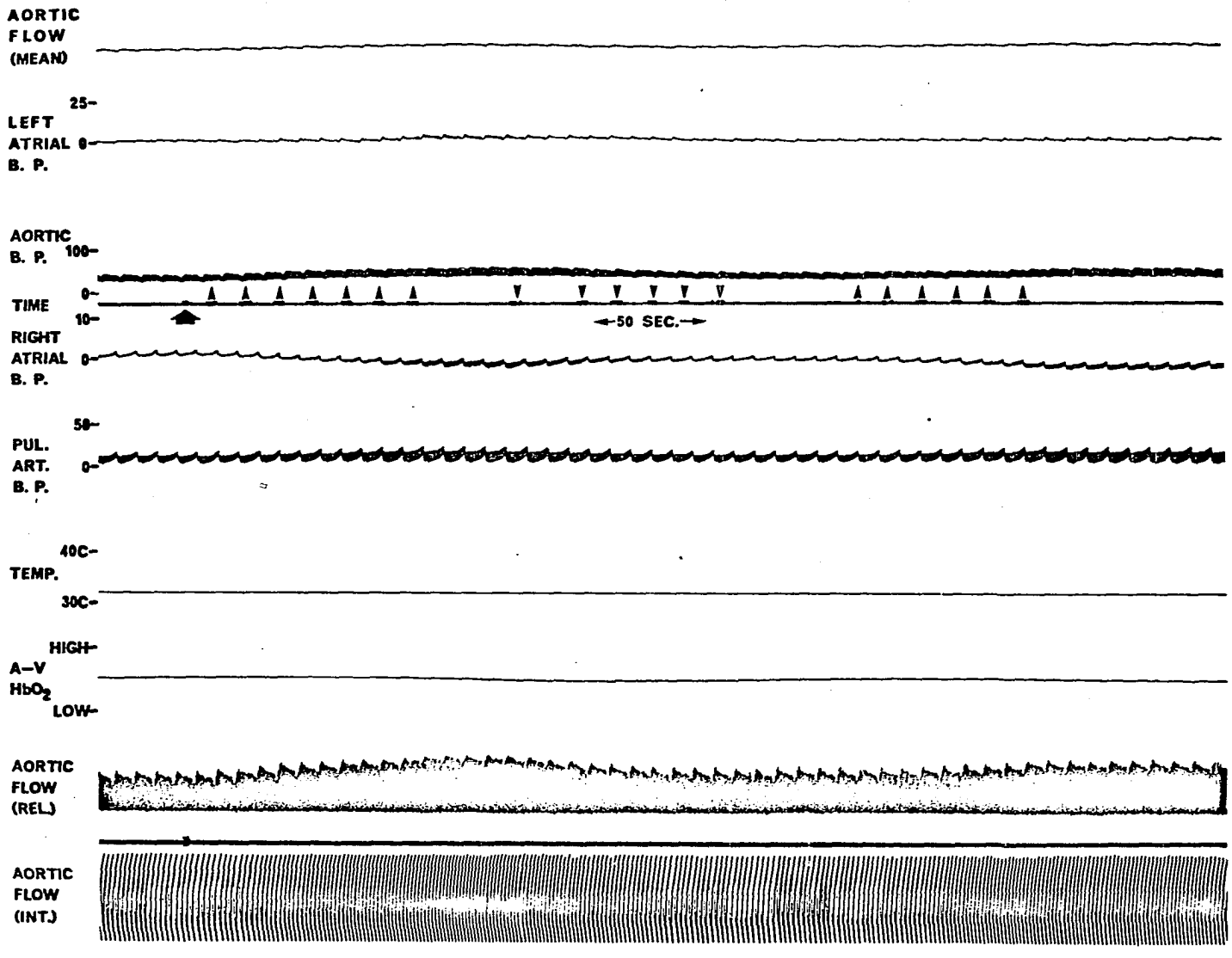

25-
LEFT
ATRIAL 0-
B. P.
AORTIC
B. P. 100-
0-
TIME
10-
50 SEC.
RIGHT
ATRIAL 0-
B. P.
50-
PUL.
ART. 0-
B. P.
40C-
TEMP.
30C-
90-
VEN. 70-
HbO2 50-
AORTIC
FLOW
(REL)
AORTIC
FLOW
(INT.)

Figure 49. A recording during an artificial heart control study in dog 28 which illustrates the effect of perturbing the system by changing the limits or reference zone controlling the right ventricle. The right ventricle is being controlled by the arteriovenous difference in oxyhemoglobin concentration. The left ventricle is being operated manually. The large arrow which points up indicates the point at which the limits were moved to a smaller arteriovenous difference in oxyhemoglobin concentration. The sampling rate for the right ventricle is 15-5. The paper speed is 1 mm. per second


AORTIC
FLOW
(MEAN)
25-
LEFT
ATRIAL 0-
B. P.
AORTIC
B. P. 100-
0-
TIME
10-
50 SEC.
RIGHT
ATRIAL 0-
B. P.
50-
PUL.
ART. 0-
B. P.
40C-
TEMP.
30C-
HIGH-
A-V
HbO2
LOW-
AORTIC
FLOW
(REL.)
AORTIC
FLOW
(INT.)