Special Instrumentation Problems Encountered in Physiological Research Concerning the Heart and Circulation in Man[1]

Earl H. Wood

Section on Physiology, Mayo Foundation, University of Minnesota, and *Mayo Clinic, Rochester*

THE FUNCTION OF THE HEART is to maintain an adequate flow of blood through the lungs and to the body. A quantitative study of this function therefore requires physical measurements of such variables as pressure, volume, velocity of flow, volume of flow, and others. For the most part, measurement of physiologic variables concerned in the heart and circulation of man requires that these determinations be carried out on intact unanesthetized human beings. Therefore, direct measurements of many of the variables must commonly be made through small needles or long, narrow-bore, flexible tubes. Since variables such as blood pressure have both static and dynamic components, their high-fidelity recording under such circumstances requires close attention to the frequency and damping characteristics of the instruments used. Adequate instrumentation must be capable of faithful reproduction of both the static component and all dynamic components of a magnitude to be of practical importance.

The highest frequencies of the dynamic components of practically important magnitudes in a complex wave form, such as an arterial pressure pulse or the action potential complex of the heart muscle (electrocardiogram), are not accurately known. It is generally considered, however, that instruments with a uniform dynamic sensitivity to the tenth harmonic of the fundamental frequency of such complex wave forms are suitable for high-fidelity recording of the wave concerned. By this criterion, since the heart rate of human beings seldom exceeds 240 beats per minute, an instrument with a uniform sensitivity from 0 to 40 cycles per second should be adequate for the recording of arterial blood pressure and most other physiologic variables associated with the cardiovascular system. Recent direct evidence (*22*) indicates that manometer systems with a uniform dynamic response to 10 cycles per second will record peripheral arterial pressure in man without significant amplitude distortion. It is of interest also that the sensitivity of the majority of clinically acceptable electrocardiographs is diminished by more than 20 per cent at a frequency of 40 cycles per second.

In the functioning cardiovascular system, the various factors of pressure, flow, velocity, rate, and so forth are all mutually interrelated and continuously varying. Therefore, accurate studies of the over-all function of the circulatory system require continuous recording of multiple variables.

The desirability of recording multiple physiologic variables in studies of cardiovascular function is well illustrated by the results of studies concerning the nature of the blackout and unconsciousness sometimes experienced by pilots as a result of exposure to positive acceleration or centrifugal force (*12, 16, 26*). Sudden exposure of a fighter pilot to a commonly experienced positive acceleration of five times the force of gravity (5*g*) will, because of the effective increase in the weight of the blood, reduce arterial pressure at head level to zero. Studies of the physiologic effects of this type of stress in human beings are carried out under controlled laboratory conditions by means of human centrifuges (*26*), perhaps the largest type of physiologic instrument designed for the study of the circulation (*1*) (Fig. 1). Physiologic recordings taken during exposure of a normal subject to positive acceleration on the human centrifuge are shown in Fig. 2. The left panel shows the changes produced by an exposure to 4.6*g* when the subject was unprotected. The increase in weight of the blood associated with this acceleration reduced arterial blood pressure temporarily to zero at head level, and a temporary loss of vision resulted. The reflex compensatory increases in blood pressure at heart level induced by the lowered blood pressure in the head region (carotid sinus) are evident during the latter portion of this exposure. The center panel illustrates the increase in arterial pressure produced by inflation of a pneumatic antiblackout suit. The panel on the right was recorded from the same subject during exposure to 5.5*g* while protected by the antiblackout suit. Protection is afforded by the increase in blood pressure at heart level produced by inflation of the suit.

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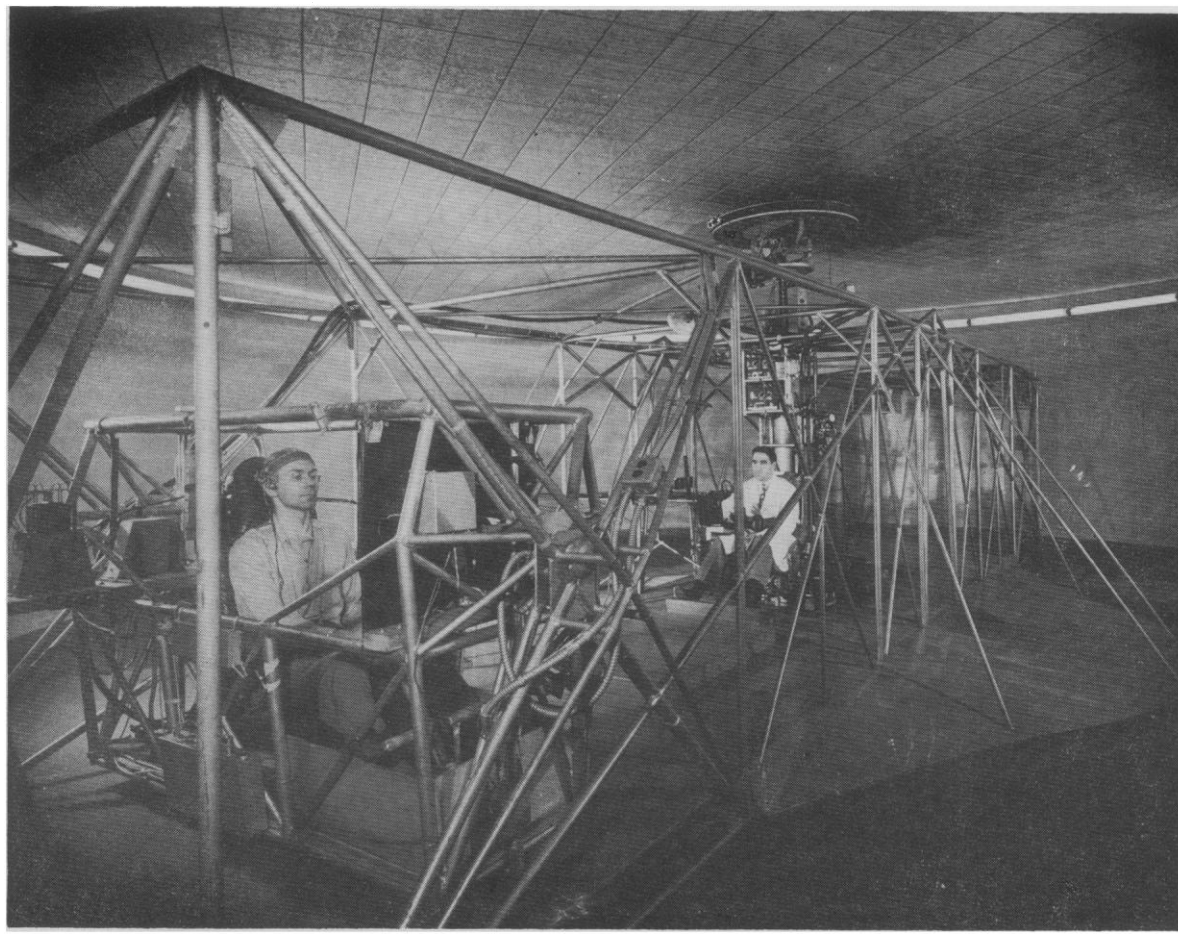

FIG. 1. Human centrifuge, designed to simulate the positive acceleration encountered in aircraft during combat or aerobatic maneuvers. This centrifuge (*1*), which is a rectangular steel frame 37 ft in length, rotates in a circular room 40 ft in diameter. The subject (left) sits in a cockpit suspended so as to be free to swing radially. The observer, sitting near the center of rotation, controls the start and the stop of the centrifuge, and tests the reactions of the subject to visual and auditory signals during each exposure.

The type and use of instrumentation for cardiovascular research are well illustrated by the technique of cardiac catheterization (*2, 20*). This procedure involves the passage of a plastic catheter, 100–120 cm in length and approximately 0.25 cm in diameter, from a peripheral vein into the great vessels and chambers of the heart. Analyses of roentgenograms, pressure tracings, and blood samples obtained from various positions in the circulatory system provide data that have proved to be of value diagnostically and for the solution of special problems concerning the physiology of the circulation and respiration in man. An assembly set up for this procedure is shown in Fig. 3. The electrical variations of the various pickup units are recorded continuously on photokymographic cameras located in an adjacent recording room. For certain of the phenomena encountered in this and other procedures it is advantageous for purposes of later analysis to record the variations at two different chart speeds. This is accomplished by simultaneous recordings on two kymographic cameras run at the different chart speeds desired (Fig. 4).

In the cardiac catheterization technique, the actual procedure is determined to a large extent by the results of measurements being made through the catheter (particularly the pressures and blood oxygen saturations) at the time. It is therefore important to have accurate means of visually monitoring the variations while they are being continuously recorded. This can be accomplished by arranging a mirror assembly so as to reflect a small portion of the galvanometer beams back to appropriately located visual scales (Fig. 5).

Examples of the physiologic recordings obtained with the oscillographic assembly are shown in Figs. 6 and 7. The individual instruments used to record the multiple variables illustrated were especially adapted commercially available devices or, for the most part,

were designed and developed specifically for the purposes of this particular application.

The discussion of these individual devices will be confined to the instruments concerned with direct measurements of the pressure and photometric measurement of percentage oxygen saturation of blood in the circulatory system of man.

Measurement of Blood Pressure

The pressures encountered in the circulation will, in nearly all instances, fall within a range from approxi-

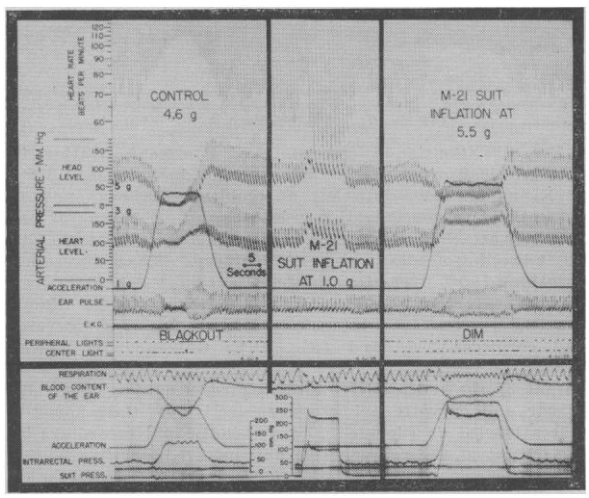

Fig. 2. Physiologic recordings taken from a normal subject during exposure on the human centrifuge to a positive acceleration of 4.6*g* without protection (left panel) and to 5.5*g* when protected by a pneumatic antiblackout suit (right panel). Black dashes show the subject's reaction times to peripheral and central light signals. Heart rate was recorded by means of an instantaneous cardiotachometer (*19*). Pressures were recorded with strain gauge manometers (*13*). Ear pulse and ear opacity were recorded with a photoelectric earpiece (*25*). Respiration was recorded by a thermocouple mounted in a mouthpiece through which the subject breathed. The upper trace marked *acceleration* is a tachometer record of the rpm of the centrifuge. The lower trace marked *acceleration* was recorded by means of a strain gauge accelerometer (Statham) mounted in the centrifuge cockpit.

mately 300 mm of mercury above to a few millimeters of mercury below ambient barometric pressure. The dynamic components of the pressure variations encountered will, for the most part, be encompassed by a frequency range of 0–50 cycles per second. For practical purposes this frequency range may be even more limited (*6, 22*). The sensitivity required varies from approximately 1 mm up to several centimeters deflection per millimeter of mercury pressure.

A manometer system suitable for direct recording of blood pressure should possess the following characteristics (*9*): high natural frequency; high stability; linear calibration; usability with long leads; insensitivity to movement, temperature, humidity, and acceleration; imperviousness to electrolyte solutions; simplicity of operation; and construction for ease of sterilization and removal of air bubbles entrapped in the hydraulic system.

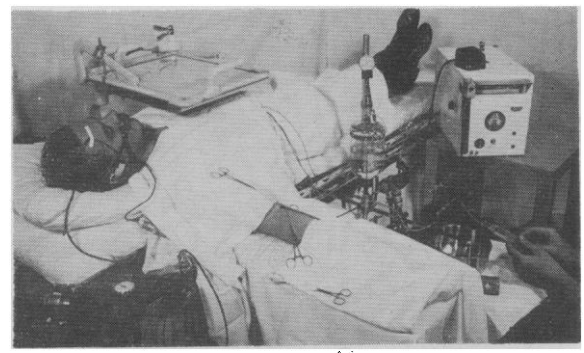

Fig. 3. Assembly of apparatus for diagnostic cardiac catheterization procedure. Subject is lying on x-ray table, and movable roentgenoscopic screen and x-ray plate holder for visualization of radiopaque catheter are in position over chest. Earpiece attached to right ear provides a continuous record of the percentage oxygen saturation of subject's arterial blood (*23*). Device extending into the nostrils and over the mouth contains 3 thermocouples, which give a qualitative record of the respiration. Continuous recordings of the electrocardiograph and heart rate are picked up from the electrocardiographic leads applied to the chest. Cardiac catheter, in place in the antecubital vein, is connected by means of a three-way stopcock to: (1) a pressurized wash bottle containing a sterile heparinized saline solution, (2) a strain gauge manometer (*13*) for continuous recording of pressures transmitted through the catheter, and (3) a cuvette oximeter for whole blood (*8, 21*) to determine the oxygen saturation of blood samples drawn through the cardiac catheter. The electrical variations from these various pickup units are recorded continuously on a kymographic camera located in an adjacent recording room.

An ideal blood pressure manometer has as yet not

Fig. 4. Photokymographic cameras used for simultaneous recording of multiple physiologic variables concerned with the heart and circulation. Camera on the right (for 18-in. width photographic paper) is run continuously at a slow chart speed (1.25 or 5 mm/sec) throughout the procedure. The camera, mounted face up directly below the front-surfaced mirror, is set for a chart speed of 29 mm/sec and adjusted in relation to the mirror so as to photograph the lower portion of the same galvanometer beams focused on the upright camera. This fast camera is run only occasionally during the procedure, at points at which study of the contours of the recorded variations might prove of value.

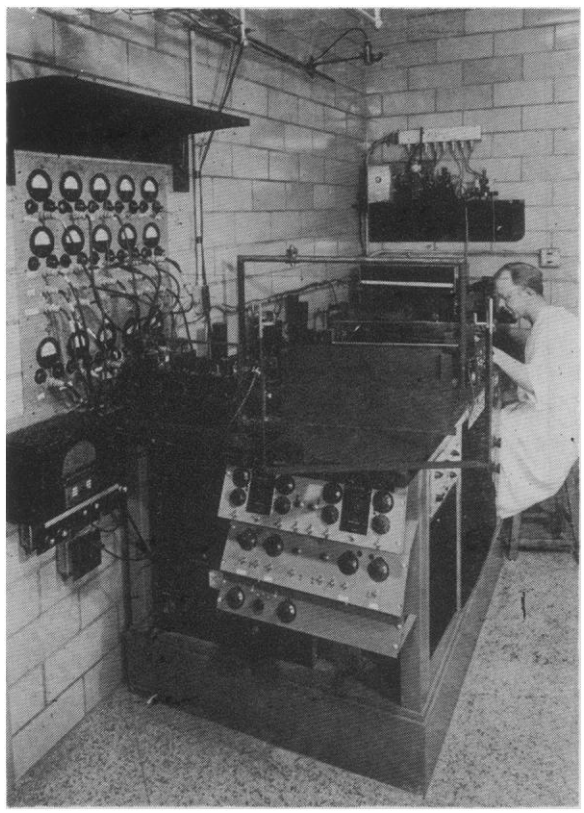

FIG. 5. Oscillographic recording assembly used for cardiac catheterization and other procedures. The various electrical leads coming from the subject terminate in the junction panel in left foreground. Twenty or more galvanometer traces can be recorded simultaneously on the photokymographic camera shown in background beside camera operator. High-sensitivity galvanometers used, with an optical arm of 4 m, for recording oximeter tracings, etc., are mounted above camera (upper background). Images from their mirrors are reflected back to the kymographic camera by means of a large front-surface mirror mounted on the oscillographic table (back of mirror visible in foreground). Lower portions of these beams are reflected by another mirror (face visible at midportion of table) to a visual scale (not shown) mounted over foreground control panel so that an operator can monitor the tracings and relay the results via a speaker system (lower left) to the adjacent room while the traces are being continuously recorded. In these types of studies a high degree of d.c. stability is required over long periods of time; therefore the use of vacuum tube amplification is avoided if possible, the electrical variations from the pickup units being recorded directly, wherever feasible, by means of high-performance galvanometers.

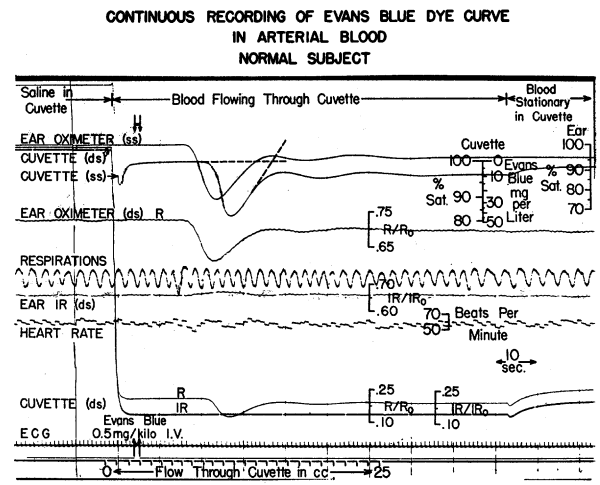

FIG. 6. Continuous recording of dye concentration in arterial blood after nearly instantaneous injection of 40 mg of Evans blue dye into left antecubital vein of a normal subject. Dye concentration was recorded by means of ear oximeter attached to left ear and cuvette oximeter attached to an indwelling needle in the radial artery. The subject was breathing 100% oxygen, so that constant and complete saturation of the arterial blood with oxygen was assured. Simultaneous single-scale and double-scale operation of the cuvette and earpiece were used (Fig. 16). Galvanometer traces labeled *ss* (single-scale) are recordings of the difference in output of the red-sensitive and infrared-sensitive photocells of ear and curvette oximeters, respectively. Galvanometer traces labeled *ds* (double-scale) are individual recordings of the output of the red-sensitive and infrared-sensitive photocells of earpiece and cuvette. R/R_o indicates the ratio of red light transmitted through the blood-containing ear or blood-filled cuvette to the light transmitted through the bloodless (pressurized) ear or saline-filled cuvette. IR/IR_o is the similar ratio for near infrared light transmission through the ear or cuvette. Respirations were recorded by monitoring the pressure variations in the oxygen mask, using a sensitive strain gauge (± 10 mm of mercury range). Heart rate was recorded by means of an instantaneous cardiotachometer (*19*). The subject's cardiac output, blood volume, and circulation time from arm to ear can be calculated from the time-concentration curve of the dye in arterial blood (*18*).

been developed. In my opinion, the strain gauge pressure transducers of the unbonded type, which have been adapted for blood pressure recording (*17*) (Fig. 8), more nearly approach fulfillment of the foregoing requirements than any of the other commercially available manometers.

Under practical conditions of use, the dynamic response of hypodermic needle or catheter manometer systems is subject to large variations that are due to the marked effect of even minute air bubbles entrapped in the connections of the hydraulic system between the gauge and the needle or catheter (*14*). Because of this fact it is important to have convenient methods of checking the dynamic response of manometer systems at the time of their use. This can be done by recording the response of the system to a square wave pressure change (Fig. 9) or to sine wave pressure variations of variable frequency generated by means of hydraulic pressure oscillators especially designed for this purpose (*9, 11, 14*) (Fig. 10). The alteration of the dynamic response characteristics of a strain gauge manometer as it is assembled into a multipurpose hypodermic manometer system (*7*) is illustrated in Fig. 11.

In the procedure of cardiac catheterization it has been found that, even when catheter manometer systems of satisfactory dynamic response are used, the pressure recordings obtained from the pulmonary artery and right ventricle are badly distorted by arti-

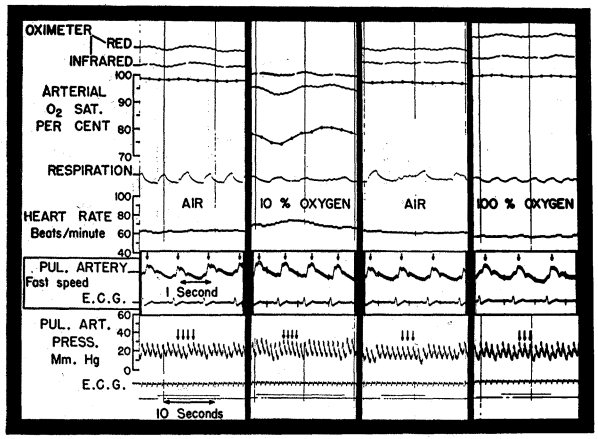

FIG. 7. Recordings from a human being during inhalation of air, 10% oxygen, and 100% oxygen. Pressure in pulmonary artery was recorded by means of miniature pressure pickup unit attached to intracardiac end of cardiac catheter (*6*). Inserts showing contours of the pressure pulse waves and of the electrocardiogram are from simultaneous records photographed at a faster chart speed (29 mm/sec). Arrows indicate identical pulses on the fast- and slow-speed recordings. Differences in contour of the pulse wave and slight differences in pressures are evident during the periods of breathing the different gas mixtures.

facts. These artifacts are due to the pressures generated within the catheter from the accelerations and decelerations of the fluid column in the lumen. They are associated with the movements of the catheter usually introduced by the heartbeat (*6, 14*). This difficulty can be eliminated by mounting a miniature manometer on the intracardiac end of the catheter (*6*). The mass (approximately 15 mg) of the movable elements in the (2.5 mm × 12 mm) variable reluctance manometer (*7*) that has been used is so small

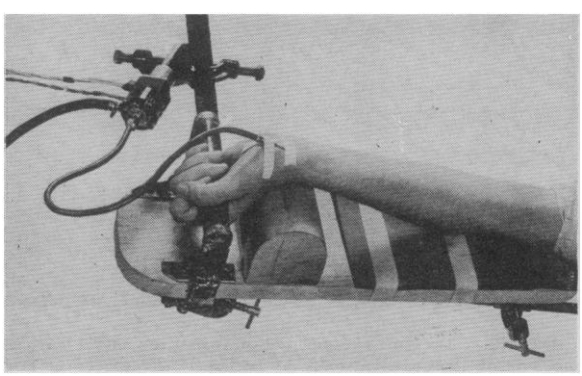

FIG. 8. Hypodermic strain gauge manometer assembly used for recording arterial pressure in the human centrifuge (*15*) (Fig. 2). Manometer is connected via lead tubing to an indwelling needle in the radial artery. The 2 pairs of electrical leads connect to a d.c. source for maintaining a constant voltage across the strain gauge Wheatstone bridge circuit and to an oscillographic galvanometer, which records the output of the strain gauge. Rubber tubing is connected to a pressure bottle filled with sterile saline solution containing an anticoagulant (heparin) for intermittent flushing of the manometer system to prevent formation of blood clots in the needle.

that the reactive forces resulting from the accelerations produced by the heartbeat do not produce appreciable pressure artifacts (*4, 5*) (Figs. 7, 12). Use of this type of manometer requires d.c. vacuum tube amplification (approximately 150,000:1), with strict limitations concerning the allowable amount of base line and sensitivity drift. Carrier wave type amplifiers have been used with reasonable success.

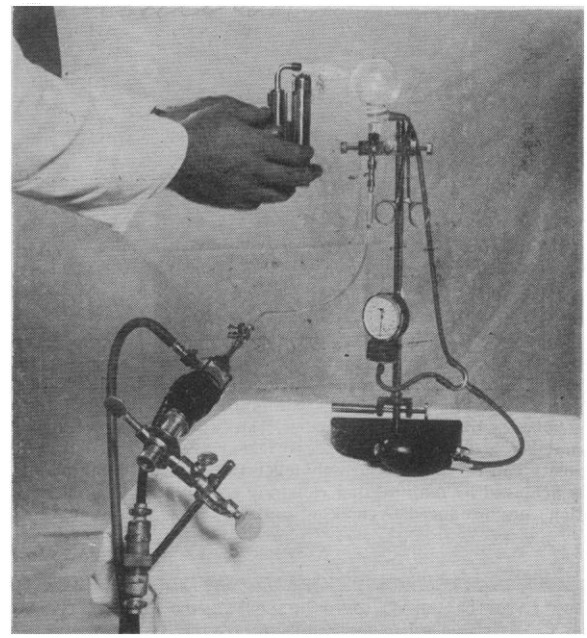

FIG. 9. Apparatus for testing the dynamic response of manometer systems by subjecting them to a square wave pressure change. The needle of the manometer assembly is inserted into the fluid contained in the pressure chamber. The pressure in the air space over the fluid is increased by means of the hand bulb to just under the bursting pressure of the finger cot covering the pressure chamber. Balloon is then exploded with a blow torch, thus producing practically an instantaneous decrease to ambient pressure.

PHOTOMETRIC MEASUREMENT OF BLOOD OXYGEN SATURATION

One of the chief functions of the circulation is to transport oxygen in the form of oxyhemoglobin from the lungs to the tissues. Measurement of the percentage oxygen saturation of the hemoglobin contained in blood is therefore important in studies of cardiovascular function. Since the blood oxygen saturation is mutually interrelated with other physiologic variables and may under certain circumstances be continuously varying, methods of measurement that allow continuous recording are desirable. Photoelectric devices, commonly called oximeters, have been developed for this purpose.

The differences in light absorption of oxyhemoglobin and reduced hemoglobin in the visible and infrared regions of the spectrum constitute the most convenient basis on which to carry out continuous photometric

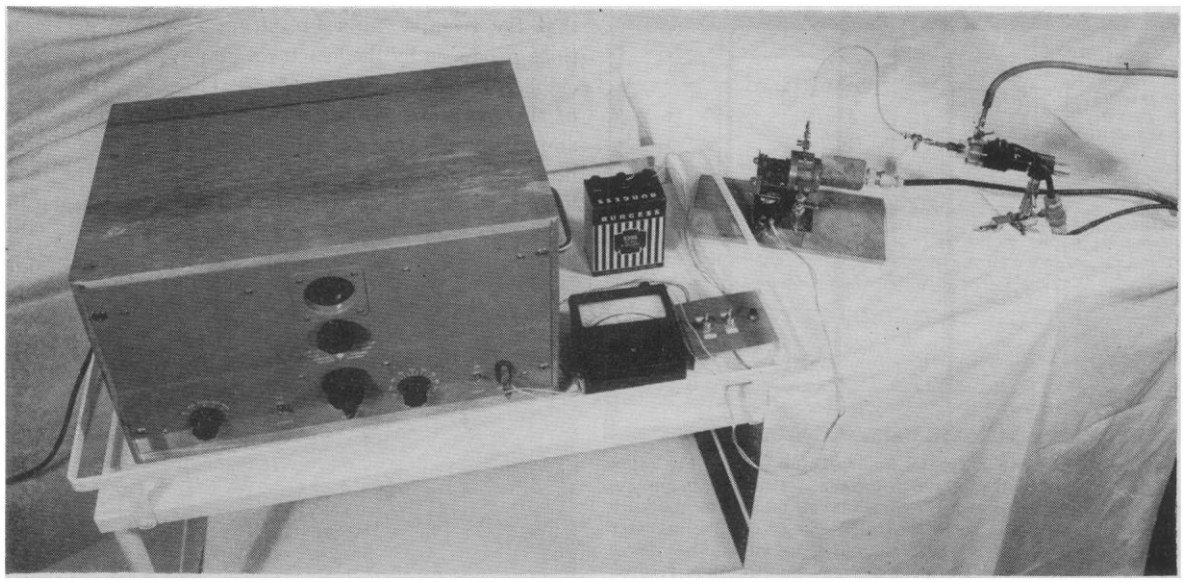

FIG. 10. Electromagnetic hydraulic transducer for studying response characteristics of manometer systems to square wave and sine wave pressure variations (*11*). Needle of the manometer assembly being tested (upper right) is inserted into a water-filled lucite chamber. Standard electronic oscillator actuates an electromagnetic drive unit coupled through a metal membrane to the lucite chamber, thus translating the sine wave oscillator current into sine wave pressure variations in the chamber. The generated pressure variations are monitored by means of an unbonded strain gauge unit coupled to the opposite end of the pressure chamber through a similar metal membrane. Constant pressure amplitude at varying frequencies is achieved by maintaining constant current (monitored by the milliammeter) to the drive unit. Square wave pressure variations are produced by making and breaking a d.c. source (B battery) to the electromagnetic driver.

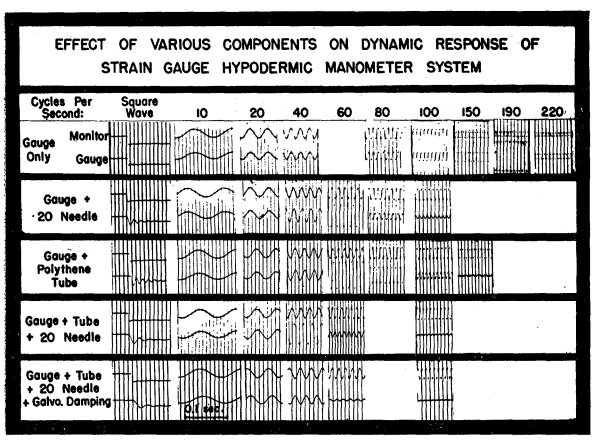

FIG. 11. Alteration of dynamic response of a strain gauge manometer (Statham gauge, range ±760 mm of mercury) produced by the hydraulic connections required to convert it to a multipurpose hypodermic manometer (*24*). Top tracing in each panel is the recording from the gauge monitoring the pressure chamber; and bottom tracing is the recording from the manometer system being tested. The 20-gauge hypodermic needle was 5 cm in length and 0.056 cm internal diameter. The polythene tubing assembly consisted of a glass hypodermic adapter for attachment to the needle, a 26-cm length of polythene tubing (2.1 I.D., 3.4 mm O.D.), and a two-way hypodermic stopcock to permit blood sampling and connection to the manometer proper. Galvanometer damping (lower panel) consisted of the use of a galvanometer with a resonant frequency of 40 c/sec, utilizing an external damping resistance of 70 ohms (optimal damping resistance: 250 ohms).

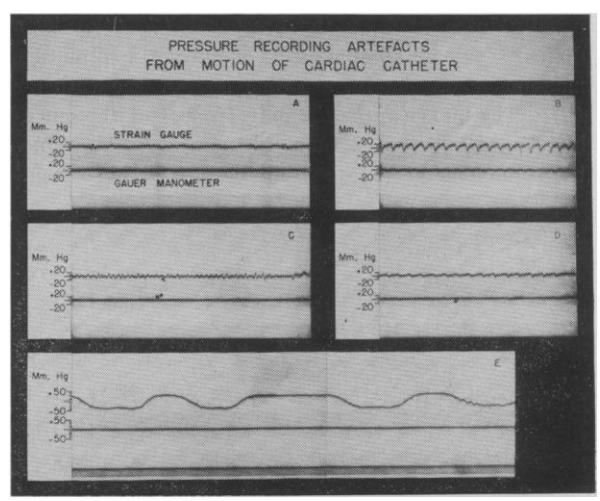

FIG. 12. Pressures generated by simultaneous identical motions of intracardiac ends of two 8 F cardiac catheters, one with a Gauer-Glenapp manometer attached to the intracardiac tip, and the other filled with fluid and with the external end attached to a strain gauge manometer, this overall system being optimally damped. *A*, vertical circular motion of tips of both catheters through a diameter of 10 cm at rate of 1 c/sec; *B*, pendular motion along axis of catheter approximately 4 cm in amplitude at rate of 2 c/sec; *C*, pendular motion transverse to axis of catheter through a distance of 4 cm at rate of 2 c/sec; *D*, catheter tip fixed and oscillatory motion imparted to the shaft of the catheter; *E*, catheter tip rotated through arc of 180° on a radius of 50 cm.

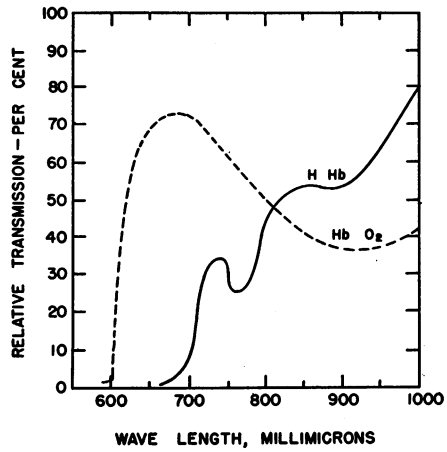

FIG. 13. Relative spectral transmission of reduced and oxygenated hemoglobin solutions (calculated from Horecker's data [*10*]).

measurements of the oxygen saturation of circulating whole blood. These differences are illustrated in Fig. 13. Under the conditions of these measurements, the oxyhemoglobin solutions transmitted approximately 70 per cent of the incident red light of a wavelength of approximately 640 mμ, whereas reduced hemoglobin absorbed practically all the light of this wavelength. At approximately 800 mμ, however, in the near infrared, the relative transmission of oxyhemoglobin and reduced hemoglobin was identical. Therefore, the transmission of light of a wavelength of 800 mμ is dependent on the *hemoglobin content* of the transilluminated solutions, whereas the transmission of light of a wavelength of 640 mμ is a function of the *percentage saturation* of this hemoglobin with oxygen. The ratio of the transmission of visible red and near infrared light can be used, therefore, to determine the percentage oxygen saturation of the hemoglobin contained in the transilluminated solutions.

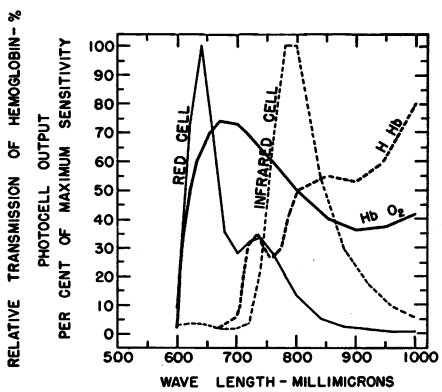

FIG. 14. Relative spectral sensitivity of oximeter photocells and spectral transmission of hemoglobin solutions. Note that maximal sensitivity of the red cell is in the spectral region of maximal difference between oxygenated and reduced hemoglobin, whereas sensitivity of the infrared cell is at a crossover, or isobestic, point of these 2 pigments.

The spectral sensitivity of the iron-selenium photocell filter combinations contained in the oximeter earpiece and the cuvette oximeter for whole blood is illustrated in Fig. 14. The maximal sensitivity of the red photocell is at 640 mμ, at which point the light transmission of oxyhemoglobin and reduced hemoglobin is maximally different. The peak sensitivity of the infrared cell is at approximately 800 mμ, at which point the light transmission of oxyhemoglobin and reduced hemoglobin is practically identical.

The cuvette oximeter for whole blood (*21*) (Fig. 3) is used for photometric determinations made directly on blood flowing or stationary in the cuvette tubing. The oximeter earpiece (*23*) can be used for similar determinations on the blood circulating in the intact ear (Fig. 15).

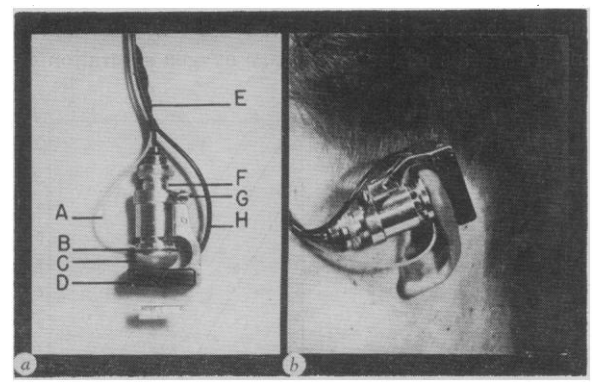

FIG. 15. Earpiece for the oximeter (*3, 23*) : *A*, polythene tubing leading into *B*, pressure chamber ; *C*, rubber diaphragm of pressure capsule (inflated to 20 mm of mercury) ; inflation of this pressure capsule to 200 mm of mercury renders portion of the ear in the optical pathway of earpiece practically bloodless ; *D*, housing for photoelectric cells ; *E*, lead wires ; *F*, housing for light source ; *G*, set screws for fixing position of pressure capsule ; *H*, strain relief and ground wire. *b* : Oximeter earpiece in place on ear.

Two methods (double-scale and single-scale) of operation of these devices have been used. The double-scale method is the more accurate but is also the more time-consuming of the two techniques. The outputs of the red and infrared cells are recorded separately. The optical density of the blood contained in the cuvette or the ear is determined by measuring first the light transmission of the bloodless (pressurized) ear or cuvette (filled with saline solution) and then the transmission with the ear or cuvette filled with blood. The logarithm of the ratio of light transmission without blood to light transmission with blood is a function of the optical density of the blood interposed in the optical pathway of these devices. The ratio of the optical density of blood in the visible red to the optical density in the near infrared is a function of the percentage saturation of the blood hemoglobin with oxygen.

The single-scale method of operation utilizes only one galvanometer, is simple in technique, and the facility of a direct reading of the percentage oxygen saturation renders it preferable to double-scale operation in applications in which the greater variability of the results obtained does not constitute a serious objection. The circuit used measures the difference in output of the red and infrared photocells. The output of the infrared cell is set to an arbitrary negative galvanometer deflection with blood in the optical pathway of the instrument. (This "infrared setting" determines the final sensitivity of the devices to changes in oxygen saturation.) The blood is then removed from the optical pathway of the instrument, and the output of the red cell is adjusted to be equal and opposite to that of the infrared cell (galvanometer deflection: zero). The galvanometer deflections then obtained when blood is allowed to reenter the instrument are a function of the percentage oxygen saturation of the blood.

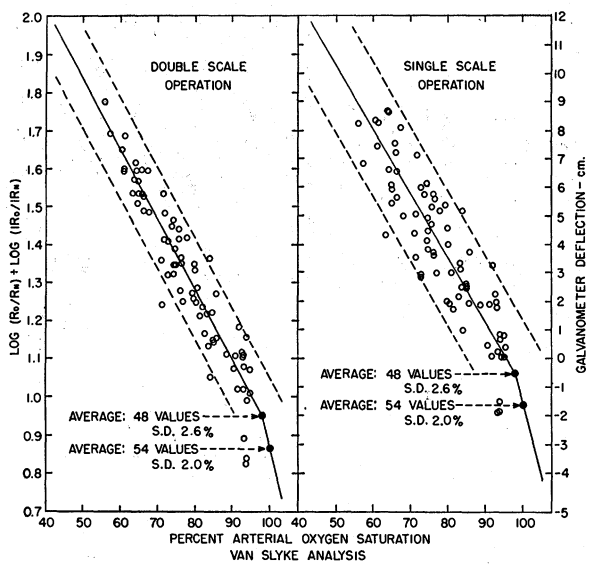

FIG. 16. Empirical calibration curve of an oximeter earpiece for determining arterial oxygen saturation in man. Simultaneous single- and double-scale operations were used, based on 177 simultaneous photoelectric and Van Slyke determinations of arterial oxygen saturation in man. The dashed lines delineate the areas representing twice the standard duration of single photometric analyses in the saturation range below 95 per cent.

Although these instruments can be used for direct measurement of blood oxygen saturation, an initial empirical calibration against manometric determinations of blood oxygen saturation is necessary, irrespective of whether the double-scale or single-scale method of operation is used (Fig. 16). In certain applications, such as the cardiac catheterization procedure, in which it is advantageous to obtain an immediate reading of blood oxygen saturation, as well as an accurate recording for later analysis, a circuit that

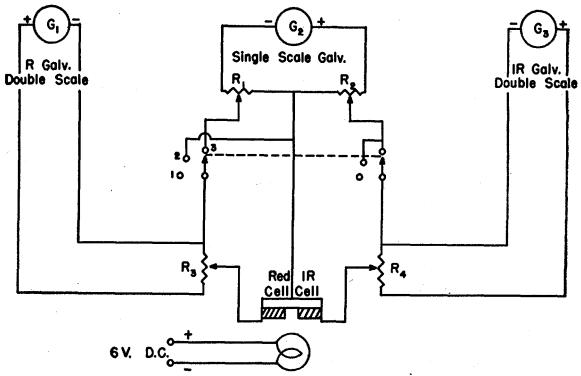

FIG. 17. Earpiece and cuvette oximeter circuit incorporating simultaneous double- and single-scale operation. R_1 and R_2, single-scale potentiometer controls for red and infrared cells, respectively; G_2, single-scale galvanometer ($R_1 + R_2$ = optimal damping resistance); R_3 and R_4, double-scale potentiometer controls for red and infrared cells, respectively; G_1, red cell galvanometer for double-scale operation (R_3 = optimal damping resistance); G_3, infrared cell galvanometer for double-scale operation (R_4 = optimal damping resistance); 1, control switch position for reading galvanometer zeros; 2, control switch position for adjusting sensitivity of infrared cell for single-scale operation (earpiece on flushed ear or blood in cuvette oximeter); 3, control switch position for adjusting sensitivity of red cell for single-scale operation (earpiece on bloodless [pressurized] ear or saline solution in cuvette oximeter). After adjustments 2 and 3 are completed, the deflections of the single-scale galvanometer produced in switch position 3 are a function of blood oxygen saturation in flushed ear or cuvette oximeter.

provides simultaneous single- and double-scale operation has been used (Fig. 17). The single-scale readings are then read visually, and the double-scale galvanometer deflections are recorded for later more accurate analysis. Calibration data obtained with an oximeter earpiece using this simultaneous single- and double-scale method of operation are illustrated in Fig. 16.

In summary, because of the dynamic character and interrelations of the physiologic variables concerned in the cardiovascular system, study of the functions of this system in the intact animal requires instrumentation capable of continuous recording of the static and dynamic components of the multiple physiologic factors involved. Reasonably satisfactory instrumentation is available for continuous recording of the electrocardiogram, heart rate, respiration, temperature, blood pressure, blood oxygen saturation, and other factors. Development is still lacking, however, in instruments capable of high-fidelity recording of many other variables of importance to the cardiorespiratory system. The perfection of such devices capable of continuously recording in the intact animal such variables as, for example, blood oxygen and carbon-dioxide tension, the cardiac output, regional blood flow, the gas composition of the breath during each respiratory cycle, and so on, would greatly facilitate studies concerned with further elucidation of the physiology of the heart and circulation in man.

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Technical Papers

Description of the Chemostat

Aaron Novick and Leo Szilard

Institute of Radiobiology and Biophysics, University of Chicago

We have developed a device for keeping a bacterial population growing at a reduced rate over an indefinite period of time. In this device, which we shall refer to as the Chemostat, we have a vessel (which we shall call the growth tube) containing V ml of a suspension of bacteria. A steady stream of nutrient flows from a storage tank at the rate of w ml/sec into the tube. The contents of the tube are stirred by bubbling air through it, and the bacteria are kept homogeneously dispersed throughout the tube at all times. An overflow sets the level of the liquid in the growth tube, and through that overflow the bacterial suspension leaves the tube at the same rate at which fresh nutrient enters it.

The chemical composition of the nutrient is such that it contains a high concentration of all growth factors required by the bacterium, with the exception of one, the controlling growth factor, the concentration of which is kept relatively low. The concentration of the controlling growth factor, a, in the storage tank will then determine the density, n, of the bacterial population in the growth tube in the stationary state, and it can be shown that, except for very low values of n, we have $n=\frac{a}{A}$, where A is the amount of the controlling growth factor needed for the production of one bacterium.

The growth rate $\alpha=\frac{1}{n}\frac{dn}{dt}$ of a strain of bacteria is a function of the concentration, c, of the controlling growth factor in the medium, and in general we may expect the growth rate, at low concentrations c, first to increase rapidly with increasing concentration and then slowly to approach its highest attainable value, α_{max}.

The Chemostat must be so operated that the washing-out time, $\frac{w}{V}$, should be lower than the growth rate α_{max} for high concentrations of the controlling growth factor. It can be shown that in that case a stationary state will become established in which the growth rate, α, will be just equal to the washing-out rate, $\frac{w}{V}$.

What happens is that n will increase until it becomes so large that the bacteria will take up the controlling growth factor from the tube just as fast as it is necessary in order to reduce c to the point where the growth rate $\alpha(c)$ becomes equal to the washing-out rate, $\frac{w}{V}$.

Using a tryptophane-requiring strain of coli and a simple lactate medium with tryptophane added, we have used both lactate and tryptophane as the controlling growth factor. Using tryptophane, we have kept bacterial populations growing over long periods of time at rates up to ten times lower than normal. We are thus able to force protein synthesis to proceed very slowly while certain other biochemical processes may continue at an undiminished rate.

A study of this slow-growth phase by means of the Chemostat promises to yield information of some value on metabolism, regulatory processes, adaptations, and mutations of microorganisms. A study of the spontaneous mutations of bacteria growing in the Chemostat has been made and is being published elsewhere.