A known quantity of X-ray-opaque tracer is injected into blood entering an organ to be examined. X-rays are passed through the organ to an imaging plane. Image records are made periodically through a cycle of the organ. Selectively delineated image areas of each record of interest are scanned to produce a signal corresponding to blackness variations across the image. The signal is so amplified as to produce an output that varies with tracer concentration across the projected area of the organ. Integrating that output for each record provides a final output representative of tracer concentration in the delineated organ portion.
Fig. 3a

MOMENT OF INJECTION

HEART BEATS

Fig. 3b

100%

LEFT VENTRICLE AGENT VOLUME

50%

C/A = STROKE VOLUME COEFFICIENT

C = STROKE VOLUME

Fig. 3c

LEFT AURICLE AGENT VOLUME

50%

25%

B/A = LEAKAGE COEFFICIENT

RESIDUAL BACKGROUND LEVEL
METHOD OF IN VIVO EXAMINATION OF ORGAN FUNCTIONS

This application is a continuation-in-part of our co-pending application, Ser. No. 110,184, filed Jan. 27, 1971, now abandoned.

This invention relates to a method and means for examining the functioning of human and animal organs by means of X-ray and similar radiation techniques, and is more particularly concerned with a technique of radiological examination based upon injection of a tracer substance into the bloodstream entering an organ under examination and observations of the progress of the tracer substance through the organ.

Typically, in vivo examination techniques of the general type to which this invention relates have been applied to the study of the functioning of the heart, as for the purpose of determining stenosis and insufficiency of the cardiac valves in order to make possible the choice of a suitable treatment or the evaluation of different therapeutic measures. The following explanation will therefore be concerned with the heart, in particular, but it is to be understood that the invention is equally applicable to the study of the functioning of other organs, and that thus limiting the discussion to the study of heart functioning is for purposes of example and convenience in explanation and is not intended to imply any limitation upon the utility of the invention.

In general, for an in vivo heart examination it has heretofore been conventional to inject a measured quantity of a tracer material into the bloodstream in the heart or directly entering the heart. Since quantitative information about heart action is needed for purposes of diagnosis, the usual prior techniques for such examination have relied upon a tracer material that was radioactive and have employed a scintillation detector or Geiger counter to determine the variations in concentration of the tracer substance arriving at a selected point in the circulatory system during the course of one or a few heart cycles. Sevelius et al., in 54 Jour. of Lab. and Clinical Medicine, No. 5 (November, 1959), p. 669, described one such technique. The radioactive tracer concentration was detected by placing a gamma ray detector on the chest wall, over the outflow tract of the heart, and measuring the chronological change in scintillation counting rate. A plot of the measurements made during the first circulation of the radioactive material through the heart was used for calculating the rate of blood flow through the heart.

Such prior techniques made necessary a substantial amount of more or less educated guessing in the evaluation of results. One factor that introduced a large unknown into the results was the collimation of the scintillation detector. If the scintillation detector had a wide collimation, so as to be receptive to radiation from a wide cone around its axis, radiation from radioactive particles near the edges of its field of view tended to go undetected, even though they represented a comparatively large concentration of tracer material. This was because the count rate of a point source falls off as the reciprocal of the distance squared, although the counted volume increases with distance. In simpler terms, with a scintillation detector having a wide-angle field of view, radioactive particle concentrations near the edges of the scintillation detector field of view tended to be recorded as substantially lower than they actually were. This problem of scintillation detector collimation was discussed by Huff et al. in Circulation Research, Vol. III (November, 1955), p. 564.

Since a scintillation detector with a wide collimation had an inherent measuring error, attempts were made to avoid the need for wide collimation by measuring variations in the concentration of radioactive tracer at a localized point or points and then deducing the desired quantitative data about heart functioning from such measurements. See, for example, M. Annis et al., U.S. Pat. No. 3,221,731, the two articles cited above, and the article "Tracer Method Examines Human Blood Circulation" in Nucleonics, July, 1959, p. 56. Of course the raw data obtained from such measurements taken at a localized point or points had to be interpreted on the basis of certain assumptions about events that had taken place in the course of blood flow between the point of tracer injection and the point or points of measurements, so that the conclusions that were based upon such measurements would be no more valid than the assumptions upon which such conclusions were also based.

The last-mentioned Nucleonics article briefly describes the technique of angiography as a diagnostic method, explaining that it comprises the introduction into the blood of a substance that is opaque to X-rays, followed by taking fast-sequence X-ray photographs. Heretofore, however, angiography has been of comparatively small value for diagnostic purposes because it did not provide quantitative information about heart functioning. In a series of angiographic pictures the frames of the tracer substance into the heart and its progress through the heart could be visually traced, but it has not heretofore been possible to obtain with that technique information about such diagnostically important quantities as the volume and displacement of the chambers of the heart, the rate of leakage between ventricles and the rate at which restricted blood flow takes place through a stenosis.

An important reason why angiography has not heretofore been regarded as particularly useful as a diagnostic tool has to do with the manner in which X-ray radiation is absorbed by an X-ray-opaque medium through which it passes. X-ray absorption by such a medium varies exponentially, rather than linearly, with the length of the column of the medium that is in the path of an X-ray beam. However, the blackening of a film, or the response of a similar radiation sensitive medium, has a substantially direct linear relationship to the amount of radiation to which it is exposed. Hence, in angiography the blackening of a cinema film due to X-ray radiation passing through the heart varies as an inverse exponential function of the concentration of X-ray absorbing substance in the radiation path.

The eye has difficulty sensing and interpreting variations in shades of darkness and lightness on a film, and at best can make a rational interpretation of blackness variations only when they correspond to substantially linear variation of the quantity being measured. The complicated relationship between film blackness and concentrations of X-ray absorbing medium therefore precludes any possibility of obtaining quantitative information about heart functioning by means of mere visual inspection of an angiographic record.

Having in mind the problems and considerations set forth above, it is the general object of this invention to
provide a method of in vivo examination of the functioning of a human or animal organ such as the heart, whereby it is possible to obtain an accurate quantitative determination of the amount of tracer substance present from instant to instant in a selected part of selected parts of the organ, so that from this it is possible to obtain the desired quantitative information about blood flow rate from part to part of the organ during its cycle and the volume of blood present at various times during the cycle.

It will thus be apparent that it is another object of this invention to provide a method and means for obtaining accurate measurements of the amount of an injected tracer substance that is present in a human or animal organ, or in a selected part of such an organ, at successive times during the course of one or a few cycles of the organ and to obtain such measurements directly from the tracer substance in the organ itself without incurring measurement errors such as those that inhere in a scintillation detector having a wide angle collimation and also without incurring the errors that inhere in taking such measurements at some site other than the organ itself and then making presumed corrections to the observed data on the basis of assumptions about the relationship between blood flow at the organ and blood flow at the observation site.

It is also an object of this invention to provide a method of the character described by which the volume of blood that is present at a given time in an organ or a selected part of an organ, can be accurately ascertained, and whereby variation of such volume from time to time during the cycle of the organ can also be ascertained to provide quantitative information about the functioning of the organ.

Hence it is a more specific object of this invention to provide a method of diagnosing cardiac deficiencies and malfunctions whereby accurate quantitative information can be obtained about the functioning of the heart, including quantitative information about the flow of blood from one to the other of the heart chambers during a heart cycle and hence about valvular stenosis or insufficiency.

It is also an object of this invention to provide a diagnostic method of the character described and apparatus for practicing the same, and which can employ X-ray cinematography, video tape or direct on-line processing of video signals to obtain the desired quantitative information.

With these observations and objectives in mind, the manner in which the invention achieves its purpose will be appreciated from the following description and the accompanying drawings, which exemplify the invention, it being understood that changes may be made in the precise method of practicing the invention and in the specific apparatus disclosed herein without departing from the essentials of the invention set forth in the appended claims.

The accompanying drawings illustrate one complete example of the embodiment of the invention constructed according to the best mode so far devised for the practical application of the principles thereof, and in which:

FIG. 1 is a diagrammatic view of apparatus used to obtain an angiocardiographic record that can be analyzed in accordance with the principles of this invention;

FIG. 2 is a block diagram of apparatus for analyzing the record;

FIG. 3a is an electrocardiograph and FIGS. 3b and 3c are plots of information obtained by the method of this invention from radiation image records made simultaneously with the electrocardiograph.

In the practice of the method of this invention a known small quantity of a suitable tracer material is injected into the blood stream at its entry into the organ being examined. Preferably the tracer substance is one that is opaque to X-rays and thus, in accordance with present knowledge and techniques, it is one that has iodine as its radiation absorbing substance.

As a specific example, for a study of an insufficiency of the mitral valves (the cardiac valves between the left ventricle and the left auricle) a measured quantity of X-ray contrast medium is injected through a catheter inserted in the left ventricle. The injection is preferably made in the latter portion of the ventricular diastole. By using a suitable catheter and a suitable injection velocity, the required comparatively small quantity of the medium can be injected rather quickly.

Because turbulence during the injection causes a practically homogeneous mixing of blood and contrast medium in the left ventricle, and because a known quantity of contrast medium has been injected, the concentration of contrast medium in the left ventricle affords a measure of the volume of blood in that chamber through the heart cycle immediately following injection.

Upon contraction of the heart subsequent to the injection, some of the blood will pass, in the normal way, out into the aorta, while a small quantity of blood will remain in the left ventricle. In the case of a mitral insufficiency, a certain quantity of the blood containing the contrast medium regurgitates to the left auricle.

For a period continuing from just before the injection through a few heart cycles subsequent to it (about 3 to 5 seconds in time), X-ray radiation is passed through the heart, from an X-ray source 5 at one side of the chest 6 to an X-ray responsive medium at the other side of the chest. In FIG. 1 the X-ray responsive medium is shown as an image intensifier 7 in cooperation with a cinema camera 8 and a video camera 9. A half-silvered mirror 10 that is arranged in a well understood relationship to the image intensifier and the two cameras 8 and 9 enables both cameras simultaneously to photograph the image on the image intensifier. The video signal output of the video camera can be fed simultaneously to a video tape recorder 11 and to a monitor 12 that permits immediate viewing of the image.

The making of radiation images continues for about 3 to 5 seconds after injection of the contrast medium in order to obtain a complete time history of a heart beat cycle. The preferred frame frequencies are 50 half-frames per second for the TV and about 75 frames per second for the cine camera, in order to afford good time resolution of the heart functioning. Dynamic blood pressure and electrocardiograph signals are recorded simultaneously.

For the purposes of this invention the bundle of radiation that is brought to the imaging plane should consist as nearly as possible of parallel rays normal to the imaging plane, so that all radiation paths between the radiation source and the imaging plane will be of substantially equal lengths. This requirement can be rather readily fulfilled when the tracer medium is an X-ray-
opaque material and the radiation source is an X-ray tube located at the opposite side of the patient from the imaging plane. With increasing distance between the radiation source and the imaging plane there will be increasing accuracy of measurement results, owing to the face that with decreasing convergence of the image-forming radiation there is a decreasing difference between the longest and the shortest paths taken by such radiation. Obviously, however, the distance between the radiation source and the imaging plane must be short enough to assure good image quality.

If a radioactive tracer material is to be employed for the purposes of the invention, and the organ to be examined has a substantial projected area (as has the heart) then, to fulfill the above stated requirement, it is necessary to use a narrowly collimated radiation responsive element (scintillation detector or so-called gamma camera) and to give that element a scanning motion across the area of the organ. Because such scanning would have to be very rapid for the purpose of studies of heart functions, and would almost necessarily have to involve a high speed physical movement of a scanning element, it is preferred to employ X-ray radiation in conjunction with an X-ray-opaque tracer substance.

Once the series of images is formed and recorded, the subsequent analysis process now to be described can be accomplished either with the use of the film record or with the videotape. Analysis of the film record entails a delay while the film is developed and fixed, whereas use of videotape has the disadvantage that the recorded signals represent an image having a lower resolution than that on a film. Direct use for analysis of the signals from the video camera 9, as they are generated, would have the advantage of making the desired information available instantaneously but would require an extraordinarily high speed computer and somewhat complicated peripheral equipment.

Analysis of the record must begin with a designation of the area or areas of the image that are to be analyzed. This designation depends upon the portion or portions of the organ that are significant to the purposes of the analysis, and it should be made by an experienced roentgenologist.

In the case of a film record, the frames that are of interest can be projected to facilitate study for designation of the portions of the organ that are to be analyzed, and those portions of the image can be suitably delineated, as, for example, by physically masking all other portions of the image. More conveniently, each selected frame of the film can be viewed with a TV camera and displayed on a monitor screen. Alternatively, the videotape recording can be so played back by means of a conventional playback apparatus 14 connected with a monitor screen 15 as to enable each frame that is of interest to be "frozen" on the monitor screen. The roentgenologist can then use a conventional light pen apparatus 16 to trace the outline of the significant portion or portions of the organ as they appear in the image displayed on the screen 15. In a known manner the light pen inserts logical "ones" into a memory unit 17 which can comprise a matrix of one-bit memory cells operatively associated in a known manner with gate means 18.

It will be apparent that manual delineation of the image areas to be analyzed would not be feasible with direct on-line processing of TV signals, owing to the short period of time occupied by a complete heart cycle. For diagnostic work on other organs having a slower cycle, manual designation of such areas might be possible with on-line processing of TV signals. With rather sophisticated peripheral equipment capable of recognizing certain differences in density levels, and perhaps also capable of certain form recognition functions, automatic designation of heart areas for analysis might be accomplished to enable direct analysis to be made from TV signals as they are generated.

After the areas for analysis have been suitably designated on each significant frame of the record, the contents of each such frame are analyzed on the basis of the film blackness (or its video equivalent) in every part of each of the designated areas.

The analysis according to the present invention applies the principle that the surface area designated for analysis, multiplied by the quantity of contrast medium per unit area of that surface, gives the volume of contrast medium in the portion of the organ imaged in that surface area. Thus, if the blackness variations across a designated area of the image are regarded as comprising a large number of incrementally small area elements, each due to an incrementally narrow pencil of radiation that had in its path a column of X-ray contrast medium, then the volume of contrast medium in the portion of the organ that corresponded to that image area is given by:

$$\text{Volume} = \int (\text{column length}) \cdot (\text{area elements}),$$

the integral being taken over the designated area.

However, before the integration can be performed, film blackening (or video signal magnitude) at each point in the designated image area or areas must be interpreted to obtain the value of the column length of contrast medium to which the blackness (or signal magnitude) at that point corresponds.

As pointed out above, the blackening at any point does not bear a linear relationship to the amount of tracer medium in the path of the radiation pencil which produced the blackening at that point. Instead, the relationship between image blackening at any point and the concentration of radiation absorbing medium along the radiation path to that point is an exponential one, and is given by Beer's law:

$$R = R_0 \cdot e^{-km},$$

where

- $R$ is the amount of radiation passing through the contrast medium to effect film blackening;
- $R_0$ is the incident radiation, i.e., the amount of radiation delivered to the organ;
- $k$ is a constant specific to the particular contrast medium; and
- $m$ is the concentration of the contrast medium.

In addition, the blackening of a film will depend upon its gamma value, which is a function of the emulsion speed of the film and of the process used in developing it.

In like manner, the response of video equipment to radiation will depend upon the above stated relationship to contrast medium concentration and also to dark current; hence the signal strength at any point on a videotape recording will correspond to blackening of the corresponding point on the concurrently exposed film frame.

If analysis is to take place directly from a film frame, the designated area of the frame is scanned with a very narrowly collimated beam of light that is passed
through the film onto a photoelectric cell, so that the output of the cell closely resembles the video signal which corresponds to the same image area. Obviously, where video signals corresponding to the designated area are immediately available, as from a videotape recording or from scanning of a film frame by a TV camera, it is more expedient to employ the video signal for purposes of the analysis.

Quantitatively, assuming that a beam of light is passed through a film and onto a photocell that delivers a current proportional to the intensity of light falling upon it, the concentration m of contrast medium that is represented by the output current of the photocell is given by:

\[ m = K_yyK \log I_0/I + A, \]

where \( K \) and \( K \) are constants, \( y \) is the gamma value of the film, \( I_0 \) is the photocell output for a film blackening that corresponds to zero contrast medium, \( I \) is film blackening for existing contrast medium, and \( A \) is film background blackening, that is, blackening due to presence of agents other than the contrast medium. As explained above, the constant \( K \) is specific to the particular contrast medium used, and the constant \( K_y \) is specific to and dependent upon the properties of the photocell, particularly its dark current value.

In FIG. 2 it is assumed that a video signal is available from the videotape playback unit 14, and that the image area to be analyzed has been suitably pointed out to the memory unit 17 as described above.

The video signal corresponding to an image frame to be analyzed is fed in succession through two non-linear amplifiers 19 and 20. The first of these amplifiers, designated 19, corrects the signal for dark current value and, if appropriate, also for film gamma value. Hence the output of the amplifier 19 corresponds at any instant to image blackness in an incrementally small area. Adjustment of the amplifier 19 to accommodate particular values of film gamma and similar characteristics of video equipment can be facilitated by the known exponent of photographic a step wedge (blackness scale) on the image frames.

The non-linear amplifier 20 has an exponential or logarithmic amplification factor in accordance with the above-expressed Beer's Law function. Hence the output of the amplifier 20 corresponds at any instant to the column of X-ray opaque medium in the path of the incrementally narrow radiation pencil that produced the blackening denoted by the signal at that instant.

Of course the amplified signal for only the designated image area or areas is to be used. Rejection of the unused signal portions can be effected either before or after signal amplification. As shown, in FIG. 2, it is effected after amplification, by gate means 18 under the control of the memory unit 17. The gate means transfers from the amplifier 20 to an integrator 21 those portions of the amplified video signal that correspond to the designated area of the image.

The output of the integrator is fed to any suitable type of readout means 22. For any one film frame that output has a magnitude which is a function of the concentration of X-ray contrast medium in the designated portion of the organ. Since, as pointed out above, the amount of contrast agent injected is a known volume, and that agent is homogeneously mixed with the blood, the output of the integrator 21 is also a function of the volume of blood in the designated portion of the organ.

For meaningful information about the functioning of an organ it is necessary to obtain quantitative information about blood volume at each of several instants through the course of a cycle of the organ. By effecting the above described signal processing for each of a number of frames of the record, taken at selected intervals during the cycle of the heart or other organ, it is possible to plot variations in volume of blood in the organ, or in a selected part or parts thereof, through the course of its cycle. Such a plot is illustrated in FIGS. 3a-3c, wherein FIG. 3c represents an electrocardiograph trace made simultaneously with a radiological record; FIG. 3b depicts the output of the integrator 21 for the left ventricle area of the image on each of a number of frames made during the period represented by FIG. 3a; and FIG. 3c is a plot similar to FIG. 3b but depicting the output of the integrator for the left auricle image area on the same frames for which FIG. 3b is plotted.

Not all of the blackening in the designated area of an organ is due to contrast medium. Some of it is of course due to skeleton (spine and ribs) and to soft tissues in the path of the radiation. But such residual background darkening normally remains at a substantially constant value through a comparatively long succession of cycles of the organ, and therefore compensation for it can be readily made in the practice of the principles of this invention.

Note that in FIGS. 3a-3c the image record was begun at least one heart cycle before the injection of contrast medium was made, and therefore the frames of the record that were made prior to the instant of injection can be analyzed in the same manner as frames made after the instant of injection, to obtain a base line corresponding to the residual background level. As can be seen from FIGS. 3b and 3c, the background level value is subtracted from the plotted values to obtain the volume of contrast medium that is present in the organ at any instant. The variation in volume of contrast medium in the left ventricle through the first full heart cycle (denoted by C in FIG. 3b) gives the stroke volume (displacement per stroke) of the left ventricle. The ratio of stroke volume to total volume of the left ventricle, the latter being given by A in FIG. 3b, yields a stroke volume coefficient for the left ventricle. FIG. 3c depicts a mitral insufficiency, inasmuch as a quantity (denoted by B) of blood has regurgitated to the left auricle. The ratio of B to A is a leakage coefficient, and it will be observed that the present invention makes it possible to obtain an accurate quantitative value of that leakage coefficient.

It will be evident that instead of manually plotting the outputs of the integrator 22 for each of several image areas analyzed, a computer could be programmed to produce a direct read-out or print-out of the desired information obtained from such plots. In so doing, the computer would make a quantitative comparison between volume signal magnitudes obtained from each of two designated image areas for each frame analyzed, and would utilize the results of such comparisons in obtaining other desired data outputs. The background level value could be automatically accounted for, either by an adjustment of the amplifier means 19 and/or 20 or by means of computer programming.

From the foregoing description taken with the accompanying drawings it will be apparent that this in-
vention provides a method of obtaining accurate quantitative information about the functioning of the heart and other organs through which the bloodstream circulates and through which a tracer substance can be caused to flow in the bloodstream.

Those skilled in the art will appreciate that the invention can be embodied in forms other than as herein disclosed for purposes of illustration.

The invention is defined by the following claims.

We claim:

1. The method of examining a selected portion of an organ through which blood circulates, to obtain quantitative information about a function of the organ, which method is characterized by:
   A. injecting into the bloodstream entering said portion of the organ a predetermined quantity of a substance that can affect the response of a radiation responsive medium to X-ray radiation;
   B. on a radiation responsive medium located at a plane at one side of the organ producing a radiological image of at least said portion of the organ with the use of radiation from an X-ray source which is spaced to the other side of the organ at a distance such that radiation therfrom reaches all portions of the image at said plane along paths of substantially equal lengths, so that variations in blackness across the image have a consistent relationship to variations in the concentration of said substance across the projected area of the organ;
   C. successively scanning incrementally small areas of said image to produce an input signal having a magnitude that varies in correspondence with variations in blackness across the image;
   D. so amplifying said input signal that the resultant amplified signal has a magnitude that varies substantially in correspondence with variations in concentration of said substance across the projected area of the organ; and
   E. integrating the portions of said amplified signal that correspond to said portion of the organ, to obtain an output having a magnitude that represents the concentration of said substance in said portion of the organ.

2. The method of examining the functioning of an organ through which blood circulates, which method is characterized by:
   A. injecting into the bloodstream, at a point near where blood flows into a portion of the organ that is to be analyzed, a predetermined quantity of a substance that absorbs X-ray radiation;
   B. during at least an interval which immediately follows such injection and which is long enough to comprehend a representative cycle of blood flow through the organ, projecting X-ray radiation through the whole of said portion of the organ from a source of such radiation at one side of the organ to a medium at the other side of the organ which makes a response to such radiation that has a magnitude corresponding to the intensity of radiation falling thereon which is disposed in a plane substantially normal to all radiation projected thereto, to thus produce an image of said portion of the organ;
   C. producing a record, for each of a succession of instants during said interval, of the response to said medium to radiation projected thereto;
   D. for at least selected ones of such records 1. producing an input that corresponds to the response of the medium at each of a large number of incrementally small areas across the whole of that portion of the image that corresponds to said portion of the organ,

2. modifying each such input in accordance with the known relationship between radiation passing through the substance and the concentration of the substance along the path of such radiation, and

3. integrating said inputs, so modified, to obtain an output representative of the quantity of the substance present in said portion of the organ at the instant of production of the image and which output can be compared with the corresponding outputs for others of said records to provide information about the variation in quantity of the substance present in said portion of the organ from time to time during said interval.

* * * * *
UNITED STATES PATENT OFFICE
CERTIFICATE OF CORRECTION

Patent No. 3,824,399 Dated July 16, 1974

Inventor(s) Lars Björk; Uno Erikson

It is certified that error appears in the above-identified patent and that said Letters Patent are hereby corrected as shown below:

Col. 3, line 5: "of" should read --or--
Col. 5, line 48 & 49: "delineated" should read --delineated--
Col. 9, line 1: "otaining" should read --obtaining--
Col. 10, line 21: "to" should read --of--

Signed and sealed this 5th day of November 1974.

(SEAL)
Attest:

McCoy M. Gibson Jr. C. Marshall Dann
Attesting Officer Commissioner of Patents
Patent No. 3,824,399

Dated July 16, 1974

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