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(71) Applicant *(for all designated States except US)*: **PAIEON INC.** [US/US]; 747 3rd Avenue, New York, NY 10017-2803 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **ASSIS, Tsuriel** [IL/IL]; 21 S. Ben Zion Street, 76465 Rehovot (IL). **KLAIMAN, Moshe** [IL/IL]; 21/2 Ha'arava Street, 70700 Gadera (IL). **ZARKH, Michel** [IL/IL]; 9 Oranim Street, 54052 Givat Shmuel (IL).

(74) Agents: **AGMON, Jonathan** et al.; Soroker - Agmon, Advocates & Patent Attorneys, Nolton House, 14 Shenkar Street, 46725 Herzliya Pituach (IL).

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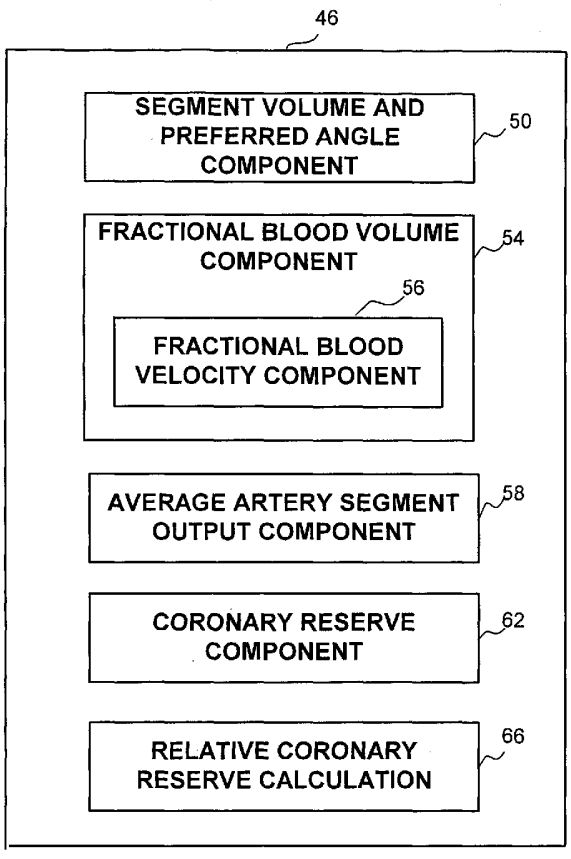

(57) Abstract: An apparatus and method for the determination of the flow, the coronary reserve and relative coronary reserve of a specific coronary artery. The apparatus and method employ a three-dimensional model (50) providing the volume of a segment of the artery at a plurality of points in time, and disclose two options for determining the arterial flow through the artery segment during one or more heart beat cycles or parts thereof. The determination of the coronary reserve (62) and relative coronary reserve (66) follow from the volume and the flow through the artery.

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METHOD AND APPARATUS FOR FINDING THE TUBULAR ORGANS BLOOD VELOCITY AND FLOW AND RELATED PARAMETERS

BACKGROUND OF THE INVENTION

FIELD OF THE INVENTION

The present invention relates to blood flow diagnosis in general, and to a method and system for determining the coronary reserve and the relative coronary reserve, in particular.

DISCUSSION OF THE RELATED ART

The coronary velocity reserve (CVR) also known as the coronary flow reserve (CFR), and generally referenced hereinafter as coronary reserve, is defined to be the ratio between the maximal and the resting coronary blood flow. The maximal coronary blood velocity occurs at times of highly intensive exercise, or it is induced when the subject is injected with coronary vasodilator such as adenosine. The coronary reserve represents the ability of the coronary arteries to supply the excess blood needed to comply with the excessive pumping requirements, relatively to normal (resting) conditions. The normal coronary reserve is greater than 3.0 and in some individuals is greater than 5.0. When the CFR is impaired (values equal to or less than 2.5) the coronary arteries are unable to supply the excess required amounts of blood. Reduced CFR is often associated with angina pectoris, diabetes mellitus, systemic sclerosis, Coronary Syndrome X and other clinical conditions. Determining the CFR is also valuable when assessing the severity of a stenosis in a coronary artery, since there are cases when a stenosis is found, but is not the sole cause of ischemia. Therefore, prior to performing a risky and expensive medical operation, determining the CFR should be considered. Flow measurement is also useful for predicting long-term success of treatment and comparison of efficacy of various treatments. Some currently available techniques for measuring the CFR include invasive methods such as a Doppler catheter, or a pressure wire, which follows a leading catheter that emits the

contrast agent. The Doppler catheter or pressure wire methods have several disadvantages. Extra intervention procedures are required, which makes the Doppler catheter or the pressure wire methods more costly, more invasive, and therefore more risky. In addition, the extra wire or catheter affect the flow itself and therefore impair the measured flow. Yet another drawback of the Doppler catheter and the pressure wire is that the catheter or wire must be accurately aligned, otherwise the results are impaired. Another method for measuring the CFR involves Magnetic Resonance (MR). This procedure is used for diagnosis only while the catheterization procedures are used for therapeutic purposes as well. The MR method is also costly and physicians are reluctant to use it.

Another method for measuring the CFR is the Digital Subtraction Analysis (DSA). When using the DSA method, the flow is evaluated directly from the angiograms, by measuring the change in the gray level in a specified region, caused by the spreading of the contrast agent. This method uses the relation between the gray level and the volume of the contrast agent (as in densitometry) to calculate the flow directly from the change in gray level between successive frames. A limitation of the DSA methods is the difficulty in calibrating the relation between the gray level and the volume. This relation depends on imaging conditions such as the X-ray energy, the extent of magnification, the distance between the source image and the receptor (SID), or others, and contrast material parameters. There are too many parameters and not enough available information to accurately determine the CFR. Another drawback of the DSA method originates from the area captured in the x-ray. Since this area is substantially larger than the area of the artery, the error calculations are mush larger, which again harms the measurements.

Yet another method for evaluating the CFR is the Contrast Propagation Algorithm (CPA). When using the CPA method, the flow is determined by observing the propagation of the haze. The limitations of the CPA are that it is a difficult task to follow the haze, due to its indistinct nature, and that it is required

to know the exact structure of the artery in order to take into account the 3D geometry. Therefore, this method is hard to execute and suffers form inaccuracies.

A parameter related to the coronary flow is the TIMI Flow Grading, which is a qualitative assessment of dye washout during contrast angiography. Using the TIMI flow grading for assessing the coronary reserve is qualitative and subjective, and therefore does not provide accurate measurements.

There is therefore a need for a relatively cost effective, easy to use, accurate and reliable method and system for measuring the CFR of a subject and other flow related measurements. It is desirable that the method will provide accurate results for flow measurement at different times during the cycle of the heart beat, and will incorporate, as a preferred embodiment, the full heart beat cycle for providing accurate average results. It is also desirable that the method can be used during the catheterization, or at a later time, and will not imply extra invasiveness beyond a standard catheterization.

SUMMARY OF THE PRESENT INVENTION

It is an object of the present invention to provide a novel method and apparatus for the determination of coronary reserve and relative coronary reserve of a specific coronary artery segment and other flow related measurements.

In accordance with the present invention, there is thus provided a method for determining the arterial blood velocity, blood flow and the arterial reserve of a subject, the method comprising the steps of: determining the 3D models, including the volumes of a fixed segment of an artery of the subject at a plurality of points in time, the time range between the points can vary from a minimum duration (between two frames) to one or more heart beat cycles; injecting contrast agent in a specific manner into the artery of the subject, the contrast agent is delivered to the segment being in a non-hyperemic state; determining arterial segment output values of the blood flow within the segment of the artery being in a non-hyperemic state, at times corresponding to the plurality of points in time; summing the arterial segment flow output values determined during the one or more heart beats, said arterial segment being in a non-hyperemic state; dividing the summed arterial segment flow output values by the duration of one or more heart beats, yielding an average non-hyperemic artery segment flow output; injecting the subject with substance that simulates hyperemia; determining the volumes of the segment of the artery being in a hyperemic state, at times corresponding to the plurality of points in time associated with the minimum time or the one or more other heart beats; injecting the contrast agent to the artery of the subject, said contrast agent is delivered to the segment being in a hyperemic state; determining arterial segment output values of the blood flow within the segment of the artery being in a hyperemic state, at times corresponding to the plurality of points in time associated with from a minimum time (between two frames) to one or more of the another heart beat; summing the arterial segment output values determined during the second heart beat, said arterial segment being in a hyperemic state; dividing the summed arterial segment flow output values by the duration of the another heart beat,

yielding an average hyperemic artery segment flow output; and determining the arterial reserve as the ratio between the average hyperemic artery segment flow output and the average non-hyperemic artery segment flow output.

The method further comprising the step of determining the relative arterial reserve as the ratio between the arterial reserve determined for a first artery segment and the arterial reserve determined for a second artery segment. The first artery segment is diseased or is suspect as being diseased and the second artery segment is healthy.

The method further comprising the step of determining the velocity of the blood flow within the segment of the artery being in a non-hyperemic state, at times corresponding to the plurality of points in time associated with from a minimum time (between two frames) to one or more heart beats.

The method further comprising the step of determining the material filling rate within the fixed segment of the first artery being in a non-hyperemic state, and in hyperemic state at times corresponding to the plurality of points in time associated with from minimum time (between two frames) to one or more heart beats. The method further comprising two methods of calculating the above filling rate both based on time curves of GL. One is analyzing the whole artery segment while the other analyzing local curves in multiple points (minimum 2).

The method further comprising flow related measurements such as TIMI grade measurements with more accuracy than the existing methods by using the local curve analyzing method for the measurements.

In accordance with another aspect of the present invention, there is provided an apparatus for determining the arterial reserve of a subject from at least two images, the apparatus comprises: a segment volume component for determining the volume of a segment of an artery; a gray level extraction component for extracting the gray level representing the material filling rate along the artery; a fractional blood volume component for determining a fraction of the volume of the blood flow along the artery at a plurality of points within a time interval, which is at the minimum the interval between two consecutive frames

and at the maximum one or more heart beats; a fractional average artery segment flow output component for determining the average artery segment flow output during of one artery during the abovementioned interval; and an artery reserve component for determining the arterial reserve as the ratio between the average artery segment flow output for an artery in a hyperemic state and the average artery segment flow output for the artery in a non-hyperemic state.

The apparatus further comprising a fractional blood velocity component for determining the velocity of the blood flow along the artery at a plurality of points in time associated with from a minimum time (two frames) to during one or more heart beats. The apparatus further comprising a relative arterial reserve component for determining the relative arterial reserve between the first artery and a second artery, said relative arterial reserve being the ratio between the arterial reserve of the first artery and the arterial reserve of the second artery. The apparatus further comprising at least one image acquiring device. The apparatus further comprising a device for transferring images acquired by an image acquiring device to a processing unit, the processing unit comprises an at least one input and output devices for receiving input and presenting output to a user. The apparatus further comprising a storage device for storing the images or the determined arterial reserve values.

The apparatus further comprising a dedicated controlled contrast material injection device for velocity calculations.

BRIEF DESCRIPTION OF THE DRAWINGS

The present invention will be understood and appreciated more fully from the following detailed description taken in conjunction with the drawings in which:

Fig. 1 is a schematic illustration of an exemplary environment in which one embodiment of the proposed invention is used;

Fig. 2 is a schematic block diagram of the software or firmware computational components of the proposed invention;

Fig. 3 is a schematic flow chart of the proposed method for measuring the coronary reserve and the relative coronary reserve.

Fig. 4 is a graph showing the gray level representing the contrast agent concentration in a specific location in an artery;

Fig. 5 is a graph showing the gray level as representing the concentration of contrast agent as a function of time and location; and

Fig. 6 is a graph illustrating the analysis of the graph shown in Fig. 5.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENT

A new and novel apparatus and method for the determination of coronary reserve and relative coronary reserve and other flow related measurements of a specific coronary artery is disclosed. The proposed method and apparatus first determines the 3D model, including the volume of a fixed segment of an artery at multiple points of time throughout a heart beat cycle. Alternatively, the method uses extrapolation of the 3D model, including the associated volumes from one time segment to another. In yet another alternative, the 3D model and is volumes are received from another source, such as CardiOp by Paieon of Rosh Ha'ayin, Israel. Then, using a contrast agent injected to the subject, the apparatus measures the rate at which the injected material fills the segment of the artery examined. The filling rate and the volume of the segment of the artery examined at the same point in time relatively to the heart beat cycle are used to determine the velocity of the blood flow at that point in time. The velocity of the blood flow over the heart beat cycle is measured in two preferred embodiments. In one preferred embodiment of the present invention, the velocity is calculated by analyzing the gray level through the whole artery segment between two consequent images, and then integrating and averaging over one or more full heart beat cycles. In the second preferred embodiment, the velocity is measured using multiple points along the artery segment, analyzing the local change over time of the gray level. Using the velocity, the process yields the coronary flow output at resting conditions. Then, the subject is injected with coronary vasodilator such as adenosine, simulating hyperemia, and the process is generally repeated. The 3D model and volume determination step can be skipped, since the volume of the large arteries might change insignificantly as the result of the injection. Additionally, since the heart beat cycle might be shorted after the injection, it is possible to down sample the series of volumes. The coronary reserve is then calculated as the ratio between the coronary output in hyperemia, and the arterial output under resting conditions. This method can be applied to any artery in the body of the subject, including the coronary arteries. In accordance with another

embodiment of the present invention, in order to determine the relative coronary reserve, the whole process is repeated for a second coronary artery, which is known to be healthy, and a coronary reserve is determined for the second artery. The ratio between the two coronary reserves is the relative coronary reserve.

Referring now to Fig. 1 depicting an exemplary environment in which one preferred embodiment of the present invention is used. As shown in the figure in question, a patient subject 4 is lying down in an operating room, being catheterized. The catheter 8 is inserted into the subject's body at the groin, or at another location and is moved through arteries to the area of the heart. Any known methods of catheterized can be used in conjunction with the present invention. At the physician's discretion, the catheter emits a certain amount of contrast agent into an artery of the patient. A computerized angiography device 12 directed at the tip of the catheter is then activated to produce one or more angiograms of the field of view. The angiograms depict the areas where the contrast agent is present in various levels of gray color, in accordance with the concentration of the agent. The resulting images depict the arteries that contain contrast agent. The higher the imaging rate, the better the accuracy of the proposed method. In accordance with a preferred embodiment, the angiograms are transferred from the catheterization work station 15, which is a standard component of a catheterization laboratory (cath-lab) to a work station 16 which uses the images and data transferred from the catheterization work station 15. The work station 16 displays information to the operator of the apparatus and sets the parameters for injecting the patient with contrast agent during the flow analysis. Once the angiograms have been taken, the patient himself does not have to be present at the site. The flow reserve calculation can be carried on immediately after the angiograms have been taken or at a later time, such as a predetermined time set by the user of the apparatus of the present invention. In other preferred embodiments of the present invention the catheterization work station 15 also comprises the apparatus of the present invention as an integrated capability. The work station 16 is preferably a computing platform, such as a personal computer, a mainframe computer, or any

other type of computing platform that is provisioned with a memory device (not shown), a CPU or microprocessor device (not shown), and several I/O ports (not shown). Alternatively, the work station 16 can be a DSP chip (not shown), an ASIC device (not shown) storing the commands and data necessary to execute the methods of the present invention, or the like. The work station 16 can further include a storage device (not shown), storing the coronary reserve determination application. The coronary reserve determination application is a set of logically inter-related computer programs or components of computer components and associated data structures that interact to determine the coronary reserve and the relative coronary reserve from the angiograms. The angiograms are preferably transferred to the work station 16 via a transferring device such as a pre-defined I/O port (not shown), DICOM-implementing interface, or analog lines. The angiograms are processed by an apparatus of the present invention. The work station 16 has input and output devices, preferably a keyboard, a mouse and a display where the physician or another stuff member can view or manipulate the angiograms and the products of the application. Alternatively, work station 16 delivers the output to another system.

In an alternative embodiment of the present invention, the coronary reserve is calculated offline, based on angiograms that were taken at an earlier time and possibly at a different location. For example, where the apparatus of the present invention receives angiograms taken from a patient located in a remote area, such as in a different building, or a different, city, state, country and then transmitted at the same time or later, such as even after the patient has recovered or his condition has worsen, via communication lines to the location where the apparatus of the present invention is located, then the angiograms can be analyzed and processed by the apparatus at such time and in other location, effectively allowing the use of the apparatus at any time or location irrespective of the location of the patient, or the time at which the angiograms were taken. Thus, no interaction with the patient is required beyond taking the angiograms.

Referring now to Fig. 2, showing the main software or firmware components of the coronary reserve determination application, generally referred to as 46. The segment volume and preferred angle component 50 is a computer program or part of a program, such as CardiOp by Paieon of Rosh Ha'ayin, Israel, when used frame by frame or when used for 3D modeling and volume extrapolation. The segment volume and preferred angle component 50 takes as input a series of images of a fixed segment of an artery, taken at n equally spaced points in time throughout a heart beat cycle, computes a three-dimensional model of the artery segment, and from that model determines a series of numbers:

$$\{V_i\}$$

where i denotes the index of the relevant point in time, and V_i. is the volume of the artery segment at time i. The segment volume and preferred angle component 50 also outputs an imaging direction in which the artery segment should be imaged. This direction minimizes the foreshortening of the artery segment of interest, and is therefore substantially perpendicular to the artery segment. Since the artery segment is generally not straight, the three-dimensional model of the artery segment uses also for compensating for the local non-perpendicularity between the imaging view and the artery segment. Alternatively, step 50 can be skipped when the three-dimensional model, outputs $\{V_i\}$ and the projection angle are provided by an external source.

The fractional blood volume component 54 receives as input a series of images taken immediately after injecting a contrast agent into the artery. The images are taken substantially perpendicularly to the artery, using the angle calculated by the segment volume and preferred angle for reserve analysis images component 50, so that the average gray level of the internal part of the artery in the image represents the amount of contrast agent present at the artery segment at that instance. The output of the fractional blood volume calculating component is the blood volume that passes through the artery segment between time i -1 and time i, for all i between 1 and n. The registration of images taken at the

different stages of the process is enabled by using the three-dimensional model of the artery segment, created or received in step 50. Since the 3D model of the artery and its imaging geometry are available, the registration task should be performed on lateral shift only, thus minimizing registration errors.

The fractional velocity component 56, determines the average velocity of the blood flow at each time segment i.Two preferred methods for velocity measure are detailed hereinafter.

In one preferred method associated with the present invention, the fractional velocity component 56 takes as input the change in the average gray level of the pixels depicting the inside of the artery in images taken at the i-1 and the i-th points of time, representing the velocity of the contrast agent flowing through the artery segment at that time (the higher the change in the gray level - the higher the velocity of the material, and vice versa). Therefore, the time derivative of the gray level represents the velocity of the material through the artery at that time. Using the volume of the artery segment, V_i, at the same point of time relatively to the heart beat cycle, and the velocity of the contrast material yields the volume of the blood passing in the artery segment during each time slot. When using this embodiment, the amount and rate of the injected contrast material should not cause the gray level image to reach saturation. The gray level over all the pixels of the cross section of the artery at location l along the artery segment in image i is denoted by $G_i^*(l)$. The projected gray level at every point l along the artery segment in image i, which takes into account the angle between the line of sight of the angiogram and the local direction of the artery, τ , is denoted by $g(G_i^*(l), \tau)$. For example, the function g can take the form of:

$$g(G_i^*(l), \tau) = G_i^*(l) * \sin(\tau)$$

Then, the projected gray level over the whole artery segment is calculated by the formula:

$$Gi = \int_L g(G_i^*(l),\tau)dl$$

The difference between the gray levels of two consecutive images, ΔGi, is therefore:

$$\Delta Gi = Gi - Gi-1$$

The linear approximation of the time derivative of the gray level,

$$\frac{\Delta Gi}{\Delta t}$$

where Δt is the duration of the i-th time segment, represents the velocity of the contrast agent along the artery segment. However, to switch from gray level change to velocity, this ratio should be calibrated using a predetermined function $f(\frac{\Delta Gi}{\Delta t}, Gi)$. When the contrast agent leaves the artery segment, the change in the gray level is negative. However, the velocity of the blood is still positive. This sign inversion is also taken care of by the function f.

Therefore,

$$Si = f(\frac{\Delta Gi}{\Delta t}, Gi)$$

where Si is the average velocity of the flow in the artery segment during the i-th time slot.

Referring now to Fig. 4, showing an alternative embodiment for the fractional velocity component 56 of Fig. 2. Fig. 4 depicts the gray level at a fixed point x at the artery segment after injecting contrast agent, as a function of time. On the left hand side 110 of the graph of Fig. 4 the gray level depicted is low or non existent, representing a state where contrast agent is not present in the relevant segment to be examined. When injecting the contrast agent to the artery, the contrast agent flows through the arteries and reaches the relevant segment, thus an increase 112 in the gray level is depicted in the graph of fig. 4. Next, the contrast agent gradually fills the segment until such time when the segment is

saturated and a steady state 114 is achieved. At that time, the segment is fully colored by the contrast agent.

Turning now to Fig. 5 showing a family of graphs of the type shown in Fig. 4, on a common coordinate system. Each graph 116, 117, 118, 119 represents the changing gray level relatively to the time, at a different location along the artery segment, x. In the example shown, graph 119 depicts the part of the segment of the artery to which the contrast agent arrives initially, while graph 116 depicts the part of the segment to which the contrast agent arrives last.

Referring now to Fig. 6 showing an illustration of a top view of the three-dimensional collection of graphs 116, 117, 118, 119 of Fig.5, where the gray level is presented by a pattern. The higher the gray level at Fig.5, the denser the pattern is, at Fig. 6. It should be noted, that although the gray level at Fig. 6 are discrete, since Fig. 6 is exemplary only, the gray levels are actually continuous. The time immediately after the injection and before the contrast agent reaches a certain point in the artery is the no-contrast region 120 in Fig. 6. The transient region 124 represents the segment location where and time in which the contrast agent gradually fills the artery. The saturation area 128 represents the segment location where and time in which the whole relevant segment is filled with the contrast agent. The tangent of the angle α 132 between the major axis 136 of the transient region 124 and the time axis, represents the velocity of the blood flow. This method provides the velocity Si for the i-th time slot of the heart beat cycle. Repeating the injection and the analysis for different time segments will provide the velocities $\{ Si \}$ for the full heart beat cycle.

The time interval between the injection of the contrast agent and the arrival of the agent to a certain location along the artery can be used for more accurate estimation of TIMI grade, by applying the velocity at multiple points method at one point, for bolus arrival time measurements.

Referring now back to Fig. 2, the average artery segment output calculating component receives the Si for the i-th time slot, and calculates the blood volume

flowing through the artery segment during the i-th time slot ΔB_i, using the formula:

$$\Delta Bi = \frac{Si * \Delta t * Vi}{L}$$

Multiplying the velocity Si by the duration of the time slot Δt yields the distance traveled by the material during the time slot. Dividing this ratio by the length of the segment, L, yields the relative part of the segment traveled by the material. Multiplying this quantity by the volume of the artery segment at that point in time, yields the quantity of blood that flew through the segment during this time slot.

The average artery segment output component, 58, first determines the overall volume of blood flow through the artery segment during the heart beat cycle, B. B is determined as the summation of the volumes of the blood flows over all time slots:

$$B = \sum_{i=1}^{n} \Delta Bi$$

The average artery segment output, Q, is the total volume, divided by the duration of the heart beat cycle, T.

Therefore

$$Q = \frac{B}{T}$$

If the overall volume of blood flow through the artery segment during the heart beat cycle, B, or the average artery segment output, Q, are of interest, their values are output by the average artery segment output component, 58.

The coronary reserve component 62 takes as input the average artery segment output in rest conditions, Qr, and the average artery segment output in hyperemia, Qh. The coronary reserve is the ratio:

$$CFR=\frac{Qh}{Qr}$$

In a preferred embodiment of the present invention. relative coronary reserve calculation component 66 takes as input the CFR of two arteries, $CFRa$ which is the artery diseased or suspect of being diseased and $CFRb$ which is of a healthy artery and calculates their ratio:

$$rCFR = \frac{CFRa}{CFRb}$$

It will be understood that if a healthy artery is not present than the relative coronary flow will not be calculated.

Referring now to Fig. 3, showing the flow diagram of the process of calculating the coronary reserve of an artery. In step 84 at least one pair of images of the artery are taken at multiple times throughout a heart beat cycle. In each pair, the two images are taken from different projection angles. From each pair of images, a three-dimensional model of the artery segment is generated, and the volume of a fixed part of the artery is determined by a relevant software program or part of a program, such as CardiOp made by Paieon from Rosh Ha'Ayin, Israel. The part of the artery of interest is defined, for example, by a fixed distance from a stenosis in the distal direction and a possibly different distance in the proximal direction. Instead of a stenosis, any other fixed point can be used as a reference point for the artery segment. Preferably, as long as possible, artery segments with no substantial branching are chosen. However, branches flow can be subtracted for accurate measurement and calculations when the artery segments do include branches. The fixed length can be anywhere from about a few millimeters to about 15 centimeters from the fixed point in the proximal and the distal directions. During step 84, the projection angle which is most perpendicular to the artery segment is calculated form the three dimensional model of the artery segment. Step 84 can be accomplished also by extrapolation of a 3D model performed at one point in time during the heart beat cycle to the entire heart cycle.

In step 88, contrast agent is injected to the artery through the use of the catheter as shown in Fig. 1 or through the use of other means such as a needle, intravenous tube and the like or a specific controlled injection system. In step 92 multiple images are taken from the projection angle calculated in step 84, throughout a heart beat cycle, immediately after the contrast agent injection. The images are taken at points in time corresponding to the times at which images were taken at step 84, i.e., at the same times relatively to the heart beat cycle. The more images taken during the heart beat cycle, the better is the resolution received and therefore the accuracy in providing the CFR and rCFR. The number of images taken depends on the duration of the heart beat cycle and on the image-acquiring rate of the imaging device. Determining the exact sequence of images taken throughout exactly one full heart beat cycle is automatically achieved by the proposed system, using data from the catheterization work station 15 of Fig. 1, or any other synchronization equipment. In step 96, the average artery segment output calculation throughout the heart beat cycle is determined using the fractional blood volume calculation component 54 of Fig. 2. and the average artery segment output calculation 58 of Fig. 2.

In step 100, a coronary vasodilator, such as adenosine, is injected to the subject, and steps 84, 88, 92, and 96 are repeated, so that the average artery segment output is calculated for the artery in hyperemia. Optionally, step 84 of determining the volume of the artery segment at multiple points can be skipped, and the volumes determined prior to the injection of the coronary vasodilator can be used also subsequent to the injection, taking into account the shortened heart beat cycle. This is possible since the coronary vasodilator mainly dilates the small vessels that infuse blood into the muscles rather than the large vessels whose volume does not change significantly. In addition, since the heart beat cycle is shortened due to the injection of coronal vasodilator, it is possible to ignore some of the volume values that were collected prior to the injection and use only a subset. Then, in step 104, the coronary reserve is calculated using the coronary reserve calculation component 92 of Fig. 2, by determining the ratio between the

average artery segment flow output following the adenosine injection (i.e. in hyperemia) and the average artery segment flow output prior to the adenosine injection (in rest condition).

In order to determine the relative coronary reserve, steps 84, 88, 92, 96, 100, and 104 are repeated for a second artery segment, i.e., the CFR is determined for a second artery segment. Then, in step 108, the relative coronary reserve is determined by the ratio between the coronary reserves of the first and the second artery segments.

Persons skilled in the art will appreciate that in order to determine the CFR and the relative CFR with higher degree of precision, the described process can be performed over multiple heart beat cycles or parts thereof rather than one, thus increasing the averaging accuracy. Since the process averages the volume of blood flowing through an artery segment over time, the number of heart beat cycles considered in resting conditions and in hyperemia need not be equal. Similarly, the number of heart beat cycles considered for the diseased artery and for a healthy artery need not be equal as well.

The above shown examples serve merely to provide a clear understanding of the invention and not to limit the scope of the present invention or the claims appended thereto. Persons skilled in the art will appreciate that other variants of the method and systems can be used in association with the present invention so as to meet the invention's goals. Different methods of determining the volume of an artery segment, or of determining the average flow through an artery segment can be employed.

The presented method and apparatus are innovative in terms of using the volume and the flow information of the artery segment either for a specific time slice or throughout a full heart beat cycle with timing adjustments of the 3D model and volumes to the velocity measurements. The proposed invention yields the CFR and the relative CFR with higher degree of precision, without requiring a higher degree of invasiveness than a standard catheterization. The invention carries out the calculations based solely on angiograms, and does not require

additional equipment or special expertise on the side of the physician, thus it is easy and cheap to employ.

The method is accurate, since the data concerning the volume of the artery and the velocity of the blood through the artery are collected independently, thus avoiding the interrelations between the factors. Furthermore, since the structure of the artery is found first, it enables the determination of optimal projection view to be used for the velocity determination stage in order to minimize the need for imaging conditions compensation. However, if such compensation is required, it is best determined once the artery's structure and orientation is known. The data for the stages is collected form the artery only, and not form other areas captured in the angiograms, thus minimizing undesired effects. The method is highly accurate also since the data is collected and analyzed separately for each frame throughout the heart beat cycle, but the total results take into account the information collected throughout the cycle. In addition, performing the gray level analysis over the whole artery segment, minimizes problems of measurement fluctuations.

It will be appreciated by persons skilled in the art that the present invention is not limited to what has been particularly shown and described hereinabove. Rather the scope of the present invention is defined only by the claims which follow.

CLAIMS

What is claimed is:

1. A method for determining the arterial flow output of a subject, the method comprising the following steps:

receiving at least one model, representing an at least one fixed segment of an at least one artery of the subject at a plurality of points in time associated with and during an at least one part of an at least one heart beat cycle;

injecting contrast agent into the at least one artery of the subject, said contrast agent is delivered to the at least one fixed segment; and

determining from angiograms taken at a predetermined projection angle, arterial segment output values of the blood flow within the at least one fixed segment of the at least one artery, at times corresponding to the plurality of points in time associated with the at least one part of the at least one heart beat cycle. .

2. The method of claim 1 further comprising the steps of

summing the arterial segment flow output values determined during the at least one part of the at least one heart beat cycle; and

dividing the summed arterial segment flow output values by the duration of the at least one part of the at least one heart beat cycle, yielding an average artery segment flow output.

3. The method of claim 1 further comprising the step of creating the model of the at least one fixed segment of the at least one artery of the subject.

4. The method of claim 1 further comprising the step of determining the projection angle from the model.

5. The method of claim 1 further comprising the step of compensating for the non-perpendicularity of the at least one fixed segment of the at least one artery of the subject.

6. The method of claim 1 further comprising the step of registering the angiograms with the model.

7. The method of claim 1 wherein the model is a three-dimensional model.

8. The method of claim 1 further comprising the step of determining the fractional velocity of the blood flow within the at least one fixed segment of the at least one artery, at times corresponding to the plurality of points in time associated with the at least one part of the at least one heart beat cycle.
9. The method of claim 8 wherein the velocity is determined by analyzing the whole artery segment for gray level changes in the artery.
10. The method of claim 8 wherein the velocity is determined by analyzing local gray level curves in multiple points of the artery.
11. The method of claim 8 further comprising a step of determining the TIMI grades from the local gray level curves in multiple points of the artery.

12. A method for determining the arterial reserve of a subject, the method comprising the following steps:

receiving an at least one first model, representing of an at least one fixed segment of an at least one artery of the subject at a plurality of points in time associated with and during an at least one part of an at least one first heart beat cycle;

injecting contrast agent into the at least one artery of the subject, said contrast agent is delivered to the at least one fixed segment being in a non-hyperemic state;

determining from an at least one first angiogram taken at a predetermined first projection angle, arterial segment output values of the blood flow within the at least one fixed segment of the at least one artery being in a non-hyperemic state, at times corresponding to the plurality of points in time associated with the at least one part of the at least one first heart beat cycle;

summing the arterial segment output values determined during the at least one part of the at least one first heart beat cycle, said arterial segment being in a non-hyperemic state;

dividing the summed arterial segment output values by the duration of the at least one part of the at least one first heart beat cycle, yielding an average non-hyperemic artery segment flow output;

injecting the subject with substance that simulates hyperemia;

receiving at least one second model, representing the at least one fixed segment of the least one artery being in a hyperemic state, at times corresponding to the plurality of points in time associated with an at least one part of an at least one second heart beat cycle;

injecting the contrast agent to the at least one artery of the subject, said contrast agent is delivered to the at least one fixed segment being in a hyperemic state;

determining from an at least one second angiogram taken at a predetermined second projection angle, arterial segment output values of the blood flow within the at least one fixed segment of the at least one artery being in a hyperemic state, at times corresponding to the plurality of points in time associated with the at least one part of the at least one second heart beat cycle;

summing the arterial segment output values determined during the at least one part of the at least one second heart beat cycle, said arterial segment being in a hyperemic state;

dividing the summed arterial segment output values by the duration of the at least one part of the at least one second heart beat cycle, yielding an average hyperemic artery segment flow output;

determining the arterial reserve as the ratio between the average hyperemic artery segment flow output and the average non-hyperemic artery segment flow output.

13. The method of claim 12 further comprising the step of creating the first or the second models of the at least one artery of the subject.

14. The method of claim 12 wherein the first or the second models are three-dimensional models.

15. The method of claim 12 further comprising the step of determining the first projection angle and the volumes of the at least one fixed segment of the at least one artery of the subject at a plurality of points in time associated with and during the at least one part of the at least one first heart beat cycle, from the first model.

16. The method of claim 12 further comprising the step of determining the second projection angle and the volumes of the at least one fixed segment of the at least one artery of the subject at a plurality of points in time associated with and during the at least one part of the at least one second heart beat cycle, from the second model.

17. The method of claim 12 further comprising the step of compensating for the non-perpendicularity of the least one fixed segment of the at least one artery of the subject.

18. The method of claim 12 further comprising the step of registering the at least one first angiogram with the first model.

19. The method of claim 12 further comprising the step of registering the at least one second angiogram with the second model.

20. The method of claim 12 further comprising the step of determining the fractional velocity of the blood flow within the at least one fixed segment of the at least one artery, at times corresponding to the plurality of points in time associated with the at least one part of the at least one first heart beat cycle.

21. The method of claim 20 wherein the velocity is determined by analyzing the whole artery segment for gray level changes in the artery.

22. The method of claim 20 wherein the velocity is determined by analyzing local gray level curves in multiple points of the artery.

23. The method of claim 20 further comprising a step of determining the TIMI grades from the local gray level curves in multiple points of the artery.

24. The method of claim 12 further comprising the step of determining the fractional velocity of the blood flow within the at least one fixed segment of

the at least one artery, at times corresponding to the plurality of points in time associated with the at least one part of the at least one second heart beat cycle.

25. The method of claim 24 wherein the velocity is determined by analyzing the whole artery segment for gray level changes in the artery.

26. The method of claim 24 wherein the velocity is determined by analyzing local gray level curves in multiple points of the artery.

27. The method of claim 24 further comprising a step of determining the TIMI grades from the local gray level curves in multiple points of the artery.

28. The method of claim 12 further comprising the step of determining the relative arterial reserve as the ratio between the arterial reserve determined for a first artery segment and the arterial reserve determined for a second artery segment.

29. The method of claim 12 wherein the first artery segment is diseased or is suspect as being diseased and the second artery segment is healthy.

30. The method of claim 12 wherein the arterial reserve is an arterial coronary reserve.

31. An apparatus for determining the arterial flow of a subject from at least two images, the apparatus comprises:

a component for receiving a model and volumes of an at least one segment of an at least one artery;

a gray level extraction component for extracting the gray level representing the material filling rate and diminishing rate along the at least one artery;

a fractional blood volume component for determining a fraction of the volume of the blood flow along the at least one artery at a plurality of points in time associated with and during an at least one part of an at least one heart beat cycle;

an average artery segment output component for determining the average artery segment output during the at least one part of the at least one heart beat cycle of the at least one artery;

an artery reserve component for determining the arterial reserve as the ratio between the average artery segment output for a first artery in a hyperemic state and the average artery segment output for the first artery in a non-hyperemic state.

32. The apparatus of claim 31 further comprising a segment volume component for determining the volume of an at least one segment of an at least one artery.

33. An apparatus for determining the arterial reserve of a subject from at least two images, the apparatus comprises:

a component for receiving a model of an at least one segment of an at least one artery;

a gray level extraction component for extracting the gray level representing the material filling rate and diminishing rate along the at least one artery;

a fractional blood volume component for determining from an at least one angiogram taken at a predetermined projection angle a fraction of the volume of the blood flow along the at least one artery at a plurality of points in time associated with and during an at least one part of an at least one heart beat cycle;

an average artery segment output component for determining the average artery segment output during the at least one part of the at least one heart beat cycle of the at least one artery;

an artery reserve component for determining the arterial reserve as the ratio between the average artery segment output for a first artery in a hyperemic state and the average artery segment output for the first artery in a non-hyperemic state.

34. The apparatus of claim 33 further comprising a segment volume component for determining the projection angle and the volume of an at least one segment of an at least one artery from the at least one model.

35. The apparatus of claim 33 further comprising a fractional blood velocity component for determining the velocity of the blood flow along the at least one artery at a plurality of points in time associated with and during the at least one part of the at least one heart beat cycle.

36. The apparatus of claim 33 further comprising a relative arterial reserve component for determining the relative arterial reserve between the first artery and a second artery, said relative arterial reserve being the ratio between the arterial reserve of the first artery and the arterial reserve of the second artery.

37. The apparatus of claim 33 further comprising at least one image acquiring device.

38. The apparatus of claim 33 further comprising a device for transferring images acquired by an image acquiring device to a processing unit, the processing unit comprises an at least one input and output devices for receiving input and presenting output to a user.

39. The apparatus of claim 33 further comprising a storage device for storing the images or the determined arterial reserve values.

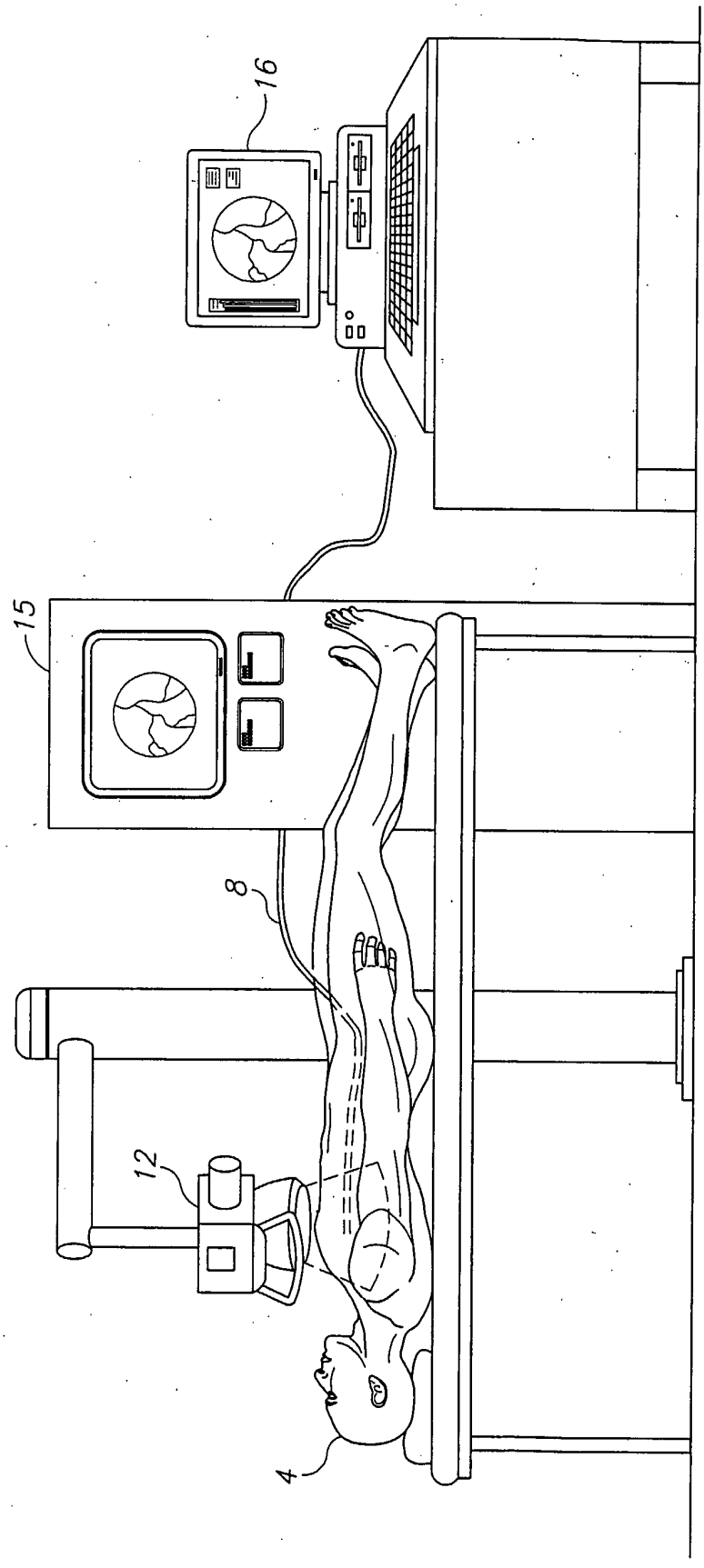

FIG.1

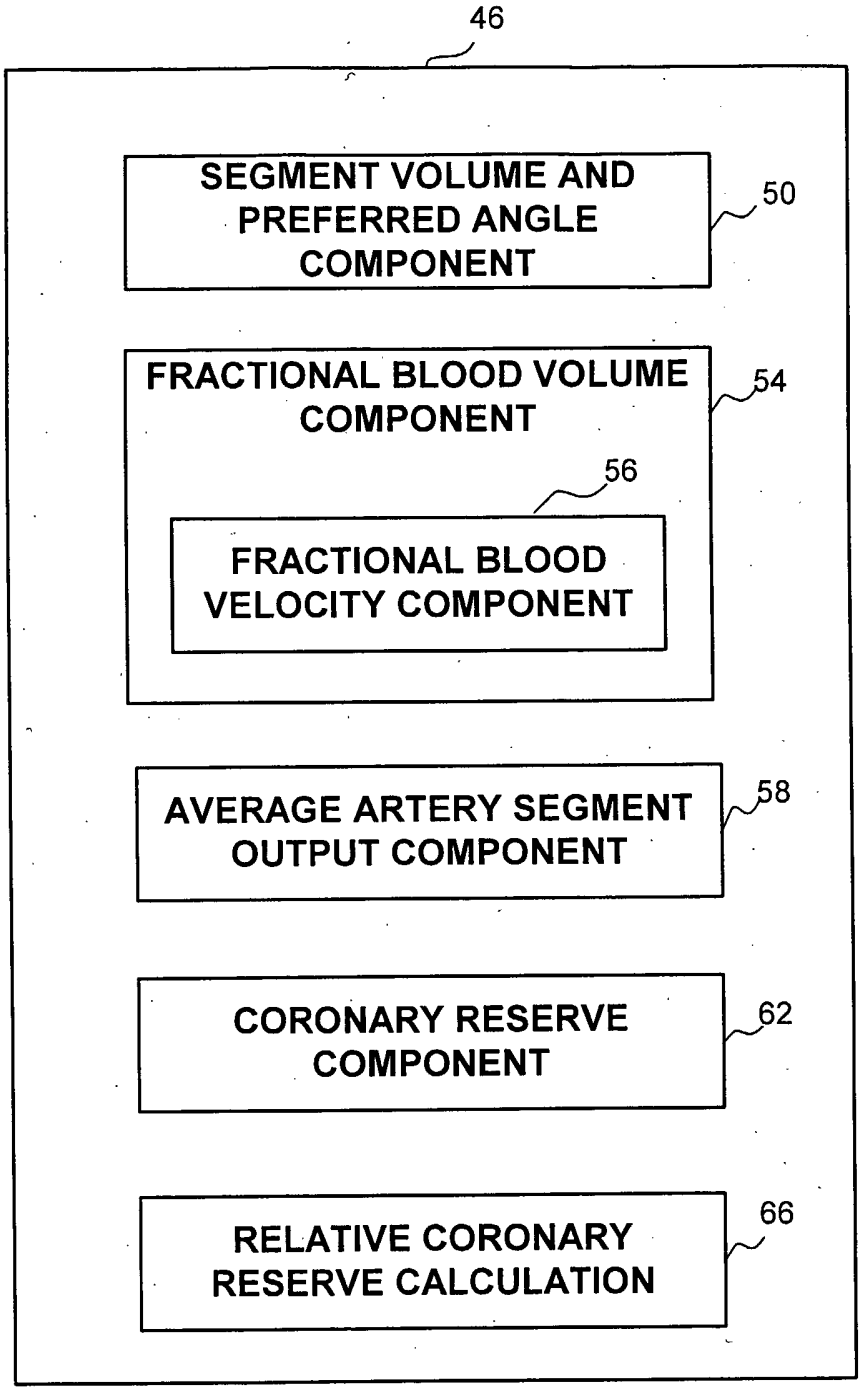
46
SEGMENT VOLUME AND PREFERRED ANGLE COMPONENT
50
FRACTIONAL BLOOD VOLUME COMPONENT
54
56
FRACTIONAL BLOOD VELOCITY COMPONENT
AVERAGE ARTERY SEGMENT OUTPUT COMPONENT
58
CORONARY RESERVE COMPONENT
62
RELATIVE CORONARY RESERVE CALCULATION
66

FIG. 2

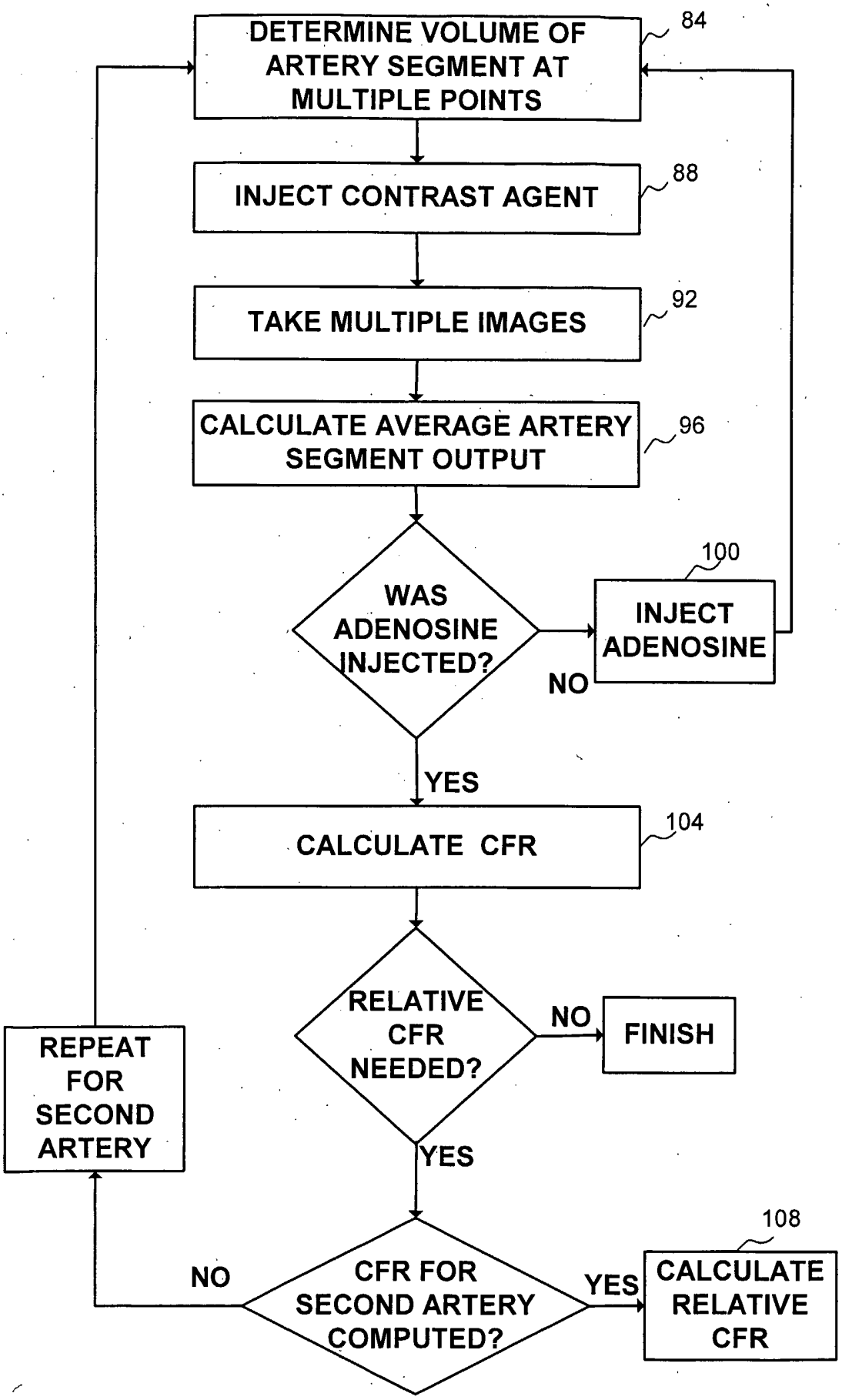
DETERMINE VOLUME OF ARTERY SEGMENT AT MULTIPLE POINTS
84
INJECT CONTRAST AGENT
88
TAKE MULTIPLE IMAGES
92
CALCULATE AVERAGE ARTERY SEGMENT OUTPUT
96
WAS ADENOSINE INJECTED?
NO
100
INJECT ADENOSINE
YES
CALCULATE CFR
104
RELATIVE CFR NEEDED?
NO
FINISH
YES
REPEAT FOR SECOND ARTERY
CFR FOR SECOND ARTERY COMPUTED?
NO
YES
108
CALCULATE RELATIVE CFR

FIG. 3

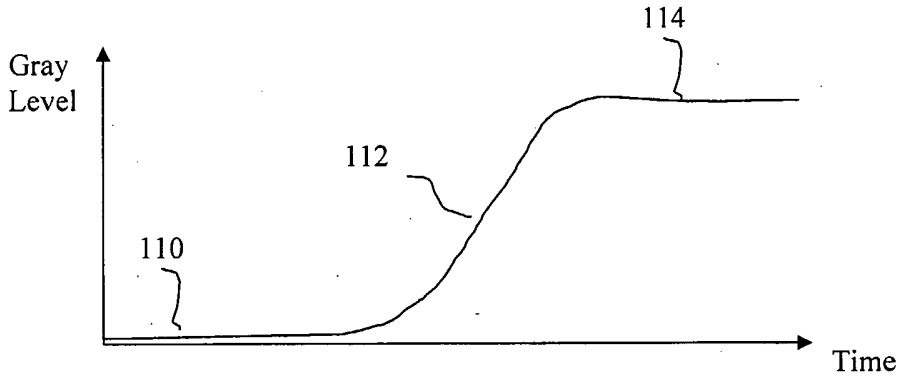

Fig. 4

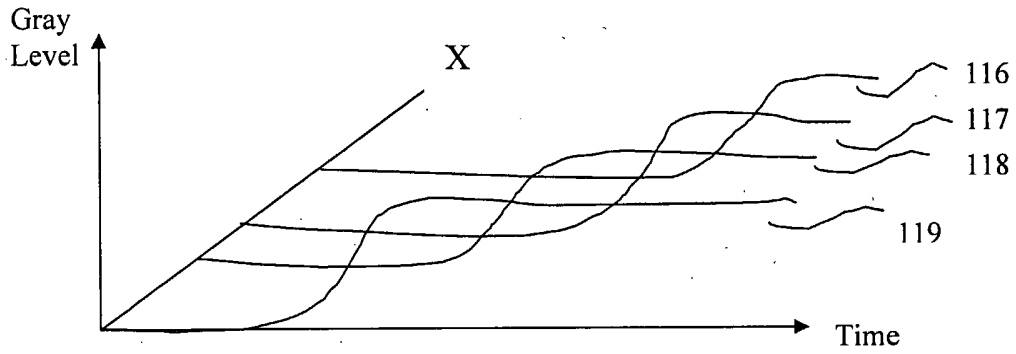

Fig. 5

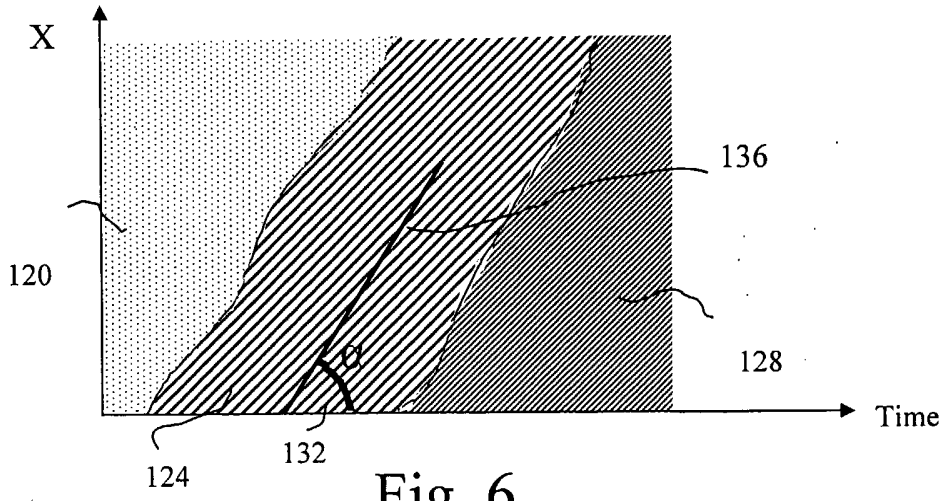

Fig. 6

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IL05/00184

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) : A 61 B 5/05
US CL : 600/407

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : Please See Continuation Sheet

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
NONE

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Please See Continuation Sheet

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5,583,902 A (BAE) 10 December 1996 (10.12.1996), See entire document	1-39
A	US 6,505,064 B1 (LIU et al) 07 January 2003 (07.01.2003), See col.2, col. 5 lines 21-28, col. 6 lines 15-52, col. 7 lines 34-37.	1-39
A	US 6,047,080 A (CHEN et al) 04 April 2000 (04.04.2000), See col. 1 lines 42-58, col. 8 lines 11-28, col. 18 lines 25-27, col. 20 lines 5-24.	1-39

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
09 February 2006 (09.02.2006)	02 MAR 2006
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US Commissioner of Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (571) 273-3201	Authorized officer Marvin Lateef Telephone No. 703-308-0858

Form PCT/ISA/210 (second sheet) (July 1998)

Continuation of B. FIELDS SEARCHED Item 1:
600/407, 410-411, 419-420,425,437,443,447,453-456, 504,507
128/916; 382/128; 378/42, 901

Continuation of B. FIELDS SEARCHED Item 3:
EAST, search terms:bloodflow/amount, heartbeat, heart cycle/phase, angiogra$4, contrast agent/medium, model$5, projection, arter$3 or vessel or vascular