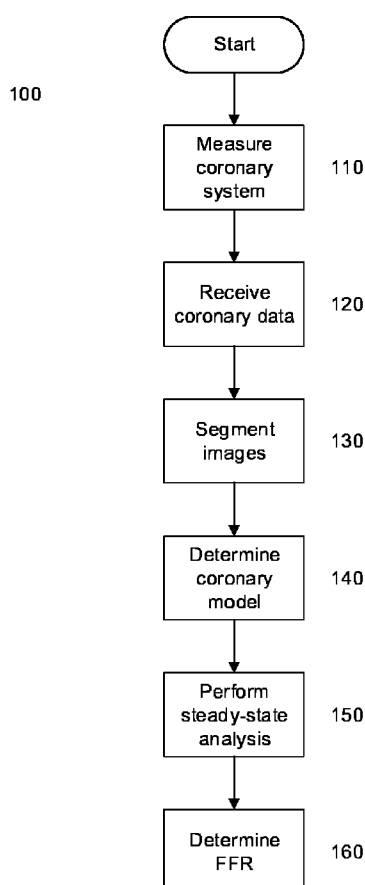




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[Continued on next page]

(54) Title: APPARATUS AND METHOD FOR DETERMINING CORONARY PHYSIOLOGY



(57) Abstract: A computer-implemented method for determining fractional flow reserve (FFR) of a coronary artery and a computer system are provided. Geometry data indicative of a geometry of a coronary system comprising the coronary artery are received; a 3D model of the coronary system is generated based on the geometry data; a pressure-flow relationship through at least a portion of the model is calculated based on steady-state analyses at a plurality of flow rates; the FFR is determined, based upon a non-linear impedance network having one or more characteristics based upon the pressure-flow relationship, and a measured proximal pressure of the coronary artery.

Fig. 1





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Apparatus and Method for Determining Coronary Physiology

BACKGROUND

Fractional Flow Reserve (FFR) is a measure of pressure difference across a coronary artery stenosis or narrowing. FFR is measured by inserting a pressure sensitive wire into the artery. Measurement of FFR is performed during maximal blood flow, hyperaemia, which is induced with drugs. Fractional flow reserve is a ratio of the pressure beyond (distal to) a stenosis relative to the pressure before (proximal to) the stenosis. FFR is known to be useful in that it interprets the characteristics of a stenosis in the context of the coronary system. FFR is defined as an absolute number where an FFR of 0.80 means that a 20% drop in blood pressure is measured across the stenosis relative to a hypothetically normal (fully patent, no stenosis) artery.

Percutaneous coronary intervention (PCI) guided by FFR is superior to standard (visual angiographic) assessment alone, but is under-used. Use of FFR to guide PCI improves clinical treatment decisions and clinical outcomes, results in the deployment of fewer stents and reduces the cost of treatment.

Methods for estimating FFR are known but some methods involve significant computational fluid dynamics (CFD) processing which can take a considerable amount of time, often at least several hours, more often around 24 hours.

It is an object of the embodiments of the invention to at least mitigate one or more of the problems of the prior art. It is an object of embodiments of the invention to provide an improved method of calculating FFR. It is an object of some embodiments of the invention to provide a method of calculating FFR which is computationally more efficient and significantly less time-consuming.

BRIEF SUMMARY OF THE DISCLOSURE

Aspects provide a method and apparatus as set forth in the appended claims.

According to an aspect, there is provided a computer-implemented method for determining fractional flow reserve (FFR) of a coronary artery, comprising: receiving geometry data indicative of a geometry of a coronary system comprising the coronary

artery; generating a 3D model of the coronary system based on the geometry data; calculating a pressure-flow relationship through at least a portion of the model based on steady-state analyses at a plurality of flow rates; determining the FFR, based upon a non-linear impedance network having one or more characteristics based upon the pressure-flow relationship, and a measured proximal pressure of the coronary artery.

According to another aspect, there is provided a computer system, comprising at least one processor; a memory storing computer executable instructions which, when executed by the at least one processor are arranged to perform a method for determining fractional flow reserve (FFR) of a coronary artery as described herein; and an interface arranged to receive, from a detector, geometry data indicative of a geometry of a coronary system comprising a coronary artery and a measured proximal pressure of the coronary artery.

BRIEF DESCRIPTION OF THE DRAWINGS

Embodiments of the invention will now be described by way of example only, with reference to the accompanying figures, in which:

Figure 1 shows a method according to an embodiment;

Figure 2 shows an example of a plurality of images through a body according to an embodiment;

Figure 3 shows an illustration of pressure gradient plotted against flow;

Figure 4 shows an example of a steady-state system according to an embodiment;

Figure 5 shows an example of a transient state system according to an embodiment; and

Figure 6 shows an illustration of transient pressure determined according to an embodiment.

DETAILED DESCRIPTION

Embodiments of the present invention provide a method and apparatus for determining an estimate of fractional flow reserve (FFR) for a coronary artery. The estimate is determined without coronary intervention such as an insertion of a measurement probe
5 into the artery.

Figure 1 illustrates a method 100 according to an embodiment of the invention. The method 100 is performed by a computer to determine the estimate of FFR. Advantageously extensive computation of computational fluid dynamics (CFD) are not
10 required, as will be explained.

The method 100 comprises a step 110 of performing a measurement of at least a portion of a coronary system comprising one or more arteries. The measurement provides data indicative of a plurality of cross-sections through the coronary system. In general, these
15 techniques are known as coronary angiography (CAG). In particular, in some embodiments of the method 100 the data may be used to produce a plurality of images corresponding to cross-sections through the coronary system at each of a plurality of angles, which may be multiple single plane, or rotational angiography. The measurement is performed by an X-ray apparatus where a sequence of images is taken
20 with an X-ray detector at a plurality of angles with respect to the patient and consequently the coronary system. It will be understood that embodiments of the invention are not limited to rotational angiography although, by way of an example only, rotational angiography is described.

Referring to Figure 2, the apparatus for rotational angiography comprises an arm, or more specifically a C-arm, which rotates around a patient and outputs image data corresponding to a series of images at each of a plurality of rotation angles 210, 220, 230, 240. A radiation source emits radiation at each rotation angle and a detector of the apparatus receives radiation transmitted through the body 300 to determine the image.
25

30

Figure 2 illustrates a patient's body 200 comprising the coronary system comprising a heart and coronary arteries. The rotational angiograph rotates around the body 300 to determine the plurality of images intersecting the body 300 at each of a plurality of angles 210, 220, 230, 240. It will be realised that the number and respective angle of

each of the images is not limited by those illustrated in Figure 2. The images may form a video of the coronary system whilst the angiograph rotates about the body. During recording of the images a contrast agent may be administered to the blood in order to improve visibility of the coronary arteries.

5

In step 120 data indicative of a plurality 2D projections through the network is received. The data may be received over a computer network. The data may be received from the apparatus arranged to determine the plurality of projections, such as the angiogram. The data may be received at a computer and stored in one or more memory devices of
10 the computer.

In step 130 the image data received in step 120 is segmented to identify one or more coronary arteries present in the image data. The segmentation may be performed by a variety of methods as will be appreciated by the skilled person. The segmentation may
15 identify a centreline of each coronary artery. The segmentation may define a series of coordinates defining a surface mesh of arteries in the image data. The arteries may be represented as a plurality of tubes, wherein the surface mesh defines the lumen of each of the tubes. The segmentation may be based upon a difference in one or both of colour and contrast between the artery and a background of each image. Segmentation data
20 are used to reconstruct the arterial geometry in 1-, 2-, or 3-dimensions. An output of step 130 is data indicative of at least some of the coronary arteries present in each image.

In step 140 a three-dimensional (3D) model of at least a portion of the coronary system is determined. The model is determined based upon the output of step 130. In
25 particular, the model may be determined based upon the surface mesh determined in step 130.

As part of step 140 one or more inlets and/or outlets are defined of tubes or lumens forming the coronary system. A volume mesh is then determined corresponding to at
30 least a portion of the coronary system. The volume mesh is a polygonal representation of an interior volume of the portion of the coronary system. As an example, the volume mesh may comprise 1-2 million volume elements, although it will be realised that this is not restrictive.

In step 150 steady-state analyses are performed on the model to calculate a pressure-flow relationship through at least a portion of the model at a plurality of fluid flow rates. The pressure-flow relationship may be calculated using CFD. However, in contrast to some prior approaches, dynamic or transient CFD calculations are not used and, instead
 5 as will be explained, only steady state CFD calculations are performed, which may be more quickly and easily calculated. Some embodiments of the invention utilise pseudo-transient pressure analysis which is based upon a plurality of steady-state analyses, as will be explained.

- 10 At each of the plurality of flow rates a corresponding pressure gradient is determined. In particular, a corresponding pressure gradient is determined at each of the first and second flow rates, although it will be appreciated that the pressure gradient at more than two flow rates may be calculated. For example, the pressure gradient at three, four or more than four flow rates may be determined. For a stenosis present in the portion of
 15 the coronary network a pressure loss across the stenosis is determined which results in an energy drop along the tube. In some embodiments the first and second flow rates may be 1ml/s and 3ml/s although it will be realized that other and further flow rates may be used.
- 20 Figure 3 illustrates a graph of flow (x-axis) against pressure gradient (y-axis) at the first and second flow rates 310, 320 for which a corresponding pressure gradient is determined in step 150. A relationship between pressure gradient and flow within the lumen of the coronary system including the stenosis may be represented as a quadratic equation. A pressure differential between the first and second flow rates, as illustrated
 25 in Figure 3, may be represented as $\Delta p = z_0 + z_1 Q + z_2 Q^2$ wherein p is pressure, Q is flow rate and z_0 , z_1 and z_2 are coefficients.

- In step 160 an estimate of FFR is determined based upon the relationship provided from step 150. In particular, the estimate of FFR is determined based upon the coefficients
 30 z_0 and z_1 and z_2 indicative of the relationship between pressure and flow.

The estimate of FFR is further based upon a network associated with the coronary network, as will be explained. Exemplary diagrams of such coronary networks are

shown as circuit diagrams in Figures 4 and 5. Figures 4 and 5 will be explained in further detail below.

Two different embodiments will now be described of step 160. A first embodiment of step 160 determines the estimate of FFR for a steady-state pressure gradient based on a first system 400 depicted in Figure 4. A second embodiment of step 160 determines the estimate of FFR for transient pressure based on a second system 500 depicted in Figure 5.

Steady State Pressure

In the first embodiment of step 160 an estimate of the FFR is determined for a steady-state pressure gradient. The FFR may be determined by an algorithm based upon the relationship of the results of the steady state analyses performed at step 150, a mean inlet pressure determined from the measurements, taken at step 110, of the coronary system 400 as shown in Figure 4 and the total distal resistance of the coronary system 400.

The coronary system 400 shown in Figure 4, has an input flow Q and an input pressure p . The coronary system 400 may comprise an artery 410. The artery 410 may have a lesion affecting the pressure gradient and flow of blood through the coronary system.

The coronary system 400 may have a number of features representing a resistance to the blood flowing through the system. These are represented in Figure 4 as two resistances (Z 420 and R 430).

It will be appreciated by the skilled person, that knowing the input flow and pressure, and the values representative of resistance Z 420, and resistance R 430; the pressure and flow can be calculated at various points indicated by Q , p_1 , and p_2 on Figure 4.

It will be appreciated the mean inlet pressure may be determined by a plurality of methods including, but not limited to, that recorded during coronary angiography.

As described above in relation to step 150 and Figure 3, a relationship between the pressure gradient and flow is defined and may be presented as a quadratic equation. The relationship may be defined as:

$$dp = (z_2 \cdot Q^2) + (z_1 \cdot Q) + z_0$$

Equation 1

where z_0 , z_1 , and z_2 are constants; dp is the pressure gradient and Q is flow. As explained above, steady-state CFD simulation is performed at a plurality of different flow rates, such as two different flow rates Q_x and Q_y , which may be, for example, between 0.5 and 2 ml/s e.g. 1ml/s and between 2 and 4ml/s e.g. 3ml/s. It will be appreciated that other flow rates may be analysed. Flow rate Q_x will give rise to a pressure gradient dp_x and flow rate Q_y will give rise to a pressure gradient dp_y . In some embodiments z_0 may be zero due to the graph of the above relationship intercepting the axes at zero. As such it is possible to calculate the remaining constants, z_1 and z_2 :

$$z_2 = \frac{dp_x Q_y - dp_y Q_x}{Q_x^2 Q_y - Q_x Q_y^2}$$

Equation 2

$$z_1 = \frac{-dp_x Q_y^2 + dp_y Q_x^2}{Q_x^2 Q_y - Q_x Q_y^2}$$

Equation 3

Using the above calculated values for z_1 and z_2 it is possible, in combination with the mean inlet pressure and the total distal resistance, a sum of the values representative of resistance Z 420 and resistance R 430 in figure 4, to determine the flow Q . The relationship between the variable and the flow may be in the form of a quadratic equation, as such, the relationship may be defined as:

$$z_2 Q^2 + z_1 Q + ZQ = p - p_i$$

Equation 4

As the pressure at p_i is equal to RQ (assuming zero pressure at p_2), it is possible to rearrange the equation to find the flow Q , as below:

$$Q = \frac{-(z_1 + Z + R) + \sqrt{(z_1 + Z + R)^2 + 4z_2p}}{2z_2}$$

Equation 5

5

Transient Pressure

In the second embodiment of step 160, an estimate of the FFR is determined for a transient pressure. As with the first embodiment of step 160, the FFR may be determined by an algorithm based upon the relationship of the results of the steady state analyses performed at step 150, a the transient inlet pressure determined from the measurements, taken at step 110, of the coronary system 500, as shown in Figure 5, and parameters of the coronary system 500 including the resistance and capacitance values over time.

15 The coronary system 500 shown in Figure 5, has an input flow Q and an input pressure p . The coronary system 500 may comprise an artery 510. The artery 510 may have a lesion affecting the pressure and flow of blood through the coronary system.

The coronary system 500 may have a number of features representing a resistance to the blood flowing through the system. These are represented in Figure 5 as two resistances (Z 520 and R 530). In some embodiments there may be a system representative of a capacitor C 540. The capacitor is representative of the system compliance which allows the build-up and release of pressure during different phases of a cardiac cycle. For example, when the cardiac cycle is in diastole, this may be representative of the capacitor 540 being charged, and when in systole this may be representative of the capacitor 540 being discharged.

It will be appreciated by the skilled person, that knowing the input flow and pressure, and the values representative of resistance Z 520, resistance R 530 and capacitor C 540; the pressure and flow can be calculated at various points indicated by Q , Q_2 , Q_C , p_1 , p_i , p_C and p_2 on Figure 5.

It will be appreciated the inlet pressure may be determined by use of an appropriate measurement instrument, as explained below.

As described above in relation to step 150 and Figure 3, a relationship between the pressure gradient and flow is defined and may be presented as a quadratic equation. It may be necessary to determine the constants of the quadratic equations as shown in Equations 2 and 3 above.

The transient inlet pressure measurement may be recorded from a medical device during step 110, in some embodiments this may be by means of a catheter inserted during invasive coronary angiography. It will be appreciated that other methods may be used to determine the transient inlet pressure of the coronary system 500.

Calculation of the transient outlet pressure of the coronary system 500 may be by means of a quadratic equation and a plurality of other equations as shown below. As the inlet pressure varies over time the capacitor C 540 in the coronary system 500 is representative of the variations in flow experienced due to the beating of the heart. The system represents the active squeeze or compression of small vessels which occurs during myocardial systole. Therefore a pressure (p_c in Fig 5) is applied to the terminal pole of the capacitor. This pressure is defined in terms of its amplitude, its timing and the rate of pressure build up and decay.

The coronary system 500 may be represented by:

$$z_2 Q^2 + z_1 Q + ZQ = p - p_i \quad \text{Equation 6}$$

$$RQ_2 = p_i - p_2 \quad \text{Equation 7}$$

$$Q_c = C \frac{d(p_i - p_c)}{dt} \quad \text{Equation 8}$$

Such that:

$$Q - Q_2 - Q_c = 0$$

Equation 9

5

Therefore:

$$Q - Q_2 = C \frac{d(p_i - p_c)}{dt}$$

Equation 10

10 Using Equations 6 – 10, it is possible to derive differential equations for Q such that $p = p(t)$, $p_2 = 0$, and $p_c = p_c(t)$ where t is the time.

Eliminating $Q_2 = \frac{p_i}{R} = \frac{p - z_2 Q^2 - (z_1 + Z)Q}{R}$ results in:

$$15 \quad Q - \frac{p - z_2 Q^2 - (z_1 + Z)Q}{R} = C \frac{d(p - z_2 Q^2 - (z_1 + Z)Q - p_c)}{dt}$$

Equation 11

$$20 \quad C z_2 \frac{d(Q^2)}{dt} + C(z_1 + Z) \frac{dQ}{dt} + \frac{z_2 Q^2}{R} + \left(1 + \frac{(z_1 + Z)}{R}\right) Q = C \frac{d(p - p_c)}{dt} + \frac{p}{R}$$

Equation 12

$$25 \quad \frac{2z_2}{(z_1 + Z)} Q \frac{dQ}{dt} + \frac{dQ}{dt} + \frac{z_2 Q^2}{(z_1 + Z)RC} + \left(\frac{z_1 + Z + R}{(z_1 + Z)RC}\right) Q = \frac{1}{z_1 + Z} \frac{d(p - p_c)}{dt} + \frac{p}{(z_1 + Z)RC}$$

Equation 13

Using Equations 11 through 13 it is possible to derive a numerical solution using a suitable numerical procedure for solving ordinary differential equations with a given initial value. One form of discretisation scheme may be the First Order Forward Euler method, however it will be appreciated other suitable discretisation methods may be used.

For example, using the First Order Forward Euler method to solve Q for a given p results in:

35

$$\begin{aligned} & \left(\frac{2z_2}{(z_1 + Z)} Q_j + 1 \right) \frac{(Q_{j+1} - Q_j)}{dt} + \frac{z_2 Q_j^2}{(z_1 + Z)RC} + \left(\frac{z_1 + Z + R}{(z_1 + Z)RC} \right) Q_j \\ & = \frac{1}{(z_1 + Z)} (dp)_j - \frac{1}{(z_1 + Z)} (dp_c)_j + \frac{p_j}{(z_1 + Z)RC} \end{aligned}$$

Equation 14

- 5 Rearranging and solving Equation 14, results in Equation 17 below, where:

$$(dp)_j = \left(\frac{dp}{dt} \right)_j$$

Equation 15

And

$$(dp_c)_j = \left(\frac{dp_c}{dt} \right)_j$$

10 Equation 16

$$Q_{j+1} = Q_j + \frac{dt}{\frac{2z_2}{(z_1 + Z)} Q_{j+1}} \left(-\frac{z_2 Q_j^2}{(z_1 + Z)RC} - \left(\frac{z_1 + Z + R}{(z_1 + Z)RC} \right) Q_j + \frac{((dp)_j - (dp_c)_j)}{(z_1 + Z)} + \frac{p_j}{(z_1 + Z)RC} \right)$$

Equation 17

- 15 This enables the calculation of the flow at a particular point in time.

Once a plurality of calculations have been undertaken it is possible to analyse the changes in the pressure gradient and flow over time. An example chart showing the output of the pseudo-transient pressure analysis is shown in Figure 6.

20

Figure 6, shows a measured proximal pressure 610 and a measured distal pressure 620. There is also a computed distal pressure 630 which is the result of the above calculation. As can be seen in Figure 6, correlation between the measured distal pressure 610 and the computed distal pressure 630 is very high. It will be appreciated other methods of displaying the data may be used.

25

It will be appreciated that embodiments of the invention allow for determination of FFR without a need for extensive computation, such as transient CFD calculations performed over many hours. Instead, only steady-state calculations are required at each of a plurality of flow rates. In this way, embodiments of the invention may be seen as

30

determining pseudo-transient FFR based upon the steady state calculations and information indicative of transient inlet pressure. An indication of the determined FFR may be output, such as by a visual display device.

- 5 Methods according to embodiments of the invention are significantly quicker to compute than transient CFD analysis. The pseudo-transient method is advantageous because it uses a plurality of steady-state analyses to provide transient results, without performing transient analysis. This provides additional physiological data which cannot be generated with a purely steady result.

10

It will be appreciated that embodiments of the present invention can be realised in the form of hardware, software or a combination of hardware and software. Any such software may be stored in the form of volatile or non-volatile storage such as, for example, a storage device like a ROM, whether erasable or rewritable or not, or in the
15 form of memory such as, for example, RAM, memory chips, device or integrated circuits or on an optically or magnetically readable medium such as, for example, a CD, DVD, magnetic disk or magnetic tape. It will be appreciated that the storage devices and storage media are embodiments of machine-readable storage that are suitable for storing a program or programs that, when executed, implement embodiments of the
20 present invention. Accordingly, embodiments provide a program comprising code for implementing a system or method as claimed in any preceding claim and a machine readable storage storing such a program. Still further, embodiments of the present invention may be conveyed electronically via any medium such as a communication signal carried over a wired or wireless connection and embodiments suitably encompass
25 the same.

All of the features disclosed in this specification (including any accompanying claims, abstract and drawings), and/or all of the steps of any method or process so disclosed, may be combined in any combination, except combinations where at least some of such
30 features and/or steps are mutually exclusive.

Each feature disclosed in this specification (including any accompanying claims, abstract and drawings), may be replaced by alternative features serving the same, equivalent or similar purpose, unless expressly stated otherwise. Thus, unless expressly

stated otherwise, each feature disclosed is one example only of a generic series of equivalent or similar features.

- 5 The invention is not restricted to the details of any foregoing embodiments. The invention extends to any novel one, or any novel combination, of the features disclosed in this specification (including any accompanying claims, abstract and drawings), or to any novel one, or any novel combination, of the steps of any method or process so disclosed. The claims should not be construed to cover merely the foregoing embodiments, but also any embodiments which fall within the scope of the claims.

CLAIMS

1. A computer-implemented method for determining fractional flow reserve (FFR) of a coronary artery, comprising:

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receiving geometry data indicative of a geometry of a coronary system comprising the coronary artery;

10

generating a 3D model of the coronary system based on the geometry data;

calculating a pressure-flow relationship through at least a portion of the model based on steady-state analyses at a plurality of flow rates;

15

determining the FFR, based upon a non-linear impedance network having one or more characteristics based upon the pressure-flow relationship, and a measured proximal pressure of the coronary artery.

20

2. The method of claim 1, wherein the pressure-flow relationship is calculated as linear and quadratic coefficients.

25

3. The method of any preceding claim, wherein the pressure-flow relationship is calculated as: $\Delta p = z_1 Q + z_2 Q^2 + z_0$ wherein p is pressure, Q is flow rate and z_0 , z_1 and z_2 are coefficients.

4. The method of claim 3, wherein z_0 is 0.

5. The method of any of claims 3 or 4 where z_2 is calculated as:

30

$$z_2 = \frac{dp_x Q_y - dp_y Q_x}{Q_x^2 Q_y - Q_x Q_y^2}$$

wherein:

Q_x is a first flow rate;

Q_y is a second flow rate;

dp_x is a pressure at the first flow rate; and

35

dp_y is a pressure at the second flow rate.

6. The method of any of claims 3 through 5, wherein z_1 is calculated by:

$$z_1 = \frac{-dp_x Q_y^2 + dp_y Q_x^2}{Q_x^2 Q_y - Q_x Q_y^2}$$

5

wherein:

Q_x is a first flow rate;

Q_y is a second flow rate;

10

dp_x is a pressure gradient at the first flow rate; and

dp_y is a pressure gradient at the second flow rate.

7. The method of claim 5 or 6, where the first flow rate is between 0.5 and 2 ml/s.

15

8. The method of any of claims 5 to 7, where the second flow rate is between 2 and 4ml/s.

9. The method of any preceding claim, wherein the non-linear impedance network comprises a first resistance representative of a lesion, wherein a magnitude of the first resistance is based upon flow rate across the lesion.

20

10. The method of claim 9, wherein the first resistance is determined based upon the pressure-flow relationship across the lesion.

25

11. The method of any preceding claim, wherein the non-linear impedance network comprises a distal impedance representative of a vascular network.

12. The method of claim 11, wherein the distal impedance network is representative of distal coronary circulation

30

13. The method of any of claims 9 to 12, wherein the distal impedance network comprises a component representative of intramyocardial pressure.

35

14. The method of claim 13, wherein the component representative of intramyocardial pressure is a second resistance.

15. The method of any preceding claim, wherein the FFR is calculated based upon a mean inlet pressure.
16. The method of claim 15, wherein determining the FFR comprises calculating as:

$$Q = \frac{-(z_1 + Z + R) + \sqrt{(z_1 + Z + R)^2 + 4z_2p}}{2z_2}$$

wherein:

Q is the calculated flow;

Z is a first resistance representative of a lesion;

R is a second resistance representative of an intramyocardial pressure;

p is the mean inlet pressure; and

z_1 and z_2 are coefficient representative of a relationship between the flow and pressure gradient.

17. The method of any of claims 1 to 14, wherein the FFR is calculated based upon a transient inlet pressure.

18. The method of claim 17, wherein determining the FFR comprises calculating:

$$Q_{j+1} = Q_j + \frac{dt}{\frac{2z_2}{(z_1 + Z)} Q_j + 1} \left(-\frac{z_2 Q_j^2}{(z_1 + Z)RC} - \left(\frac{z_1 + Z + R}{(z_1 + Z)RC} \right) Q_j + \frac{((dp)_j - (dp_c)_j)}{(z_1 + Z)} + \frac{p_j}{(z_1 + Z)RC} \right)$$

wherein:

Q_{j+1} is the $j+1^{\text{th}}$ calculated flow;

Q_j is the j^{th} calculated flow;

t is a time;

Z is a first resistance representative of the lesion;

R is a second resistance representative of an intramyocardial pressure;

C is a distal impedance representative of a vascular network;

z_1 , z_2 , $(dp)_j$ and $(dp_c)_j$ are coefficient representative of a relationship between the flow and pressure gradient.

19. The method of claim 18 where $(dp)_j$ is calculated as:

$$(dp)_j = \left(\frac{dp}{dt} \right)_j$$

wherein:

p is a pressure at time j

5 t is a time at time j

20. The method of any of claim 18 or 19, where $(dp_c)_j$ is calculated as:

$$(dp_c)_j = \left(\frac{dp_c}{dt} \right)_j$$

wherein:

10 p is a pressure at the calculation of Q_j

t is a time at time at the calculation of Q_j .

21. The method of any preceding claim, wherein the flow rates are steady-state flow
15 rates.

22. The method of any preceding claim, wherein the geometry data comprises a plurality of angiogram images.

20 23. Computer software which, when executed by a computer, is arranged to perform a method according to any preceding claim; optionally the computer software is stored on a computer-readable medium.

24. A computer system, comprising:

25 at least one processor;

a memory storing computer executable instructions which, when executed by the at least one processor are arranged to perform a method
30 according to any of claims 1 to 22;

an interface arranged to receive, from a detector, geometry data indicative of a geometry of a coronary system comprising a coronary artery and a measured proximal pressure of the coronary artery.

25. The computer system of claim 24, comprising an output device, wherein the processor is arranged to cause the output device to output an indication of the determined the FFR.

5 26. The computer system of claim 25, wherein the output device is a visual display device.

27. A method or apparatus substantially as described hereinbefore with reference to the accompanying drawings.

10

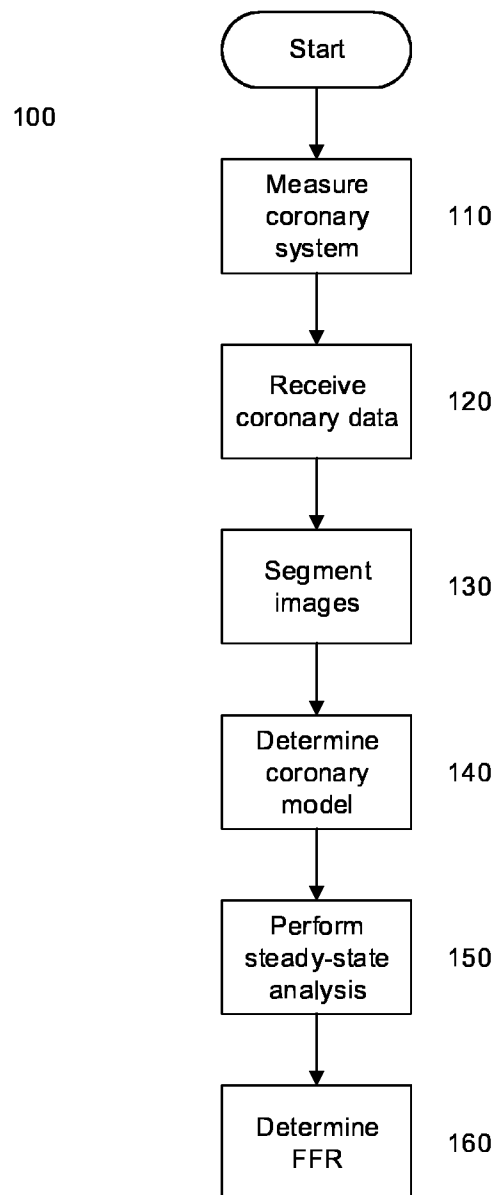


Fig. 1

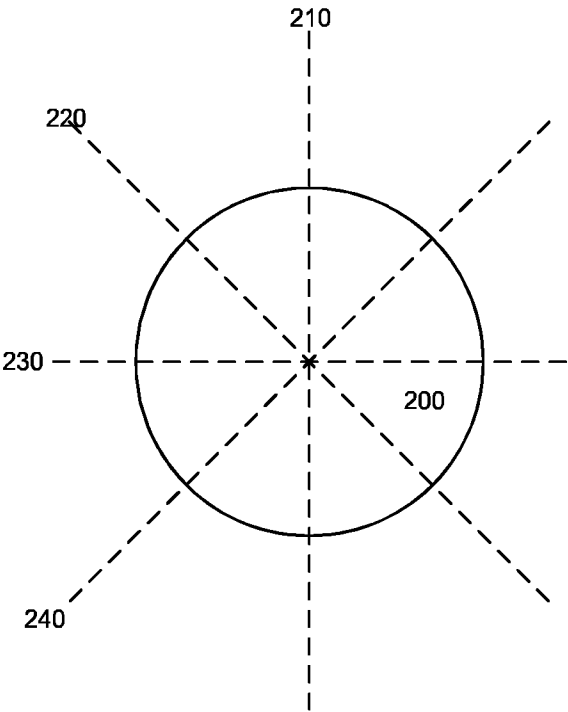


Fig. 2

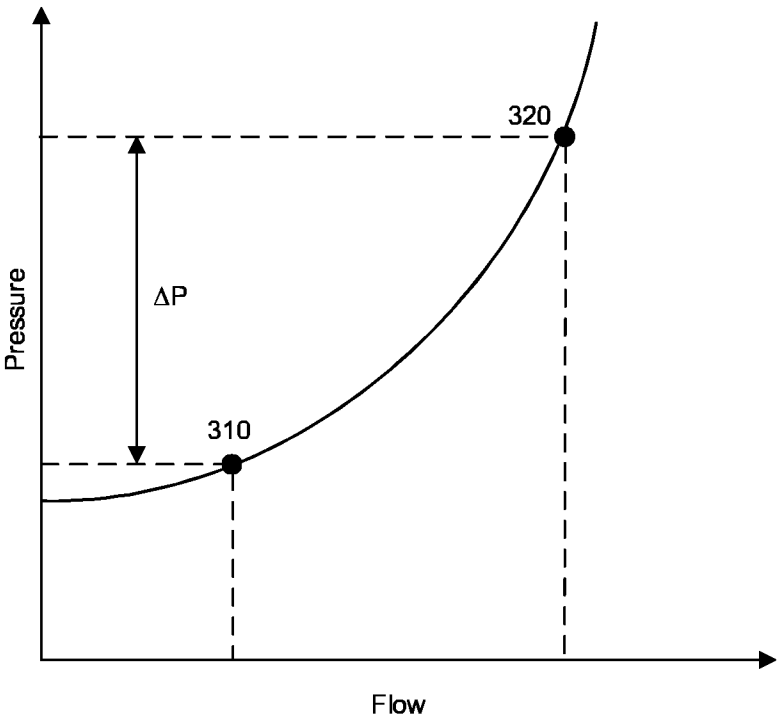


Fig. 3

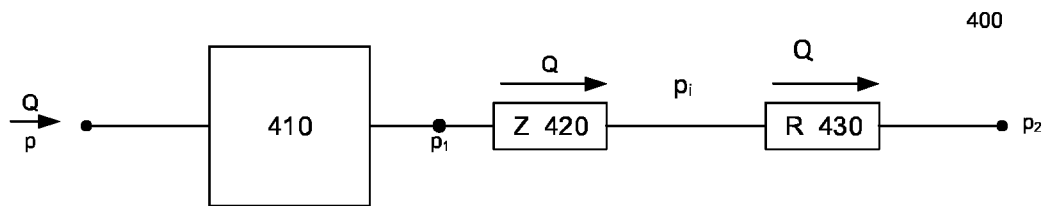


Fig. 4

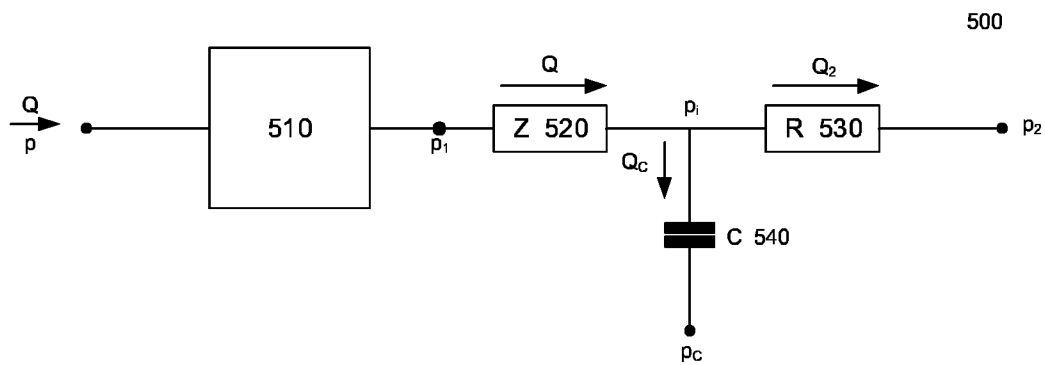


Fig. 5

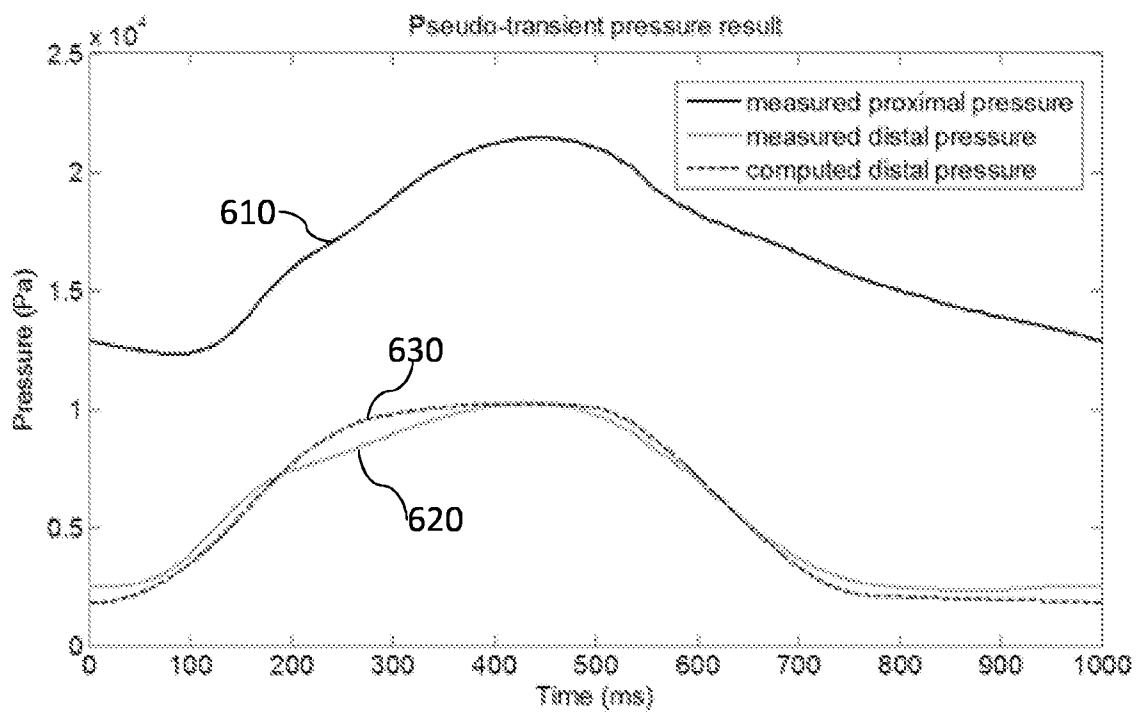


Fig. 6

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2016/053942

A. CLASSIFICATION OF SUBJECT MATTER
INV. G06F19/00
ADD.

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)
G06F

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

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

EPO-Internal, BIOSIS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	MORRIS P. D. ET AL: "'Virtual" (Computed) Fractional Flow Reserve", JACC: CARDIOVASCULAR INTERVENTIONS, vol. 8, no. 8, 24 June 2015 (2015-06-24), pages 1009-1017, XP055356796, AMSTERDAM, NL ISSN: 1936-8798, DOI: 10.1016/j.jcin.2015.04.006 abstract page 1010, left-hand column, lines 16-25 page 1011, right-hand column, lines 14-19 page 1015, left-hand column, lines 14-19 figure 1; table 1 ----- -/--	1-27



Further documents are listed in the continuation of Box C.



See patent family annex.

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Date of the actual completion of the international search

21 March 2017

Date of mailing of the international search report

31/03/2017

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INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2016/053942

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	TAYLOR C. A. ET AL: "Computational Fluid Dynamics Applied to Cardiac Computed Tomography for Noninvasive Quantification of Fractional Flow Reserve", JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY, vol. 61, no. 22, 1 June 2013 (2013-06-01), pages 2233-2241, XP055073689, ISSN: 0735-1097, DOI: 10.1016/j.jacc.2012.11.083 abstract page 2236, left-hand column, line 6 - page 2240, left-hand column, line 15 figures 3,4,6	1-27
X	----- US 2015/038860 A1 (FONTE TIMOTHY A [US] ET AL) 5 February 2015 (2015-02-05) the whole document	1-27
X	----- US 2014/024932 A1 (SHARMA PUNEET [US] ET AL) 23 January 2014 (2014-01-23) the whole document	1-27
A	----- US 2013/060133 A1 (KASSAB GHASSAN S [US] ET AL) 7 March 2013 (2013-03-07) paragraphs [0005], [0061] -----	1-27

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/GB2016/053942

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2015038860 A1	05-02-2015	AU 2014296238 A1	25-02-2016
		AU 2017200000 A1	02-02-2017
		CA 2919714 A1	05-02-2015
		CN 105580019 A	11-05-2016
		EP 3028196 A1	08-06-2016
		JP 2016528975 A	23-09-2016
		KR 20160038038 A	06-04-2016
		US 2015038860 A1	05-02-2015
		WO 2015017571 A1	05-02-2015

US 2014024932 A1	23-01-2014	US 2014024932 A1	23-01-2014
		US 2016073970 A1	17-03-2016

US 2013060133 A1	07-03-2013	NONE	
