(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
22 August 2019 (22.08.2019)

WIPO | PCT

(10) International Publication Number
WO 2019/159094 A1

(51) International Patent Classification:
A61B 8/06 (2006.01) *A61B 8/08* (2006.01)

(21) International Application Number:
PCT/IB2019/051196

(22) International Filing Date:
14 February 2019 (14.02.2019)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
102018000002712 15 February 2018 (15.02.2018) IT

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

(54) Title: METHOD AND SYSTEM FOR THE MEASUREMENT OF HAEMODYNAMIC INDICES

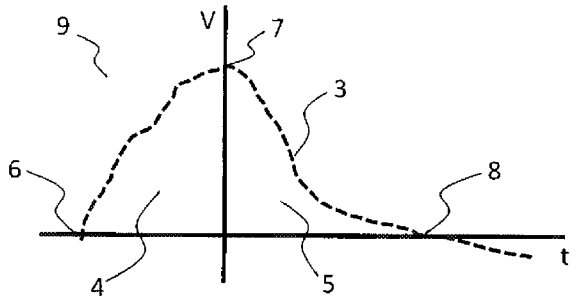

Fig.2

(57) Abstract: Method and relative system for the measurement of haemodynamic indices, said method comprising: acquiring an ultrasound image of at least one segment of an arterial vessel; identifying in said image at least one sample volume; obtaining a time series indicating the blood velocity, or velocity signal (9), in said sample volume and in at least one cardiac cycle; calculating, by means of a processor, a first area (4) equal to the area subtended by the velocity signal (9) between the sample (6) relating to the instant of systole start of said at least one cardiac cycle and the sample (7) of systolic peak; calculating, by means of a processor, a second area (5) subtended by the velocity signal (9) between the sample (7) of systolic peak and the sample (8) relating to the instant of end diastole of said at least one cardiac cycle; calculating the relationship between the second area (5) and the first area (4); selecting a time instant of interest in said at least one cardiac cycle; obtaining the spatial distribution of the velocity in said time instant of interest, or instantaneous distribution of the velocity; identifying the maximum value and the minimum value of the instantaneous distribution of the velocity; and calculating the relationship between the maximum value and the minimum value.

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Published:

— *with international search report (Art. 21(3))*

— *in black and white; the international application as filed contained color or greyscale and is available for download from PATENTSCOPE*

"METHOD AND SYSTEM FOR THE MEASUREMENT OF HAEMODYNAMIC INDICES"

DESCRIPTION

TECHNICAL FIELD OF THE INVENTION

The present invention relates to the area of clinical monitoring and of diagnostic systems and, in particular, the systems and methods of vascular investigation by means of Doppler ultrasonography. In this context, the object of the present invention is a method for measuring haemodynamic indices and the relative system implementing this method. These indices can be used for the monitoring of atherosclerotic disease.

For the purpose of the present description, the expression "monitoring of atherosclerotic disease" refers to monitoring of the progression of possible existing atherosclerotic plaques, the identification of new plaques and the follow-up of arterial revascularization operations, whether performed via bypass surgery or whether they are performed via the endovascular route by means of the application of stents.

STATE OF THE ART

Doppler ultrasonography has now for many years been commonly used for measuring haemodynamic parameters such as, for example, the velocity of the blood in the arterial vessels. In fact, thanks to the interaction between the ultrasounds transmitted by means of a special probe and the erythrocytes in movement in the blood flow, it is possible to obtain a measurement of this velocity by making use of the well-known Doppler effect. Due to the latter, the frequency of the ultrasounds reflected by the erythrocytes in movement varies with respect to the frequency of the ultrasounds coming from the probe and impacting on said erythrocytes, in a manner dependent on the velocity of the same erythrocytes. More particularly the velocity of the erythrocytes and, therefore, of the blood flow is given by the following equation:

$$V = \frac{f_D c}{2 f_0 \cos\theta}$$

where f_D is the frequency of the ultrasounds reflected by the erythrocytes, c is the speed of sound in the blood, f_0 is the frequency of the ultrasounds impacting on the erythrocytes, that is the ultrasounds transmitted by the probe, and θ is the angle between the direction of the beam of ultrasounds impacting and the direction of the blood flow.

The velocity of the blood flow can in this way be calculated and measured in time, so as to obtain a time series of velocity values, or velocity signal. The values assumed by this signal in particular instants have for some time been used as indicators for the diagnosis and follow-up of particular pathological states. For example the systolic peak velocity, commonly known in the field with the acronym PSV (peak systolic velocity) and the velocity of end diastole, otherwise known as EDV (end diastolic velocity), are used as diagnostic indicator of carotid stenosis. In general it is known that the trend of the velocity of the blood during the various phases of the cardiac cycle and the spatial distribution of the velocity can vary in the presence of atherosclerotic disease, whether coronary or carotid or of the abdominal arteries. [Rzucidlo E.M., Zwolak R.M., *"Arterial duplex scanning"*, in Rutherford R.B., editor: *"Vascular Surgery"*, ed. 6, Philadelphia, 2005]. At the state of art, methods providing for the measurement and the processing of the blood velocity are described in US6210168 B1 where a bilinear interpolation is proposed of the maximum value and the minimum value of an instantaneous distribution of the velocity; and in US 20117196237 A1, where it is described the creation of a velocity vector-marker to be displayed in sample volumes of ultrasound images.Once the presence of an atherosclerotic plaque has been determined and its current extent evaluated and, therefore, the current degree of occlusion of the artery concerned, the problem remains of determining what will be the future evolution of the plaque. Prior art methods (US2010/249620 A1) exist for determining the risk of atherothrombosis (i.e. the risk of plaque rupture) based on the measuring of the diameter value of the lumen by means of ultrasound imaging and on comparing the blood shear stress to a critical threshold blood shear stress, the

critical threshold blood shear stress being calculated based on the a reference blood viscosity value, and/or the blood flow velocity value and the diameter value of said lumen at a location corresponding to a location on said plaque.

In fact, even if in the current state the plaque can have such an extension as not to need an operation of revascularization, it is possible that this plaque progresses, in time, reducing the lumen to a clinically significant percentage, that is such as to justify an operation. Also in the case wherein no plaque is currently visible and since it cannot be ruled out that it develops in the future, it could be found to be fundamental to evaluate the risk with appropriate prognostic indices.

As mentioned above, Doppler ultrasonography is used not only for diagnostic purposes but also as an instrument for the follow-up of arterial revascularization operations both by the endovascular route (e.g. operations which foresee the insertion of stents) and surgically (e.g. bypass operations). In these cases it is of vital importance to identify in time the risk that these operations fail due to new occlusions. The success of revascularization operations is, in fact, linked not only to the characteristics of the obstructed section operated on but also the characteristics of the haemodynamic downstream of said section. As will be explained in greater detail here below, the outcome of the revascularization is closely dependent on the peripheral resistances downstream of the section which has been operated on.

SUMMARY OF THE INVENTION

The object of the present invention is, therefore, that of providing a method and relative system allowing measurement of particular haemodynamic indices to be used for the forecast of the evolution of a possible existing atherosclerotic plaque or for the forecast of the development of a plaque in arterial sections currently not yet affected by any obstruction.

This object is achieved by the method that is the subject of the present invention, said method comprising the following steps:

- acquiring an ultrasound image of at least one segment of an arterial vessel;

- identifying in said image at least one sample volume;
- obtaining a time series indicating the blood velocity, or velocity signal, in said sample volume and in at least one cardiac cycle;
- selecting a time instant of interest in said at least one cardiac cycle;
- obtaining the spatial distribution of the velocity in said time instant of interest, or instantaneous distribution of the velocity;
- identifying the maximum value and the minimum value of the instantaneous distribution of the velocity; and
- calculating the relationship between the maximum value and the minimum value.

The relationship between the maximum value and the minimum value is referred to, for the purpose of the present description, as turbulence index (TI) and can be expressed by the following formula:

$$TI = \frac{V_{Max}(t_{peak})}{V_{Min}(t_{peak})}$$

where t_{peak} is, preferably, but not exclusively, the systolic peak instant. Following experimental studies in vitro and in vivo on animals, it has been seen that the growth factors, such as the growth factor derived from the platelets or PDFG (platelet-derived growth factor), is the basic growth factor of the fibroblasts or BFGF (basic fibroblast growth factor), notoriously responsible for the formation of myointimal hyperplasia first and atherosclerosis later, are produced in high quantities in the zones subjected to high shear stress. [Sterpetti A.V., Cucina A., Morena A.R., Di Donna S., Santoro D'Angelo L., Cardillo B., Cavallaro A., Stipa S. *"Shear stress increases the release of interleukin-1 and interleukin-66 by aortic endothelial cells"*, Surgery, 1993 November, 114(5): 911–914], [Sterpetti A.V., Cucina A., Fragale A., Lepidi S., Cavallaro A., Santoro D'Angelo L. *"Shear stress influences the release of platelet derived growth factor and basic fibroblast growth factor by arterial smooth muscle cells"*, Eur J Vasc Surg, 1994, 8: 138–142]. The cells more prone to proliferation are, instead, those subjected to low shear stress, since a high shear stress inhibits the proliferation of smooth muscle cells. [Sterpetti

A.V., Cucina A., Santoro D'Angelo L., Cardillo B., Cavallaro A., *"Shear stress modulates the proliferation rate, protein synthesis, and mitogenic activity of arterial smooth muscle cells"*, Surgery, 1993 June, 113(6): 691–699]. These results produce the hypothesis of how, due to the formation of the atherosclerotic plaque, the contemporary presence of zones with high and low shear stress is necessary. Following further studies in vitro and in vivo on animals it was, finally, possible to highlight how a turbulence index greater than 5 predicts a progression of the atherosclerotic plaque towards a condition of occlusion of the vessels, in particular in the carotids at the level of the bifurcation.

A second object of the present invention is, moreover, that of providing a method and relative system which allows the measurement of haemodynamic indices indicative of the peripheral resistances downstream of an arterial reconstruction performed by means of the insertion of a stent by the endovascular route or by means of the creation of a bypass surgically. These indices, by virtue of the fact of being indicative of these resistances, can, then, be used as prognostic indices of the favourable outcome or otherwise of revascularization operations.

This object is achieved by the method that is the subject of the present invention, said method comprising the following steps:

- acquiring an ultrasound image of at least one segment of an arterial vessel;
- identifying in said image at least one sample volume;
- obtaining a time series indicating the blood velocity, or velocity signal, in said sample volume and in at least one cardiac cycle;
- calculating, by means of a processor, a first area equal to the area subtended by the velocity signal between the sample relating to the instant of systole start of said at least one cardiac cycle and the systolic peak sample;
- calculating, by means of a processor, a second area subtended by the velocity signal between the systolic peak sample and between the sample relating to the instant of end diastole of said at least one cardiac cycle; and

- calculating the relationship between the second area and the first area;

The sample volume is preferably selected downstream of a region of interest comprising a stent or a section involved in surgical revascularization by means of bypass. For the purpose of the present description, the expression "downstream" is understood to mean that the sample volume is selected in the arterial section comprised between the region of interest and the periphery. The expression "upstream" indicates instead a location between the heart and the region of interest.

The relationship between the second area and the first area is colled, for the purpose of the present description, current peripheral resistance index (CPRI) and can be expressed by the following formula:

$$CPRI = \frac{A_{post}}{A_{pre}}$$

where A_{pre} is the area subtended by the velocity signal between the sample relating to the instant of systole start and the instant of systolic peak and $A_{post}$is the area subtended by the velocity signal between the instant of systolic peak and the instant of end diastole. It is known how the peripheral resistances downstream of the obstructed section, and therefore the velocity of the blood flow, are correlated to the probability of success of revascularization operations [Rzucidlo E.M., Zwolak R.M., *"Arterial duplex scanning"*, in Rutherford R.B., editor: *"Vascular Surgery"*, ed. 6, Philadelphia, 2005]. Following experimental studies in vitro and in vivo on animals, it has been seen how the peripheral resistances depend on the relationship between the area subtended by the velocity signal after the systolic peak and the area subtended by the velocity signal before the systolic peak. It has been shown, moreover, how a current peripheral resistance index greater than 2 is predictive of the failure of the stent or of the bypass, in particular in the coronary arteries and in the arteries of the lower limbs. Finally, the CPRI can also be used as a prognostic index of the evolution of an atherosclerotic plaque and can be used together with the IT to perform this evaluation. In this case too, a CPRI greater than 2 is indicative of a clinically significant risk that the plaque evolves towards occlusion of the vessel, to the extent of requiring an operation.

The object of the present invention is also a system which allows implementation of the method described above and calculating a single one or both the IT and CPRI indices. This system comprises:

- a duplex ecograph scanner configured for the ultrasound image acquisition of at least one segment of an arterial vessel and for the measurement of the velocity of the blood in said at least one segment and in at least one cardiac cycle;
- at least one input device for allowing an operator to select a sample volume in the arterial segment acquired and/or of a cardiac cycle within a time range of acquisition and/or of a time instant of interest in said at least one cardiac cycle;
- a processor, or computer, configured for the storage, the display and the processing of the images acquired and of the haemodynamic indices measured, said processing comprising the following operations:
    - extracting at least one time series indicating the blood velocity, or velocity signal, from the velocity values measured in said sample volume and in at least one cardiac cycle;
    - calculating, by means of a processor, a first area equal to the area subtended by the velocity signal between the sample relating to the instant of systole start of said at least one cardiac cycle and the systolic peak sample;
    - calculating, by means of a processor, a second area subtended by the velocity signal between the sample relating to the instant of end diastole of said at least one cardiac cycle and the systolic peak sample; and
    - calculating the relationship between the second area and the first area;

  and/or the following steps:

    - selecting a time instant of interest in said at least one cardiac cycle;
    - obtaining the spatial distribution of the velocity in said time

instant of interest, or instantaneous distribution of the velocity;

- identifying the maximum value and the minimum value of the instantaneous distribution of the velocity; and
- calculating the relationship between the maximum value and the minimum value.

The computer of the system of the present invention can, therefore, be configured for the calculation of only the turbulence index (TI), of only the current peripheral resistances index (CPRI) or for the calculation of both. This computer can, moreover, be configured for the generation of a first alert signal if the CPRI is greater than 2 and/or a second alert signal if the IT is greater than 5.

These and other objects of the present invention will be made clearer by the following detailed description of some preferred embodiments of the present invention, to be understood by way of a non-limiting example of the more general concepts claimed.

BRIEF DESCRIPTION OF THE DRAWINGS

The following description refers to the accompanying drawings, in which:

- Figure 1 is a graphic representation of a carotid artery at the level of its bifurcation where the arrows represent the direction of the blood flow. In Figure 1 the zones with low shear stress are indicated by means of dotted flow lines, while the zones with high shear stress are indicated by means of unbroken flow lines; and
- Figure 2 shows an example of velocity signal in a cardiac cycle.

DETAILED DESCRIPTION OF THE INVENTION

Referring to Figures 1 and 2, a first embodiment of the method of the present invention comprises:

- acquiring an ultrasound image of at least one segment of an arterial vessel;
- identifying in said image at least one sample volume;
- measuring by means of an ultrasound Doppler system the velocity of the blood passing through said sample volume for at least one cardiac cycle;

- selecting a cardiac cycle, if the measuring was performed for more than one cardiac cycle;
- extracting a velocity signal (9) from the velocity values measured, said velocity signal (9) having a length equal to said cardiac cycle and the first sample (6) corresponding to the instant of systole start of said cardiac cycle.
- calculating, by means of a processor, a first area (4) equal to the area subtended by the velocity signal between the sample (6) relating to the instant of systole start of said at least one cardiac cycle and a second sample (7) relating to the instant of systolic peak;
- calculating, by means of a processor, a second area (5) subtended by the velocity signal between the second sample (7) and a third sample (8) relating to the instant of end diastole of said at least one cardiac cycle; and
- calculating the relationship between the second area (5) and the first area (4);

The sample volume can be selected inside a region of interest comprising an atherosclerotic plaque and/or a stent and/or a section involved in surgical revascularization by means of bypass. Alternatively, the sample volume can be selected downstream of this region of interest comprising an atherosclerotic plaque and/or a stent and/or a section involved in surgical revascularization by means of bypass. In the latter case the distance between the sample volume and the region of interest is equal to at least double the length of the plaque and/or of the stent and/or of the section involved in revascularization, said distance being calculated from the end of the plaque or from the mean point of the plaque or of the start of the plaque. For the purpose of the present description, length of the plaque refers to its largest dimension.

Referring to Figures 1 and 2, a second embodiment of the method of the present invention comprises:

- acquiring an ultrasound image of at least one segment of an arterial vessel;
- identifying in said image at least one sample volume;
- measuring by means of an ultrasound Doppler system the velocity of the blood passing through said sample volume for at least one cardiac cycle and

a second cardiac cycle;

- extracting a first time series from the velocity values measured during the first cardiac cycle, said first series having such a length as to cover the first cardiac cycle and the first sample corresponding to the instant of systole start of the first cardiac cycle;
- extracting a second time series from the velocity values measured, said second series having such a length as to cover the second cardiac cycle and the first sample corresponding to the instant of systole start of the second cardiac cycle; and
- calculating the velocity signal as series of the mean values between the amplitudes of the second and of the third time series in each time instant.
- calculating, by means of a processor, a first area (4) equal to the area subtended by the velocity signal between the sample (6) relating to the instant of systole start of said at least one cardiac cycle and a second sample (7) relating to the instant of systolic peak;
- calculating, by means of a processor, a second area (5) subtended by the velocity signal between the second sample (7) and a third sample (8) relating to the instant of end diastole of said at least one cardiac cycle; and
- calculating the relationship between the second area (5) and the first area (4);

Also in the second embodiment the sample volume can be selected with the same methods explained in detail for the first embodiment.

Referring to Figures 1 and 2, a third embodiment of the method of the present invention comprises:

- acquiring an ultrasound image of at least one segment of an arterial vessel;
- identifying in said image at least one sample volume;
- obtaining a time series indicating the blood velocity, or velocity signal, in said sample volume and in at least one cardiac cycle;
- selecting a time instant of interest in said at least one cardiac cycle; said time instant of interest being preferably the systolic peak instant;

- obtaining the spatial distribution of the velocity in said time instant of interest, or instantaneous distribution of the velocity;
- identifying the maximum value and the minimum value of the instantaneous distribution of the velocity; and
- calculating the relationship between the maximum value and the minimum value.

The maximum value will be identified in the zones with low shear stress (1) and the minimum value will be identified in the zones with high shear stress (2).

Referring to Figures 1 and 2, a fourth embodiment of the method of the present invention comprises:

- acquiring an ultrasound image of at least one segment of an arterial vessel;
- identifying in said image at least one sample volume;
- measuring by means of an ultrasound Doppler system the velocity of the blood passing through said sample volume for at least one cardiac cycle;
- selecting a cardiac cycle, if the measuring was performed for more than one cardiac cycle;
- extracting a velocity signal (9) from the velocity values measured, said velocity signal (9) having a length equal to said cardiac cycle and the first sample (6) corresponding to the instant of systole start of said cardiac cycle.
- calculating, by means of a processor, a first area (4) equal to the area subtended by the velocity signal between the sample (6) relating to the instant of systole start of said at least one cardiac cycle and a second sample (7) relating to the instant of systolic peak;
- calculating, by means of a processor, a second area (5) subtended by the velocity signal between the second sample (7) and a third sample (8) relating to the instant of end diastole of said at least one cycle;
- calculating the relationship between the second area (5) and the first area (4);
- selecting a time instant of interest in said at least one cardiac cycle; said time instant of interest being preferably the systolic peak instant;
- obtaining the spatial distribution of the velocity in said time instant of

interest, or instantaneous distribution of the velocity;

- identifying the maximum value and the minimum value of the instantaneous distribution of the velocity; and
  - calculating the relationship between the maximum value and the minimum value.

Referring to Figures 1 and 2, a fifth embodiment of the method of the present invention comprises:

- acquiring an ultrasound image of at least one segment of an arterial vessel;
- identifying in said image at least one sample volume;
- measuring by means of an ultrasound Doppler system the velocity of the blood passing through said sample volume for at least one cardiac cycle and a second cardiac cycle;
- extracting a first time series from the velocity values measured during the first cardiac cycle, said first series having such a length as to cover the first cardiac cycle and the first sample corresponding to the instant of systole start of the first cardiac cycle;
- extracting a second time series from the velocity values measured, said second series having such a length as to cover the second cardiac cycle and the first sample corresponding to the instant of systole start of the second cardiac cycle; and
- calculating the velocity signal as series of the mean values between the amplitudes of the second and of the third time series in each time instant.
- calculating, by means of a processor, a first area (4) equal to the area subtended by the velocity signal between the sample (6) relating to the instant of systole start of said at least one cardiac cycle and a second sample (7) relating to the instant of systolic peak;
- calculating, by means of a processor, a second area (5) subtended by the velocity signal between the second sample (7) and a third sample (8) relating to the instant of end diastole of said at least one cardiac cycle;
- calculating the relationship between the second area (5) and the first area (4);

- selecting a time instant of interest in said velocity signal;
- obtaining the spatial distribution of the velocity in said time instant of interest, or instantaneous distribution of the velocity;
- identifying the maximum value and the minimum value of the instantaneous distribution of the velocity; and
- calculating the relationship between the maximum value and the minimum value.

Also in the fourth and in the fifth embodiment the sample volume can be selected with the same methods explained in detail for the first and second embodiments.

The system which allows the implementation of the five embodiments of the method described above comprises:

- a duplex ecograph scanner configured for the ultrasound image acquisition of at least one segment of an arterial vessel and for the measurement of the velocity of the blood in said at least one segment and in at least one cardiac cycle;
- at least one input device for allowing an operator to select a sample volume in the arterial segment acquired and/or of a cardiac cycle within a time range of acquisition and/or of a time interval of interest in said at least one cardiac cycle;
- a processor, or computer, configured for the storage, the display and the processing of the images acquired and of the haemodynamic indices measured.

In a first embodiment of the system of the present invention, this processing comprises the following operations:

- extracting a velocity signal (9) from the velocity values measured, said velocity signal (9) having a length equal to said cardiac cycle and the first sample (6) corresponding to the instant of systole start of said cardiac cycle;
- calculating, by means of a processor, a first area (4) equal to the area subtended by the velocity signal between the sample (6) relating to the instant of systole start of said at least one cardiac cycle and a second sample

(7) relating to the instant of systolic peak;

- calculating, by means of a processor, a second area (5) subtended by the velocity signal between the second sample (7) and a third sample (8) relating to the instant of end diastole of said at least one cardiac cycle; and
- calculating the relationship between the second area (5) and the first area (4);

In a second embodiment of the system of the present invention, this processing comprises the following operations:

- extracting a first time series from the velocity values measured during the first cardiac cycle, said first series having such a length as to cover the first cardiac cycle and the first sample corresponding to the instant of systole start of the first cardiac cycle;
- extracting a second time series from the velocity values measured, said second series having such a length as to cover the second cardiac cycle and the first sample corresponding to the instant of systole start of the second cardiac cycle; and
- calculating the velocity signal as series of the mean values between the amplitudes of the second and of the third time series in each time instant.
- calculating, by means of a processor, a first area (4) equal to the area subtended by the velocity signal between the sample (6) relating to the instant of systole start of said at least one cardiac cycle and a second sample (7) relating to the instant of systolic peak;
- calculating, by means of a processor, a second area (5) subtended by the velocity signal between the second sample (7) and a third sample (8) relating to the instant of end diastole of said at least one cardiac cycle; and
- calculating the relationship between the second area (5) and the first area (4);

In a third embodiment of the system of the present invention, this processing comprises the following operations:

- obtaining the spatial distribution of the velocity in a time instant of interest, previously selected by an operator;
- identifying the maximum value and the minimum value of this

distribution; and

- calculating the relationship between the maximum value and the minimum value.

In a fourth embodiment of the system of the present invention, this processing comprises the following operations:

- extracting a velocity signal (9) from the velocity values measured, said velocity signal (9) having a length equal to said cardiac cycle and the first sample (6) corresponding to the instant of systole start of said cardiac cycle.
- calculating, by means of a processor, a first area (4) equal to the area subtended by the velocity signal between the sample (6) relating to the instant of systole start of said at least one cardiac cycle and a second sample (7) relating to the instant of systolic peak;
- calculating, by means of a processor, a second area (5) subtended by the velocity signal between the second sample (7) and a third sample (8) relating to the instant of end diastole of said at least one cardiac cycle;
- calculating the relationship between the second area (5) and the first area (4);
- obtaining the spatial distribution of the velocity in a time instant of interest, previously selected by an operator;
  - identifying the maximum value and the minimum value of the instantaneous distribution of the velocity; and
  - calculating the relationship between the maximum value and the minimum value.

In a fifth embodiment of the system of the present invention, this processing comprises the following operations:

- extracting a first time series from the velocity values measured during the first cardiac cycle, said first series having such a length as to cover the first cardiac cycle and the first sample corresponding to the instant of systole start of the first cardiac cycle;
- extracting a second time series from the velocity values measured, said second series having such a length as to cover the second cardiac cycle and

the first sample corresponding to the instant of systole start of the second cardiac cycle; and

- calculating the velocity signal as series of the mean values between the amplitudes of the second and of the third time series in each time instant.
- calculating, by means of a processor, a first area (4) equal to the area subtended by the velocity signal between the sample (6) relating to the instant of systole start of said at least one cardiac cycle and a second sample (7) relating to the instant of systolic peak;
- calculating, by means of a processor, a second area (5) subtended by the velocity signal between the second sample (7) and a third sample (8) relating to the instant of end diastole of said at least one cardiac cycle;
- calculating the relationship between the second area (5) and the first area (4);
- obtaining the spatial distribution of the velocity in a time instant of interest, previously selected by an operator;
- identifying the maximum value and the minimum value of the instantaneous distribution of the velocity; and
- calculating the relationship between the maximum value and the minimum value.

The computer of the system in any one of the five embodiments described above is further configured in order to generate a first alert signal if the relationship between the second area and the first area is greater than 2 and/or a second alert signal if the relationship between the maximum value and the minimum value is greater than 5.

The method of the present invention can also be applied in different conditions of the patient and the indices obtained in the different conditions can in turn be combined so as to form new and further indices indicative of pathological states or of the possibility of success of operations of revascularization. More particularly it is possible to perform a measurement of the current peripheral resistances index both in basal conditions and after having performed an injection of papaverine. The relationship between the current peripheral resistances index in basal conditions (Base $_{CPRI}$) and of the peripheral resistances index after injection of papaverine (Papaverine $_{CPRI}$) gives rise

to a new prognostic index of the possibility of success or otherwise of the operation of revascularization both in the case of stent and of bypass. This relationship, referred to for the purpose of the present description as predicted peripheral resistances index (PPRI), is, therefore, given by the following equation:

$$PPRI = \frac{CPRI_{Base}}{CPRI_{Papaverine}}$$

A PPRI index lower than 2 presupposes the failure of the arterial reconstruction or revascularization whether performed with stent or by bypass.

The method of the present invention can, therefore, be adapted for the calculation of the PPRI, foreseeing the following steps:

- acquiring an ultrasound image of at least one segment of an arterial vessel;
- identifying in said image at least one region of interest;
- selecting downstream of said region of interest a sample volume;
- obtaining a time series indicating the blood velocity in basal conditions, or base velocity signal, in said sample volume and in at least one cardiac cycle;
- injecting a solution of papaverine:
- obtaining a time series indicating the blood velocity, following the injection of papaverine, or velocity signal after injection of papaverine, in said sample volume and in at least one cardiac cycle;
- identifying in the base velocity signal a sample relative to the instant of systolic peak, or systolic peak sample;
- identifying in the velocity signal after injection of papaverine a sample relative to the instant of systolic peak, or systolic peak sample;
- calculating, by means of a processor, a first area equal to the area subtended by the base velocity between the sample relating to the instant of systole start of said at least one cardiac cycle and the systolic peak sample;

- calculating, by means of a processor, a second area subtended by the base velocity signal between the sample relating to the instant of end diastole of said at least one cardiac cycle and the systolic peak sample; and/or
- calculating a first index as the relationship between the second area and the first area;
- calculating, by means of a processor, a third area equal to the area subtended by the velocity signal after injecting papaverine between the sample relating to the instant of systole start of said at least one cardiac cycle and the systolic peak sample;
- calculating, by means of a processor, a fourth area subtended by the velocity signal after injecting papaverine between the sample relating to the instant of end diastole of said at least one cardiac cycle and the systolic peak sample;
- calculating a second index as the relationship between the fourth area and the third area; and
- calculating the relationship between the first index and the second .

In this context an object of the present invention is also a kit for monitoring of atherosclerotic disease comprising an injectable solution containing papaverine, means for the administration by means of injection of said solution and the system described above.

Finally, here it is specified that the method described above can be implemented at least partially in the form of a program for processor or computer. To this end, this program comprises portions of code which, when performed by said processor, or computer, are apt to implement the method described above. These portions of code can be contained in a medium readable by a processor, or computer, which can be a magnetic medium such as, for example, a hard disk or an optical medium, such as for example a CD-ROM or a DVD or, further, an electronic medium such as ROMs, or flash RAM. The portions of code or, more generally, the information contained in said medium readable by a processor, or computer, can be compressed or encrypted.

CLAIMS

1. Method for the measurement of haemodynamic indices, comprising:
   - acquiring an ultrasound image of at least one segment of an arterial vessel;
   - identifying in said image at least one sample volume;
   - obtaining a time series indicating the blood velocity, or velocity signal (9), in said sample volume and in at least one cardiac cycle;

   characterised in that it comprises the following steps:
   - calculating, by means of a processor, a first area (4) equal to the area subtended by the velocity signal (9) between the sample (6) relating to the instant of systole start of said at least one cardiac cycle and the sample (7) relating to the instant of systolic peak;
   - calculating, by means of a processor, a second area (5) subtended by the velocity signal between the sample (7) relating to the instant of systolic peak of said at least one cardiac cycle and the sample relating to the instant of diastole end (8); and
   - calculating the relationship between the second area and the first area.

2. Method according to claim 1, further comprising the following steps:
   - selecting a time instant of interest in said at least one cardiac cycle;
   - obtaining the spatial distribution of the velocity in said time instant of interest, or instantaneous distribution of the velocity;
   - identifying the maximum value and the minimum value of the instantaneous distribution of the velocity; and
   - calculating the relationship between the maximum value and the minimum value.

3. Method according to claim 1 or 2, wherein the sample volume is selected inside

a region of interest comprising an atherosclerotic plaque and/or a stent and/or a section involved in surgical revascularization by means of bypass.

4. Method according to claim 1 or 2, wherein the sample volume is selected downstream of a region of interest comprising an atherosclerotic plaque and/or a stent and/or a section involved in surgical revascularization by means of bypass.

5. Method according to claim 4, wherein the distance between the sample volume and the region of interest is equal to at least the double of the length of the plaque and/or of the stent and/or of the section involved in revascularization, said distance being calculated from the end of the plaque or from the median point of the plaque or of the start of the plaque.

6. Method according to any one of the preceding claims, wherein obtaining a velocity signal comprises:

- measuring by means of an ultrasound Doppler system the velocity of the blood passing through said sample volume for at least one cardiac cycle;
- selecting a cardiac cycle, if the measuring was performed for more than one cardiac cycle;
- extracting the velocity signal (9) from the velocity values measured, said velocity signal having a length equal to said cardiac cycle and the first sample (6) corresponding to the instant of systole start of said cardiac cycle.

7. Method according to any one of claims 1 to 5, comprising:

- measuring by means of an ultrasound Doppler system the velocity of the blood passing through said sample volume for at least one cardiac cycle and a second cardiac cycle;
- extracting a first time series from the velocity values measured during the first cardiac cycle, said first series having such a length as to cover the first cardiac cycle and the first sample corresponding to the instant of systole

start of the first cardiac cycle;

- extracting a second time series from the velocity values measured, said second series having such a length as to cover the second cardiac cycle and the first sample corresponding to the instant of systole start of the second cardiac cycle; and
- calculating the velocity signal as series of the median values between the amplitudes of the second and of the third time series in each time instant.

8. Method according to any one of the preceding claims, wherein the time instant of interest is the instant of systolic peak of said at least one cardiac cycle.

9. System for the measurement of haemodynamic indices, comprising:
   - a duplex ecograph scanner configured for the ultrasound image acquisition of at least one segment of an arterial vessel and for the measurement of the velocity of the blood in said at least one segment and in at least one cardiac cycle;
   - at least one input device for allowing an operator to select a sample volume in the arterial segment acquired and/or of a cardiac cycle within a time range of acquisition and/or of a time interval of interest in said at least *one* cardiac cycle;

characterised in that it comprises further:

- a processor, or computer, configured for the storage, the display and the processing of the images acquired and of the haemodynamic indices measured, said processing comprising the following operations:
  - extracting at least one time series indicating the blood velocity, or velocity signal (9), from the velocity values measured in said sample volume and in at least one cardiac cycle;
  - calculating, by means of a processor, a first area (4) equal to the area subtended by the velocity signal (9) between the sample relating to the instant of systole start (6) of said at least one cardiac

cycle and the sample (7) relating to the instant of systolic peak;

- calculating, by means of a processor, a second area (5) subtended by the velocity signal (9) between the sample relating to the instant of systolic peak (7) of said at least one cardiac cycle and the sample relating to the instant of diastole end (8); and
- calculating the relationship between the second area (5) and the first area (4).

10. System according to claim 9 wherein the processing comprises the following steps:

- selecting a time instant of interest in said at least one cardiac cycle;
- obtaining the spatial distribution of the velocity in said time instant of interest, or instantaneous distribution of the velocity;
- identifying the maximum value and the minimum value of the instantaneous distribution of the velocity; and
- calculating the relationship between the maximum value and the minimum value.

11. System according to the claim 9 or 10 wherein the computer is further configured in order to generate a first alert signal if the relationship between the second area and the first area is greater than 2 and/or a second alert signal if the relationship between the maximum value and the minimum value is greater than 5.

12. Kit for haemodynamic indices comprising:

- an injectable solution containing papaverine;
- means for the administration by means of injection of said solution; and
- the system according to any of claim from 9 to 11.

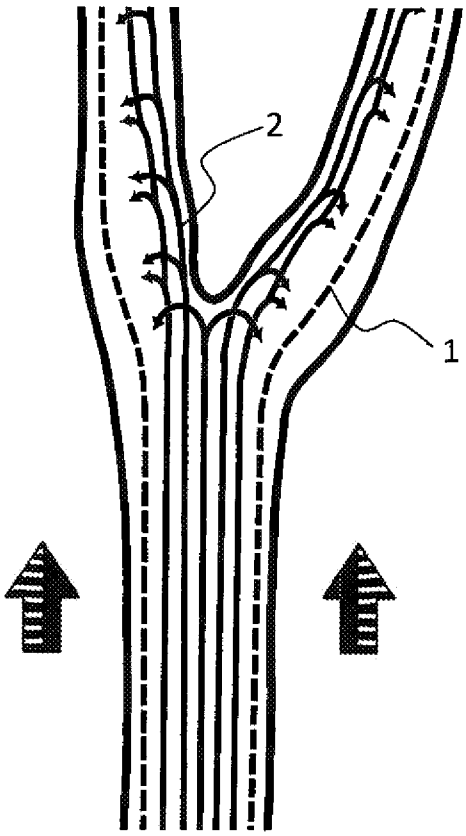

Fig.1

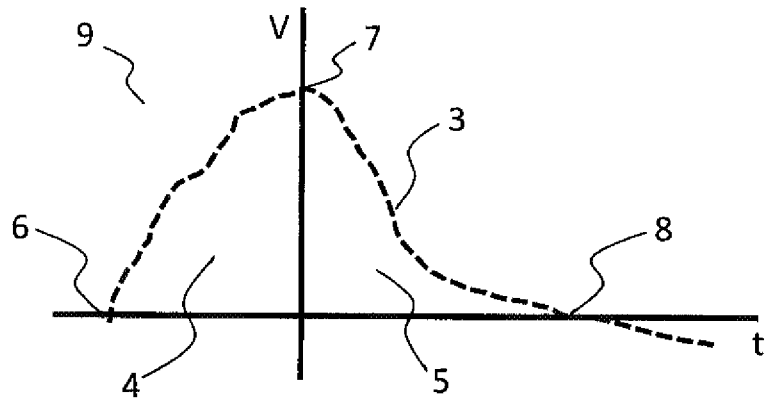

Fig.2

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2019/051196

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61B8/06 A61B8/08
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)
A61B

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, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2010/049052 A1 (SHARF YEHUDA [IL] ET AL) 25 February 2010 (2010-02-25) abstract figures 1-12b paragraph [0039] - paragraph [0342] -----	1-12
A	US 6 210 168 B1 (AIGER DROR [IL] ET AL) 3 April 2001 (2001-04-03) abstract figures 1-12 column 4, line 38 - column 14, line 43 -----	1-12
A	US 2010/249620 A1 (CHO DANIEL J [US]) 30 September 2010 (2010-09-30) abstract figures 1-6 paragraph [0059] - paragraph [0100] -----	1-12
	-/--	

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

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"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

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
5 April 2019	16/04/2019

Name and mailing address of the ISA/	Authorized officer
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INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2019/051196

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2011/196237 A1 (PELISSIER LAURENT [CA] ET AL) 11 August 2011 (2011-08-11) abstract figures 1-13 paragraph [0042] - paragraph [0261] -----	1-12

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2019/051196

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