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(54) Title: METHOD AND APPARATUS FOR COMBINED MEASUREMENT OF HEMOGLOBIN AND OXYGEN SATURATION

(57) Abstract: The present invention relates to a method for accurately detecting SpO_2, partly by using determination of blood characteristics including hemoglobin, in a fluid medium using the reflection of at least one light beam.

Method and apparatus for combined measurement of hemoglobin and oxygen saturation.

The present invention relates to a non-invasive method for determination of SpO_2, including a first determination of blood characteristics including hemoglobin (EVF/hematocrit), in a vessel containing a mixture of liquid and blood cells using the orientation effects of the red blood cells. The present invention also relates to an apparatus for performing the method.

Background to the invention

There are different non-invasive methods known for measurement of hemoglobin. These methods make use of absorption of energy at a certain light wavelength, of the red blood cells (RBCs). Carim et al disclose in US 5755226 a non-invasive method and apparatus for the direct non-invasive prediction of hematocrit in mammalian blood using photopletysmography (PPG) techniques and data processing. However, this method only makes use of the ability of the RBCs to absorb energy. This method is also quite complicated regarding the formulas which are to be used when calculating the predicted hematocrit. Thus the method is time consuming. This method has not taken into account the red blood cell orientation and distribution in blood vessels.

Further, a method and an apparatus, are disclosed in WO 97/15229 for determining hemoglobin concentration in blood. The method is used for detecting hemoglobin in the microvascular system beneath the mucosal membranes on the inside of the lip of a human subject by introducing a measuring tip into the mouth of a subject. This means that the measuring tip of the apparatus must have some kind of sterile shell before it may be placed in the mouth. This sterility of the measuring tip means

that either the apparatus must be autoclaved before measuring or that a disposable plastic tip has to be used when performing the method. This method further uses the reflection of light for determining the concentration of hemoglobin.

Photopletmysmography and pulse oximetry has been thoroughly investigated by two of the present inventors ("Photopletmysmography, methodological studies and applications", Lars-Göran Lindberg, Linköping Studies in Science and Technology Dissertations, No 262, 1991 and "Pulse oximetry - methodological considerations", Magnus Vegfors, Linköping University Medical Dissertations, No 347 1992, both hereby incorporated by reference thereto).
They found e.g. that when pulse oximeter was tested on an artificial bed different flow conditions greatly affected the accuracy of the pulse oximeter. Different states of the blood, diluted and haemolysed blood changed the pulse oximeter accuracy indicating that orientation of red blood cells and the viscosity of blood as a whole may play important role for the generation of the two PPG signals utilised in pulse oximetry. (in Lindberg above)

Further there was mentioned in Vegfors' paper above about some previous studies which have indicated that pulse oximeter accuracy may be dependent on blood haematocrit. For ethical reasons, it is impossible to study the accuracy of pulse oximetry on humans at very low haematocrit levels. Therefore, little human data is available during anaemia. Some investigations document an increasing negative bias in mildly anaemic subjects.

The majority of pulse oximeters uses transmitted light to calculate the oxygen saturation. This limits the probe application to for example finger tips, toes or ear lobes.

There is therefore an increasing interest in reflection pulse oximetry. (Vegfors above) Further examples of pulse oximeters are described in the historical review "History of Blood Gas Analysis. VI. Oximetry", J. W. Severinghaus and P.B. Astrup, Journal of Clinical Monitoring, Vol 2, No. 4, October 1986, pp 270-287 (hereby incorporated by reference thereto).

Since haematocrit values outside normal ranges are known to effect the accuracy of pulse oximetry a combined measurement of haemoglobin and oxygen saturation it would be desirable with a method and apparatus which makes it possible to alert for false pulse oximetry readings and perform on-line corrections.

Accordingly, there is a need for new methods for detecting SpO_2 which takes into account blood characteristics including Hb, and accordingly also the blood cell orientation and thus give a more accurate detection value. Further, methods which do not involve an extra step of making the apparatus sterile before measuring or disposable tips are desirable. The new methods should also be less sensitive to variations in the blood pressure, e.g. the pulsative, (systolic) pressure.

Summary of the invention

The present invention solves the above problems by increasing the accuracy of pulse oximetry measurements by reflection and transmittance measurements:

- on central arterial blood vessels better reflecting the oxygenation than peripheral vascular beds,

- on-line correction for haematocrit values affecting the accuracy,

- simultaneous results of oxygen saturation and blood values (such as haematocrit) improving the quality and safety

in patient monitoring.

In accordance with a first aspect of the present invention there is provided a new non-invasive method for accurate determination of SpO_2 from a mixture of liquid and blood cells contained in a light pervious vessel comprising:
a) directing light beams against the mixture;
b) determining at least one blood characteristic other than SpO_2 including hemoglobin of the mixture by analyzing the intensity of the light reflected from the mixture, or the intensity of the light reflected from the mixture in combination with the intensity of the light transmitted through the mixture; and
c) determining oxygen saturation, SpO_2, of the mixture by analyzing the intensity of the light transmitted through the mixture.

In the new method, (b) and (c) may be performed in the reverse order or even simultaneously.

In accordance with the invention, the new method further comprises establishing whether the result of c) is relevant with respect to the result of b).

Advantageously, (c) is performed by pulse-oximetrically determining oxygen saturation.

With regard to the determination of oxygen saturation, first, (a) is performed by directing at least one light beam with a wavelength in the red light range against the vessel, and directing at least one light beam with a wavelength in the infrared light range against the vessel. Then, (c) is performed by detecting the intensities of the red light and infrared light transmitted through the mixture, calculating a quotient of the detected intensities, red/infrared, of the transmitted light, and determining SpO_2 by analyzing the quotient.

By analyzing the quotient of the detected intensities of transmitted light the advantage is achieved that influences from pressure and flow, in particular pulsating flow, of the liquid mixture is compensated for, whereby the determined SpO_2 will be accurate. The quotient is analyzed by comparing it with previously obtained quotients for known values of SpO_2.

With regard to the determination of the blood characteristic (i.e. at least hemoglobin), (b) is performed by:
i) detecting the intensity of the light of the light beams reflected from the mixture and the intensity of the light of the light beams transmitted through the mixture;
ii) calculating a quotient of the detected intensity of the transmitted light and detected intensity of the reflected light or a quotient of the detected intensity of the reflected light and detected intensity of the transmitted light; and
iii) analyzing the quotient to determine the blood characteristic.

By analyzing the quotient of the detected intensities of transmitted and reflected lights the advantage is achieved that influences from pressure and flow, in particular pulsating flow, of the liquid mixture is compensated for, whereby the determined blood characteristic (hemoglobin) will be accurate. The quotient is analyzed by comparing it with previously obtained quotients for known values of the blood characteristic in question.

Alternatively, first, (a) is performed by directing at least two light beams with different wavelengths against the vessel, then, (b) is performed by:
i) detecting the intensities of the light of the light beams reflected from the vessel;
ii) calculating a quotient of the detected intensities of the

reflected lights; and

iii) analyzing the quotient to determine the blood characteristic.

In accordance with a second aspect of the present invention there is provided an apparatus for accurate determination of SpO_2 from a mixture of liquid and blood cells contained in a light pervious vessel comprising:

- light sources for directing light beams against the vessel,

- means for determining a blood characteristic other than oxygen saturation, SpO_2, including hemoglobin and capable of analyzing the intensity of the light reflected from the vessel, or the intensity of the light reflected from the vessel in combination with the intensity of the light transmitted through the mixture, and

- means for determining oxygen saturation, SpO_2, of the mixture, preferably pulse-oximetrically, and of analyzing the intensity of the light transmitted through the mixture.

In accordance with the invention, the apparatus further comprises means for establishing whether the determined value of SpO_2 is relevant with respect to the determined value of the blood characteristic.

The light sources comprise a first light source for emitting a first light beam with a wavelength in the red light range against the vessel, and a second light source for emitting a second light beam with a wavelength in the infrared light range against the vessel.

The apparatus may further comprise a first detector for detecting the intensity of the light of the red first light beam transmitted through the vessel, and a second detector for detecting the light of the infrared second light beam

transmitted through the vessel. The oxygen saturation determining means may comprise a processor adapted to calculate a quotient of the detected intensities of the transmitted red and infrared lights and to determine the value of the oxygen saturation by analyzing the quotient.

The light sources suitably comprise a third light source for emitting a third light beam against the vessel, and the apparatus may further comprise a third detector for detecting the intensity of the light of the third light beam reflected from the vessel and a fourth detector for detecting the intensity of the light of the third light beam transmitted through the vessel. The blood characteristic determining means may comprise a processor adapted to calculate a quotient of the detected intensities of the reflected and transmitted lights of the third light beam and to determine the value of the blood characteristic by analyzing the quotient.

The apparatus may further comprise registration means for storing the determined blood characteristic and SpO_2 , and optionally means for visualization of the determined blood characteristic and SpO_2.

In accordance with a third aspect of the present invention there is provided use of an apparatus according to the second aspect of the present invention in a dialysis device.

Detailed description of the invention

The term "light source" is to be understood to encompass one or more light emitting elements, such as light diodes.

With the expression "blood characteristics" is meant in the present application characteristics of blood such as concentration of blood components, e.g. hemoglobin, total

hemoglobin, red blood cells, white blood cells, platelets, cholesterol, albumin, thrombocytes, lymphocytes, drugs and other substances, viscosity, blood pressure, blood flow, blood volume, blood cell illnesses, abnormal blood cell appearances, anemia, leukemia, lymphoma.

With the expression "hemoglobin" is meant in the present application oxyhemoglobin, reduced hemoglobin, carboxy hemoglobin, methemoglobin and sulphhemoglobin.

With the expression "red blood cells", also known as erythrocytes, is meant in the present application whole or partly lysed red blood cells which contain hemoglobin.

With the expression "light pervious vessel" is meant in the present application a blood vessel in an animal, a pipe, a tube or a tubing which is light pervious. The pipe, tube or tubing may be manufactured from acrylonitrile butadiene styrene (ABS), polycarbonate or acrylic glass (polymethylmethacrylate; PMMA) which gives a non-flexible material or from polyvinyl chloride (PVC) or silicon rubber, plasticized PVC, e.g. PVC plasticized with dioctylphtalate, diethylhexylphtalate or trioctyltrimellitate, which gives a flexible material. PMMA is the most preferred non-flexible material. The light pervious vessel may further be used when performing liquid transfusions or blood transfusions. The elasticity of the material may be varied in a wide range. The animal containing a blood vessel is preferably a mammal, most preferred a human being.

As used herein, "light" refers generally to electromagnetic radiation at any wavelength, which includes the infrared, visible and ultraviolet portions of the spectrum. A particularly preferred portion of the spectrum is that portion where there is relative transparency of the tissue, such as in the visible and near-infrared wavelengths. It is to be

understood that for the present invention, light may be nonpolarized or polarized light, coherent light or incoherent light and illumination may be steady pulses of light, amplitude modulated light or continuos light.

Light sources which may be used in the method and the apparatus according to the invention are e.g. light emitting diodes (LEDs) or laser diodes or combinations thereof such as VCSEL (vertical cavity surface emitting laser) . Preferably less expensive LEDs are used. Today there are also new strong light emitting diodes which may be used in the method and the apparatus according to the invention. Flash lamp light sources are also conceivable for use in the present invention. The light source may further be capable of emitting monochromatic light, i.e. a monochromator. Quartz halogen lamps or tungsten lamps may also be used as light sources. Optical light fibres, for guiding the light to and from the measured spot, and or direct illumination on the measured spot may also be used.

Detectors which may be suitable for use when performing the method according to the present invention, are phototransistors, photodiodes, photomultipliers, photocells, photodetectors, optical power meters, amplifiers, CCD arrays and so on.

In the present application the expression "means for determining blood characteristics including hemoglobin" refers to any non-invasive apparatus for determining blood characteristics including hemoglobin in a liquid comprising blood cells. Preferred examples of such non-invasive apparatuses are given below and in the appended claims.

In the present application the expression "means for determination of SpO_2" refers to any apparatus for measuring oxygen saturation non-invasively in a liquid comprising blood

cells. Preferably pulse-oximetrically measuring apparatuses are preferred as e.g. are dislosed in Vegfors above and in Severinghaus et al above, disclosing e.g. the Minolta pulse oximeter. The Minolta pulse oximeter uses 650 nm and 805 nm. The apparatus in Vegfors above is the most preferred, as is diclosed below.

The mixture of liquid and blood cells in the method of the present application is preferably flowing, but it may as well be standing such as is the case for a fluid medium in a blood bag. The mixture of liquid and blood cells may comprise plasma or any other liquid as e.g. water or dialysis liquids. The plasma is preferably in or from a mammal. The liquid may as well be any other fluid comprising blood cells which may be obtained during or after the processing of blood.

Further, the method according to the present application is also characterized by that it may be performed on a mammal such as domestic animals or human beings, preferably on a human being.

The method according to the invention may be performed on any part of the human body or the body as a whole comprising a greater blood vessel, preferably a vein, an arteriole or artery, most preferred a blood vessel with a diameter >0.1 mm. The detection is, according to a preferred embodiment of the present invention, performed on an arm, a toe or a finger. The detection is most preferably performed on a wrist or on a finger on the third phalanx.

The present invention, especially the SpO_2 measuring part thereof, is based upon the principle that individual wavelengths of light are absorbed differently by various components of arterial blood. One application of this principle is used to measure oxygen saturation of arterial blood. In

pulse oximetry two wavelengths of light emitted from suitable light sources are used, one with a wavelength within the red light range and one within the infrared range. The oximeter passes light through a monitoring site and measures the relative absorption of red light preferably at 660 nanometers (by reduced haemoglobin, Hb) and infrared light preferably at 940 nanometers (by oxyhaemoglobin, HbO_2). Because HbO_2 and Hb absorb different amounts of light at each of these two wavelengths, the oximeter can compare the ratio of each absorbance and convert it into an SpO_2 value. More specific it may preferably be expressed $(AC_{660}/DC_{660})/(AC_{940}/DC_{940})$ or AC_{660}/AC_{940} at constant DC levels. Pulse oximetry reduces the effect of other absorbers by looking only on the pulsative absorbances. The oximeter considers only the absorbers in the arterial blood. This is thus in analogy with the measuring global principle of the present innovation for haemoglobin especially, and can thus be attained by including preferably 940 nanometers and preferably 660 nanometers light sources and suitable detectors.

In one preferred embodiment of the method according to the present invention, one or more of the detected intensity of the light of said light beam(s) reflected from the vessel and the detected intensity of the light of said light beam(s) transmitted through the vessel, is transmitted over a wireless connection to a unit for performing step a), e) and/or f), preferably using a module for wireless communication. The wireless communication is preferably performed using a Bluetooth™ standard based communication path.

In the method according to the invention preferably light beam(s) are directed essentially perpendicular to a measuring area of the vessel.

In the method according to the invention preferably the wavelength of the light in (a), when transmitted light also is detected, is from 200 nm to 2000 nm, preferably from 770 nm to 950 nm, most preferred approximately 770, 800, 850, 940 or 950 nm.

In one preferred embodiment of the method according to the invention preferably at least two light beams with different wavelengths in (a) are directed against the mixture and selected such that the light absorbance of the red blood cells, as the first light beam passes theerethrough, is relatively insignificant, whereas the wavelength in the second light beam is selected such that the light absorbance of the red blood cells, as the second light beam passes therethrough, is relatively significant.

In one preferred embodiment of the method according to the invention preferably at least two light beams with different wavelengths in (a) are directed against the vessel, preferably essentially in parallel with each other, wherein one with a wavelength of from 770 to 950 nm and the other with a wavelength of from 480 to 590 nm.

In one preferred embodiment of the method according to the invention, in (a) light is emitted from at least four light sources, preferably six light sources, wherein the light sources being adapted to appear on either side of the detector(s), preferably the light sources are arranged in groups of two, most preferred in groups of three when six light sources are present, most preferred the light sources form an "H" with one detector in the centre. Preferably the "H" above is tilted approximately 90° during the measurement on preferably a wrist when looking from the direction of the arm or the blood vessel. The measurement is further preferably performed on the

inside of the wrist.

In one preferred embodiment of the method according to the invention, in (a) light is emitted from two light sources, which are positioned and thus appearing on two different opposite sides of a vessel containing the mixture, and detection of reflected light from and transmitted light through the vessel is performed by at least two detectors, preferably by only two detectors.

In one preferred embodiment of the method according to the invention (b) comprises the following steps:

I) sweeping a window over a curve with detected values from transmission and/or reflection, wherein the size of said window preferably is approximately 60 % of the period time, divided equally to the right and to the left;

II) if no value within said window is higher than the middle value, designating the value a maximum point whereupon moving the window by leap half of the window length, or if a value exceeds the middle value moving the window only one step;

III) designating the minimum points in the same manner as in II) but with regards to minimum values instead of maximum values;

IV) obtaining the height of the AC-signal by subtracting from a value on a connection line involving two maximum points, the vertically laying value of an in between laying minimum point;

V) repeating step IV) at least 8 times, and summarizing the values from IV) and dividing the sum with the number of observations, thus obtaining a median AC-value; and

VI) optionally obtaining the DC-signal by adding the total height of the minimum point in IV) to the median AC-signal of step V);

whereby preferably using a computer program for obtaining said

AC-signal and optionally said DC-signal.

In one preferred embodiment of the method according to the present invention the wavelength of the red light is approximately 660 nm and the wavelength of the infrared light is approximately 940 nm.

In the method according to the invention, preferably the determined SpO_2 and determined blood characteristics including hemoglobin are presented simultaneously.

In the method according to the invention, preferably the determined SpO_2 is corrected by using the determined blood characteristics including hemoglobin.

The method according to the present invention may, according to a preferred embodiment, be used for determination of blood characteristics including hemoglobin in extracorporeal equipments including e.g. dialysis apparatuses (dialysers), cell savers, dialysis monitors, or on a blood bag device (which includes assemblies), or on a slaughter house device, or on a blood fractionation device. The light pervious vessel, preferably a tube or pipe, may in this embodiment of the present invention have a diameter >0.1 mm. In dialysis apparatuses it may be desirable to see how much hemoglobin and the SpO_2 value which is present in a fluid which is subjected to any form of dialysis, preferably hemodialysis. During dialysis it may further be desirable to measure the hemoglobin concentration in order to follow changes in blood volume of the patient and SpO_2 in said patient. Regarding blood bag constructions and blood bag assemblies, the method according to the invention may be applied to tubings, bags, filters or any other component that may be used in association with blood bags which may contain whole blood or buffy coat i.e. concentrate of white blood cells (leukocytes). The method may also be used

during blood transfusions on tubings, or during blood donations as well. In slaughter houses, the method according to the present application may be useful when recovering blood from slaughter animals and when further processing that blood to give whole blood for use directly in food or fractionate it to obtain the blood components albumin, immunoglobulins and so on. The method according to the present application may also be used when counting blood cells i.e. a process when you count red and white blood cells. This may be done in an apparatus such as a blood cell counter e.g. a Coulter counter manufactured by Coulter Diagnostics of Miami Florida. The method according to the invention may also be used in association with blood analysing, blood typing and other blood gas analyses, in addition to SpO_2. The method according to the invention may also be used when fractionating human blood in a blood fractionating unit. It may be desirable to use the method according to the present application when plasma is obtained from donors. The method may also be useful when obtaining buffy coats from a donor or when these buffy coats are further processed for producing e.g. cytokines such as interferon alpha. The method may be useful to determine how the lysis of the RBC:s are performing during the purification of white blood cells which subsequently after one or more steps involving RBC lysis with e.g. ammonium chloride, are exposed to virus e.g. Sendai virus during incubation in a suitable medium e.g. Eagles Minimal Essential Medium, EMEM.

The method, according to the present application, is preferably performed on a blood vessel, tube or pipe.

According to a preferred embodiment of the present invention the light beams are preferably directed essentially perpendicular to a measuring area of a vessel containing the

mixture.

According to a preferred embodiment of the present invention, at least two light beams are directed against the vessel from two light sources and detection of the intensity of the reflected light from the vessel is performed by at least one detector, preferably by only one detector.

According to yet another preferred embodiment of the method according to the present invention, in step a) at least two light beams, preferably with two different wavelengths, are directed against the vessel, from two light sources, (which may be incorporated in the same shell, e.g. a chip), which are positioned and thus appearing on one common side of the measuring object. These light sources may when used together in a chip be lightened alternately. One of the light beams may have a wavelength of from 770 nm to 950 nm, preferably 770, 800, 850, 940 or 950 nm, and the other may have a wavelength of from 480 nm to 590 nm, preferably 500 nm.

An apparatus according to one preferred embodiment of the present invention may comprise at least four light sources and at least two detectors for reflected light, wherein two light sources have different wavelengths for directing two light beams appearing on the same side of the vessel, wherein preferably one light source is having a wavelength of from 770 to 950 nm and the other a wavelength of from 480 to 590 nm.

In an apparatus according to one preferred embodiment of the present invention at least two components of the apparatus may communicate with each other over a wireless connection, preferably over a module for wireless communication. The module for wireless communication may comprise at least one transmitter and one receiver.

In an apparatus according to a preferred embodiment of the

present invention there may be one module for wireless communication between at least three components, i.e. light sources, light detectors, and the processor and/or one module for wireless communication between the processor and the registration means.

In an apparatus according to a preferred embodiment of the present invention the wireless communication may be performed using a Bluetooth™ standard based communication path.

In an apparatus according to a preferred embodiment of the present invention the light sources may be positioned essentially perpendicular to a measuring area of the vessel.

In an apparatus according to a preferred embodiment of the present invention the wavelength of at least one of the light is from 200 nm to 2000 nm, preferably from 770 nm to 950 nm, most preferred approximately 770, 800, 850, 940 or 950 nm.

An apparatus according to a preferred embodiment of the present invention may have two light sources for directing two light beams with different wavelengths on the same side of the vessel, whereby one of the light beams having a wavelength of from 770 nm to 950 nm, preferably 770, 800, 850, 940 or 950 nm, and the other light beam having a wavelength of from 480 to 590 nm, preferably 500 nm.

An apparatus according to a preferred embodiment of the present invention may comprise at least four light sources on one common side, preferably at least six light sources, wherein the light sources being adapted to appear on either side of the detector(s), preferably the light sources are arranged in groups of two , preferably groups of three, wherein the light sources preferably form an "H" with one detector in the centre.

An apparatus according to a preferred embodiment of the present invention may have the form of a wrist, finger or toe

fitting test device equipped with the light sources and the detectors.

In an apparatus according to a preferred embodiment of the present invention the test device comprises a thimble-like shell to be applied on a finger or toe, the light sources and the detectors being arranged to direct the light beams and detect the light intensities within the shell.

In an apparatus according to a preferred embodiment of the present invention at least three sources and the detectors are positioned in the shell comprising a constriction whereby said light sources and detectors are positioned and thus appearing in said constriction, whereby said shell preferably is a part of a thimble design for covering a finger or a toe.

An apparatus according to a preferred embodiment of the present invention may have at least four light emitting diodes on one common side, preferably at least six light emitting diodes and one detector which together form an "H" with the detector in the centre, fixed on a patch which in turn is making part of a handcuff construction suitable for wrist measurements, wherein the distance between the light sources and the detector preferably is, for determining blood characteristics including Hb and also SpO_2, from 4 to 12 mm when referring from the centres of respective component, most preferred said distance is approximately from 8 to 9 mm. If wrists (containing Radialis) or thicker parts of the body, like upper parts of the arms, are to be measured, when regarding blood characteristics including Hb and also SpO_2, the above distances between the fibres (light source and detector) may be from 6 to 12 mm. For thicker parts (like arms containing Brachialis) of the body the distance may be from 12 to 30 mm. When measuring on wrists or thicker parts of the body a

pressure may preferably be put on the measurement locus. The method according to the present invention may further be used when measuring on vessels situated below the ankles (containing Dorsalis pedis). Thus the present invention may have, for especially the determination of blood characteristics including Hb, light source(s) and detector(s) on different distances as set out above depending on which measuring area is to be monitored, which enables reaching the aimed vessel and thus the detection of the blood characteristics including Hb. The distance between detector(s) and light source(s) may, as set out above, thus be from 1 to 20 mm depending on the measuring area.

In an apparatus according to one preferred embodiment of the present invention the light sources and the detectors for reflection may be fixed at the edge of the patch, which may house a finger, a toe or wrist, preferably a wrist, wherein preferably the patch is a flexible plastic patch anchored to a strap for fastening to the wrist wherein the strap preferaby has a locking device.

In an apparatus according to one preferred embodiment of the present invention the light sources and detectors for reflection may be incorporated in the above patch whereby the electric components are fixed on one side of a printed circuit card covered with black-coloured silicone and the optical components are fixed on the other side covered with transparent silicone.

In an apparatus according to one preferred embodiment of the present invention the patch is rectangular with a size of 51 x 35 mm, and the light sources and detector arranged as an "H" are fixed in a corner of said patch.

In an apparatus according to one preferred embodiment of

the present invention the processor is adapted to convert the reflection values to a concentration value of the determined blood characteristics, preferably by making a quotient of the detected reflected intensities.

In an apparatus according to one preferred embodiment of the present invention the processor may comprise a computer program for performing the method according to the present invention.

In an apparatus according to one preferred embodiment of the present invention the wavelength in the red light range of I) is approximately 660 nm and the wavelength in the infrared light is approximately 940 nm.

According to one embodiment there is provided a computer program stored on a data carrier for performing the method according to the present invention.

By combining the method and the apparatus of the present invention with cable-free communication this allow for broadening the use of said method and apparatus by making it more user-friendly. The cable free communication may allow for internet-billing, patient information follow up and statistics, software package updates and service. The user may by ordering via a modem get the necessary codes to perform a certain number of tests much in the same way as with cellular phones.

The radio communication standard Bluetooth™ has opened the opportunity for cable-free equipment in the hospital environment. Bluetooth™ technology enables electronic devices to communicate with one another without cables. Bluetooth™ modules comprising a transmitter and a receiver may replace cables in many applications. Figure 18 shows a system including a computer and a SpO_2 (including determination of blood characteristics) detector where there is no need for cables

between them when using the Bluetooth™ technology.

Bluetooth™ technology, developed by L M Ericsson, may use the ISM band 2.45 Ghz and may ensure interruption-free communication. The system may work with quick frequency hopping of 1,600 hops per second. The output power from the transmittor may be low and may be adapted to work at a maximum distance of 10 meters. The distance between the wireless communicable components in the apparatus of the present invention may however be variable from 1 cm up to 10000000 miles.

In the apparatus according to the present application at least one of the detectors may be capable of receiving reflected light and be positioned alongside the light source.

According to a preferred embodiment of the apparatus according to the present application the detector, capable of receiving reflected light, is positioned alongside the light source.

According to a preferred embodiment of the apparatus according to the present application the apparatus may have the form of a finger or toe fitting test device or a handcuff equipped with the light source(s) and the detector(s).

The above test device according to the present application may according to a preferred embodiment comprise a thimblelike shell, in short thimble, which is preferably used for detection of SpO_2 (including blood characteristics including hemoglobin) in fingers or toes, where at least three light sources and the detectors are positioned as part of the thimble construction. The thimble embodiment may also be useful for detection of hemoglobin in paws on domestic animals.

The above test device according to the present application may according to a preferred embodiment comprise a handcufflike shell, in short handcuff, which is preferably used for

detection of SpO_2 (including blood characteristics including hemoglobin) in fingers, toes or arms, preferably wrists or fingers, where at least three light sources and the detectors are positioned as part of the handcuff construction. The handcuff embodiment may also be useful for detection of SpO_2 (including hemoglobin) in paws and legs on domestic animals.

The apparatus (especially the test device thereof) according to a preferred embodiment of the present invention may comprise a thimble-like shell to be applied on a finger or toe, the light source and the detectors being arranged to direct the light beam and detect the light intensity within the shell. This embodiment may have at least three light sources and the detectors positioned in the same shell, optionally comprising a bend (constriction), whereby said light sources and detectors are positioned and thus appearing in said bend (constriction), whereby said shell preferably is a part of a thimble or handcuff construction for covering a finger, a toe or a wrist. The above test device may thus be shaped to fit a wrist, toe or a finger.

The thimble and handcuff embodiments are essentially characterized by that they comprises at least three light emitting diodes (LED) positioned on one side together with at least one detector (and two detectors for detecting transmitted light). The above components may be housed in a shell comprising:

a) a first part in close proximity to said components i.e. diode and detectors, which preferably houses the components in a flexible way comprising a flexible material preferably a polymeric material, most preferred silicon rubber.

b) an optional second part also comprising a flexible material, preferably a polymeric material, most preferred silicon rubber.

The first part may also comprise a black plastic material, most preferred epoxy plastic or PMMA. The shell may be cast in industrial scale or may be hand made according to methods known to a person skilled in the art. When silicon rubber is cast to make first and optionally the second part, preferably a colour powder (dye) is added to the rubber. The shorter the wavelength, the larger are the problems with external light, which thus may be minimized by adding dye to the material. Preferably the dye is black to minimize disturbances from other light sources. The shell may be fixed in a position on e.g. a finger, toe or wrist through that the first and, if present, the second part are held together, preferably linked together by gluing the parts together or make the parts stick together in any other way. Further the shell preferably forms an inward bend, an internal constriction, preferably the first part of the shell, where the finger, toe or wrist may be positioned during the measuring. The shell may have an arbitrary shape which surrounds said inward bend or constriction. In this way the finger, toe or wrist may be "squeezed" so that a blood vessel is easily accessible for the measuring method according to the present invention. This squeezing may be acheived by mechanical means or by just pressing by hand. By using a clamping device, which may comprise e.g. a rubber band together with a clamping ring , or a strap device, it may also be possible to fix the thimble or handcuff and squeeze the measuring object.

The flexible material in the first part may also be made out of natural rubber or any pure flexible polymer or any co-polymer. The flexible material may also comprise one or more polymers. The materials in both parts do preferably not contain allergenic substances and thus the thimble is preferably well

tolerable to the skin of a mammal. The shell allows for a finger, toe or wrist of a subject to be "sqeezed" so that preferably a blood vessel is easily accessible for the measuring method according to the present invention. The blood vessel is preferably an artery, vein or arteriol. The detection is preferably performed on a wrist or finger on the third phalanx.

The test device according a preferred embodiment of the present invention may comprise a thimble-like shell to be applied on a finger or toe, the light source and the detectors being arranged to direct the light beam and detect the light intensity within the shell.

Another preferred embodiment of the present invention is an apparatus having additional light sources, the light sources being adapted to appear on either side of the detector(s) for detecting reflected light on a common side.

Another preferred embodiment of the present invention is an apparatus having at least three additional light sources, preferably at least five additional light sources, thus totalling at least four light sources (preferably six light sources), wherein the light sources being adapted to appear on either side of the detector(s) on a common side, preferably in groups of two, most preferred groups of three, whereby the components preferably form an "H" with the detector in the centre. The preferred embodiment with six light sources, preferably six light emitting diodes, and one detector may preferably form an "H" with the detector in the centre.

This further embodiment, the handcuff, which is one preferred embodiment of the invention according to the present application is exemplified by a design which is described in example 3 in detail and also in figure 16. In the handcuff

embodiment of the present invention, the distance between the light source(s) and the detector may be from 4 to 12 mm when referring from the centres of respective component, preferably it is approximately 8 mm. In figure 16 this is the distance between the LEDs and the photodetector in the middle. Preferable the components are fixed to the edge of the bend, which may house a finger, a toe or wrist, preferably a wrist.

The handcuff according to one embodiment of the present invention may preferably be present as a flexible plastic patch anchored to a strap for fastening to the wrist, wherein the strap in turn may be locked, using a locking device, during the measurement, thus squeezing the wrist. This embodiment can be seen in figure 15 and 16. As can be seen in figure 16, the components may preferably be arranged, as an "H", in the corner of a flexible essentially rectangular patch. The patch may preferably have rounded corners and a size of 51 x 35 mm. The patch may additionally preferably have an elevated side, to be in touch with the measuring area e.g. skin of a human, where the light sources and the detector appear. The patch may preferably have a size of 51 x 35 mm and the elevation 31 x 47 mm, leaving a margin of 2 mm to the outer size. The components, when arranged as an "H", may preferably be fixed in a corner of the smaller of the smaller rectangle, i.e. 31 x 47 mm, as can be seen in the figure 16. The "H" is preferably tilted approximately 90° during the measurement on e.g. a wrist when looking from the direction of the arm or the blood vessel. Preferably the measurement may performed on the inside and outside of the wrist, whereby the detectors for the detecting of transmitted light (red and infrared) are present on the outside of the wrist.

The light sources and the detectors may further preferably

be fixed at the edge of the patch, which may house a finger, a toe or wrist, preferably a wrist, most preferred the patch is a flexible plastic patch anchored to a strap for fastening to the wrist wherein the strap preferaby has a locking device. Additionally the apparatus may have the light sources and detector incorporated in the patch whereby the electric components are fixed on one side of a printed circuit card covered with black-coloured silicone and the optical components are fixed on the other side covered with transparent silicone, which ensures electrical isolation, reduction of stray light and the possibility for sterilization. The patch may preferably be rectangular with a size of 51 x 35 mm, and the light sources and detector may be arranged as an "H" fixed in a corner of said patch.

The vessel in which the blood characteristics is to be monitored may be identified by proper choice of the separation between the light source(s) and the detector(s). The theoretical analysis and experimental verification of this optical technique has been presented by I. Fridolin, K. Hansson and L.-G. Lindberg in two papers which have been accepted and are to be published in Physics in Medicine and Biology (Optical non-invasive technique for vessel imaging I and II, Department of Biomedical Engineering, Linköping University, Sweden). The following is a summary of their analysis and experimental verifications.

Light reflection from human tissue depends on many parameters, such as optical wavelength, source-detector separation, size and aperture of the light source and detector and optical properties of the blood and tissues. The separation between the light source and the detector fibre was varied between five centre-to-centre distances: 2, 3 ,4, 5 and 6 mm.

The analysis agreed with the earlier conclusion that to increase the influence from deeper tissue on the measured signal, a larger light source-detector separation should be selected.

The resultant mathematical analysis and verified experimental results can be summarized as:
At larger separation values the photons forming maximum photon paths and detected by the photodetector originate from deeper layer than for short separation values. This is illustrated in figure 14. Figure 14 is a schematic diagram of photon migration at two different source-detector separations and for different FL (α) (FL(0) and FL(π/2)). FL = fibre pair position relative the Lining of the vein. Two positions of the light source and the photodetector fibres relative to the lining of the vein were considered. An angle α is defined to characterize different positions. The abbreviation FL(0) means that the light source and the photodetector are positioned in parallel and FL(π/2) that the light source and the photodetector are positioned perpendicular to the vessel. Monte Carlo simulations have shown that for human tissues in the near infrared region photons penetrate approximately 2 mm before being detected if the separation is about 2 mm between the source and the detector.

The blood vessels in terms of veins may be determined at three vascular levels in combination with a fixed fibre diameter (1 mm) using the probe and technique above summarized and according to;
* a superficial vascular level (approximately 1 mm). This may be sufficient to set the minimal distance between the illuminating and detecting fibre (2 mm during the above experiments.

* an intermediate vascular level (approximately 2 mm). The minimal distance between the illuminating and detecting fibre may preferably be 2 - 3 mm
* a deep vascular level (approximately 3 mm). The distance between the illuminating and detecting fibre may preferably be greater than 3 mm.

The result of this above summarized research makes it possible to determine blood characteristics and monitor physiological parameters on a selected vascular bed, vein or artery, such as blood flow, blood constants and oxygen saturation e.g. on a selected vascular bed in veins or arteries.

If wrists (containing Radialis) or thicker parts of the body, like upper parts of the arms, are to be measured, when regarding SpO_2 (and blood characteristics including Hb), the above distances between the fibres (light source and detector) may be from 6 to 12 mm. For thicker parts (like arms containing Brachialis) of the body the distance may be from 12 to 30 mm. When measuring on wrists or thicker parts of the body a pressure may preferably be put on the measurement locus. The method according to the present invention may further be when measuring on vessels situated below the ankles (containing Dorsalis pedis).

The theoretical solution for light distribution in tissue, described in paper II above, may be the base for describing how hemoglobin can be measured in reflection mode. Equation 32 provides a general solution in which equation μ_a and μ_s describes the influence of the optical coefficients and H and B (or Z) the influence on pulsative variations in vessel diameter during the cardiac pulse.

The light sources is are connected by cords to any power source, which may be an oscillator or a battery. The oscillator

may be connected to amplifiers and LED-Drivers. These drivers may be connected to one or more LEDs. Detectors, e.g. photodiodes for reflection may be connected to at least one current/voltage converter, which in turn may be connected to the amplifiers. The signals may then pass to Band pass Filters and subsequently to analog outputs or to a μ-controller which is connected to a Read out unit.

For the performance of the method according to the invention one or more calibration curves may be used. One calibration curve stored in a memory of a processor, which preferably is part of a computer, may allow the readily conversion from the quotient reflection/transmission %, which may be stated: AC_R/AC_T or DC_R/DC_T, or reflection/reflection % which may be stated: AC_R/AC_R or DC_R/DC_R, obtained when directing light beam(s) against the vessel and subsequently detecting the reflection and transmission or only reflection, to a hemoglobin value in mmol/l. By analyzing the quotient of the detected intensities of reflected or, reflected and transmitted light, the advantage is achieved that influences from pressure and flow, in particular pulsating flow, of the liquid mixture is compensated for, whereby the determined blood characteristics including will be accurate, and accordingly also SpO_2. The quotient is analyzed by comparing it with previously obtained quotients for known values of the blood characteristic in question. The calibration curve may preferably be obtained by analysing in parallel with the method according to the present invention, drawn blood samples from volontary healthy persons and patients on a Hemocue apparatus or blood gas analyser. A spectrophotometric absorption curve in reflection mode or recording curve in reflection mode may also be used in conjunction with the method above. The obtained values for

measuring SpO_2, preferably in form of a quotient described above, may be compared to an already existing calibration curve, thus enabling an easy conversion to a SpO_2 value.

Apparatuses according to the present invention may further big matrix probes comprising several light sources (more than six) and detectors (more than one) which may have the form of a ring, plate, cube, sphere.

The apparatus according to the present application may according to an additionally preferred embodiment be comprised in a dialysis apparatus, preferably for performing hemodialysis.

The apparatus according to the present invention may be divided geographically on the body, thus e.g. further having a SpO_2 measuring part to be used in an ear and connected thereto, optionally wireless, the Hb measuring part in a finger, wrist or a toe.

The apparatus according to the present application may according to an additionally preferred embodiment have at least two, preferably at least four , most preferred six, light sources which are positioned and thus appearing on a common side of the measuring object during detection. When two or more LEDs are used they are preferably interchangable with each other. They may further preferably emit light with different wavelengths. Measuring the intensity of the reflected light at one or more wavelengths with light sources of suitable wavelengths may also attain the independence of blood characteristics on blood flow and blood pressure. Similar measuring technique may be used to compensate for differences in tissue absorbencies over the artery between individuals. The LEDs may be present in the same handcuff (a patch thereof) or thimble.

The apparatus according to the present application may according to an additionally preferred embodiment have at least two light sources, wherein the first light source emits light of a wavelength which is relatively not absorbable by red blood cells, and the second light source emits light of a wavelength which is relatively absorbable by red blood cells. The above first and second light sources may preferably be directed substantially in parallel with each other.

The apparatus according to the present application may according to an additionally preferred embodiment have at least two light sources, preferably at least four light sources, most preferred at least six light sources, which are positioned and thus appearing on the same common side of the measuring object during detection, where at least one light source (preferably a LED) emits green light and at least another light source (preferably a LED) emits NIR light of from 770 nm to 950 nm. The at least two light sources direct two light beams against the same side of the vessel, one of the light beams having from 770 nm to 950 nm and the other light beam having a wavelength of from 480 to 590 nm. Preferably the green light is emitted in the green wavelength range i.e. 480-590 nm, most preferred at 500 nm.

By directing two light beams with a wavelength <1500 nm a better sensitivity of the method may be obtained. In this above preferred embodiment of the present invention one light beam has a longer wavelength, preferably NIR (Near InfraRed) light, and the other has a shorter wavelength preferably in the range of 200-580 nm, most preferred green light, 400 or 500 nm. Using green light in the other light source is advantageous because green light is heavily absorbed by red blood cells.

The processor for analyzing said intensity of said

reflected (and tranmitted) light detected by the detector(s) and for determining SpO_2, including the blood characteristics including hemoglobin, may be included in a computer (CPU). Further, the registration means may also be included in a computer. The visualization may be accomplished by any visualization means, but is preferably accomplished by using a computer display and/or a printer device. The processing of the data obtained during the measurement may also include quotient forming of reflection/transmission, transmission/reflection (for SpO_2, transmission/transmission) with or without AC and/or DC with or without multiplying of one or more of the obtained data in order to compensate for variations in volume or flow. If any additional light sources and detectors are used in the invention (especially in the determination of blood characteristics including Hb) according to the present invention, there may be several quotients formed with basis from the detected intensities depending on the number of detected intensities available. There may also be included a computer program in the processor for search for the optimal measuring spot, especially when using a matrix comprising several light sources and detectors, for controlling/verifying reliable strength of the signal, for performing algorithm calculations, for evaluating data against stored standard curves, for displaying (and storing) the results together with patient data and relevant quality criteria. The output of the results from measuring using the present invention may be accomplished on a connected printer device, optionally connected via the visualization means.

Of course, it may be possible to process the reflection signals in a manual way and hereby determine SpO_2, including the blood characteristics including hemoglobin. The results may

also be visualized in a manual way by e.g. plotting the results in a diagram. The signal(s) detected by the detector(s) may further preferably be analysed using the following procedure: As the PPG-signal is consisting of two parts, a constant signal and a pulsating signal superposed on the constant signal, first maximum and minimum points are calculated. The maximum points are calculated through sweeping a window over a curve plotted by values of detected light intensities. The size of the window is adjusted according to the frequency of the AC-signal (the pulse) to approximately 60% of the period time, divided equally to the right and to the left. If no value within the window is higher than the value in the middle, this value is designated a maximum point, whereafter the window is moved by leaps half of the window length in order to avoid that a plateau formed curve is registrated as many maximum points. If any value within the window exceeds the value in the middle, the window is moved only one step. In a corresponding way the minimum points are calculated.

For each minimum point an AC-height is calculated as the height to the connection line between the maximum points closest to the left and to the right of the middle (mean) point, respectively, taken from the in between lying minimum point. Of nine subsequetly following AC-heights, the median height is selected as the representative of the AC-signal, in order to filter away artefacts that may give rise to erroneously detected minimum or maximum points. The DC-signal is then calculated as the total height to the minimum point that laid basis for the AC-signal, plus the AC-signal. Figure 19 shows an example of the above procedure. Step d) in the summary of the invention above may preferably comprise the following steps:

I) sweeping a window over a curve with detected values from transmission and/or reflection, wherein the size of said window preferably is approximately 60 % of the period time, divided equally to the right and to the left;
II) if no value within said window is higher than the mean (middle) value, the value is designated a maximum point whereupon the window is moved by leap half of the window length, or if a value exceeds the middle value the window is moved only one step;
III) the minimum points are designated accordingly in the same manner as in II) but with regards to minimum values instead of maximum values;
IV) the height of the AC-signal is obtained by subtracting from a value on a connection line involving two maximum points, the vertically lying value of an in between lying minimum point;
V) repeating step IV) at least 8 times, and summarize the values from IV) and dividing the sum with number of observations, thus obtaining a median AC-value
VI) optionally obtaining the DC-signal by adding the total height of the minimum point in IV) to the median AC-signal of step V). Preferably these above steps are accomplished by using a computer program for obtaining said AC-signal and optionally said DC-signal. Preferably the computer program is stored on a data carrier for performing the above steps I) to VI). Preferably the data carrier is part of the processor (or central processing unit, CPU) designated iv) above, in one preferred embodiment of the present invention, or a separate floppy disc to be inserted and used by the processor. The processor may preferably comprise a computer program for performing the method according to the present invention, as e.g. set forth in the summary of the invention and in the

preferred embodiments of the present invention, and/or the above steps I to VI.

Another embodiment of the present invention is also a computer program stored on a data carrier for performing the method according to the present invention, as e.g. set forth in the summary of the invention and preferred embodiments of the present invention, and/or the above steps I to VI.

When measuring on the skin the equation may look similar except that the light may be reduced depending on the absorption of light and the light scattering in the tissue. The intensity may be compensated at different blood flows when performing the current invention, the method and using the apparatus. When performing skin measurement, this is preferably performed over a large blood vessel, e.g. on the wrist or on the finger of the third phalanx. The blood vessel preferably contains a blood volume which markedly differs from the blood volume in the surroundings (which may comprise capillaries). It should be noted that the method and apparatus according to the present invention may preferably be used for measuring SpO_2 (including the central blood characteristics) as represented in larger vessels such as arteries. This may be achieved by compensating for the influence of blood pressure and blood flow on the measured intensities of the reflected and transmitted light, by taking the quotient between the reflected and transmitted light. The effect used in the present method and apparatus according to the present invention may also be used for measuring the change in SpO_2 (and blood characteristics) in one individual or in an extracorporeal system when the blood haemoglobin value is constant. This is further illustrated in example 4 where this was performed by using an apparatus according to the present invention. Using the method it is thus

possible to follow changes in SpO_2 (and in blood volume and pathological changes in the body).

The present invention with its method and its apparatus may also be adapted to detect oxygen together with SpO_2, as 97-98 % of all oxygen in the blood of a human being is transported by hemoglobin molecules in the blood. Of course the method may also be used for detecting SpO_2 (and red cells themselves) as hemoglobin is normally incorporated in the red blood cells, unless they are lysed. As the viscosity of blood corresponds to the amount of red blood cells in the blood, the method may also be used for detection of viscosity as well. The method and apparatus according to the present invention may also be used to determine the hematocrit (Hct). The difference between hemoglobin (which is the grams of hemoglobin per volume of blood) and hematocrit (which is the volume of blood cells per volume of blood) is determined by the concentration of hemoglobin within the cells which determines the index of refraction of the cells.

Several different blood constants are used in diagnostics. Some are interchangeable and there are generally accepted relationships between these. The generally accepted relationships are:

Constant	Measures	Calculation
RBC EPC	number of red blood cells per unit volume of blood *or* erythrocyte particle concentration	
Hb	concentration of haemoglobin in blood	

Hct	hematocrit or erythrocyte	Hct=RBCxMCV
EVF	erythrocyte volume fraction. Fraction of red blood cell volume of total volume.	
MCV	erythrocyte volume, *abr.* mean corpuscular volume	MCV=EVF/RBC
MCH	weight of haemoglobin in erythrocytes, *abr.* mean corpuscular haemolglobin	MCH=Hb/RBC
MCHC	concentration of haemoglobin in erythrocytes, abr. mean corpuscular haemoglobin concentration	MCHC=Hb/EVF

Further, human blood is made up of formed elements and plasma. There are three basic types of formed blood cell components: red blood cells, white blood cells (leukocytes) and platelets. The red blood cells contain hemoglobin that carries oxygen from the lungs to the tissues of the body. Normally the hemoglobin concentration varies between 132 - 163 gram/litre in men, and 116 - 148 gram/litre in women. The hematocrit (Hct) normally varies between 39 - 49 % (EVF 0.39 - 0.49) in men, and 37 - 44 % (EVF 0.37 - 0.44) in women. White blood cells are of approximately the same size as red blood cells, but they do not contain hemoglobin. A normal healthy individual has approximately 5,000,000 red blood cells per cubic millimeter of

blood (the human body contains approximately 5 litres of blood), and approximately 7,500 white blood cells per cubic millimeter of blood. Therefore, a normal healthy individual will have approximately one white blood cell (leukocyte) for every 670 red blood cells circulating in the vascular system. The white blood cells (WBCs) are responsible for the immune system in a mammal, preferably a human being. E.g. certain WBCs engulf intruder agents.

Concerning platelets, they are the smallest of the formed blood cell components, being typically less than 1 μm in diameter. Platelets are less abundant than red cells, but more abundant than white blood cells. A normal healthy individual has approximately one platelet for every 17 red blood cells circulating in the vascular system for a total of about two trillion.

In summary, the method and apparatus according to the present invention may be used to determine SpO_2 (and various characteristics of the vascular system) through the use of known relationships between parameters, as for the cases when determining indirectly the amount of white blood cells and/or platelets. (For WBCs the factor is 1/670 of the red blood cells and for platelets it is 1/17). Thus the blood characteristics in steps a) in the method according to the invention may also include white blood cells and/or platelets. Cholesterol and albumin concentration may also be determined when using the known hemoglobin concentration in connection with the method described in GB 2 329 015, hereby incorporated by reference thereto. The above method refers to non-invasive measurement of blood component concentrations.

The method and apparatus according to the invention also enables SpO_2 determination and diagnosing of irregularites or

diseases in a mammal e.g. anemia where there is a shortage of red blood cells. Bulimia patients often suffer from anemia in which accurately determination of SpO_2 may be accomplish using the method and apparatus according to the present invention. Further, also congestive heart failure and cardiac arythmies may be detected using the method and apparatus according to the invention. Further, the method and the apparatus gives an indirect possibility of measuring platelet diseases such as thrombocytopenia. This could be indicative for problems of menostasis and coagulation. An elevated level of certain white blood cells is further indicative of a viral infection. Leukocytosis and leukopenia are also thinkable indications which may be possible to detect indirectly. Other diseases of the phagocytic and Immune Systems may also be detectable. Neonatal monitoring is another application area for the present invention. Operative monitoring is also a conceivable application. The apparatus may be set to a "zero-level" at the start of an operation, in order to compensate for stable interactive effects (skin colour, lipids and so on) and thus a readily monitoring of SpO_2 (and blood characteristics including hemoglobin) may be acheived.

The current invention, the method and apparatus, also enables an accurate measurement of SpO_2 in patients blood, without any risks associated with drawing blood (e.g. AIDS, hepatitis A, B and C etc). Drawing blood by using injection needles is also a painful method, especially for individuals requiring many blood samples to be drawn. These drawbacks may be eliminated by using the method and apparatus according to the present invention. Further the method and apparatus according to the present invention is especially suitable for measurements on children.

The present invention also refers to use of an apparatus according the present application in a dialysis apparatus (or dialysis device).

The examples which follow illustrate embodiments of the present invention, but are not intended to limit the scope in any way.

Description of the figures

Figure 1 shows schematically a flow model for detection of light reflection.

Figure 2 shows the orientation of red blood cells at an intermediate or high level of shear rate or blood flow.

Figure 3 shows light absorption in blood due to different absorbing matter.

Figure 4 shows light scattering due to red blood cells.

Figure 5 shows the relative change in transmitted light *versus* blood flow for two different types of red blood cells.

Figure 6 shows the relative change in transmitted light intensity *versus* blood flow for two types of blood cells.

Figure 7 shows essentially the experimental setup of an example (example 2).

Figure 8 shows a diagram with the relative change of the quotient reflection/transmission (%) i.e. AC_R/AC_T, on the y-axis and the hemoglobin concentration in mmol/l on the x-axis.

Figure 9 shows reflection and transmission vs. hemoglobin concentration.

Figure 10 shows the thimble-like shell construction according the apparatus of the present invention comprising two light sources, from four different views, without cords.
The numbers in the figures have the following explanations:

1. Green Light Emitting Diode (LED) and NIR LED;

they are interchangable

2. Detector

3. Detector

4. Second part comprising a stiffer material

5 First part comprising a flexible material

The A-A, B-B, C-C are sections of the thimble.

Figure 11 shows a block diagram illustrating schematically how the thimble (the shell is not shown; only light sources and detectors is shown) is connected. The numbers in the figure has the following explanations:

1. oscillator

2. LED-Driver λ 1

3. LED-Driver λ 2

4. LED λ 1 or 2

5. Photodiode reflection

6. Subject

7. Photodiode transmission

9. Current/Voltage converter

10. Current/Voltage converter

11. Lowpass Filter

12. Lowpass Filter

13. Sample and Hold amplifier

14. Sample and Hold amplifier

15. Band pass Filter

16. Band pass Filter

17. Analog output

18. Analog output

19. μ-controller

20. Read out unit

Figure 12 shows a block diagram illustrating schematically how the thimble (the shell is not shown; only light sources and

detectors is shown) is connected in another embodiment of the thimble. The numbers in the figure has the following explanations:

1. oscillator
2. LED-Drivers
3. LED
4. Photodiode reflection
5. Photodiode transmission
6. Subject
7. Current/Voltage converter
8. Current/Voltage converter
9. Lowpass Filter
10. Lowpass Filter
11. Sample and Hold amplifier
12. Sample and Hold amplifier
13. Band pass Filter
14. Band pass Filter
15. Analog output
16. Analog output
17. µ-controller
18. Read out unit

Figure 13 shows the intensity of the reflected pulsative light versus increasing systolic pressure.

Figure 14 shows at larger separation values the photons forming maximum photon paths and detected by the photodetector originate from deeper layer than for short separation values.

Figure 15 shows a probe of one preferred embodiment of the apparatus according to the present invention, where only reflected light was detected, fastened on the wrist of a subject. The probe was placed on the wrist over the radial artery.

Figure 16 shows the probe comprising a patch made of flexible material. The probe was placed on the wrist, on the inside of the arm, over the radial artery.

Figure 17 shows three diagrams illustrating when saline was injected in the flow direction close to the probe in figure 15 and 16. Only the intensity of the reflected light was recorded and the change in signal corresponded to the dilution effect in the blood. The two diagrams in the bottom of figure 17 shows a recording on a patient with atrial fibrillation, i.e. the PPG and ECG signals.

Figure 18 shows an apparatus according to the present invention, including a computer and a SpO_2 (including blood characteristics) measuring apparatus, including cable-free Bluetooth™ equipment for wireless communication of data between seperate elements of the apparatus.

Figure 19 shows the PPG-signal with DC-signal, AC-signal, minimum points and maximum points.

Experimental details

Example 1

Detection was performed using the following equipment:
-A tube of acrylic glass (PMMA) with an inside diameter of 3 mm
-Two optical fibres with a diameter of 0.094 mm. One fibre was for transmission of light (light source) and the other for receiving reflection of light (photo detector).
-A glass tube with an outside diameter of 0.210 mm for housing the optical fibres placed in parallel with each other.
-Whole blood from volonteers, which was pumped through the tube made up of PMMA.

Figure 1 shows schematically the flow model for detection

of light reflection. Figure 2 shows the orientation of red blood cells at an intermediate level of shear rate. Figure 3 shows light absorption in blood due to different absorbing matter. Figure 4 shows light scattering due to red blood cells.

The results from this experiment suggest that the light is spread in a special way when hitting the red blood cells in the tube. This probably depends on the shape of the blood cells, bi-concave disc, which forces the cells to orientate in different way as they move in the circular tube. This is demonstrated with optical technique through placing two optical fibres in a small catheter, where one of the fibres works as a light source and the other as photodetector as set out above. The fibre pair is moved from one periphery to the other in a cross-section of a circular tube.

Figures 5 and 6 are summaries of experimental results. The intensity of the light transmitted from the red blood cells flowing through a tube of acrylic glass. The experimental setup was the same as in the above mentioned experiments.

Figure 5 shows the relative change in transmitted light *versus* blood flow for two different types of red blood cells. The "stiff cells" are red blood cells, which were treated with glutaraldehyde in order to make them stiff i.e. they had lost their ability to change shape with the stress created by the flow.

The results show that one important characteristic of the red blood cells is their flexibility. This results in a change of shape - elongation - and orientation with increasing flow as demonstrated by the reduced transmission intensity with increasing flow. Red blood cells without this flexibility (stiff) show little or no orientation effect with flow as measured with light transmission change.

Figure 6 shows the relative change in transmitted light intensity *versus* blood flow for two types of blood cells. The "spherical cells" are red blood cells treated with non-isotonic buffer solution. This makes the cells loose their bi-concave disc shape. This results in a close contact and orientation with increasing flow as demonstrated by the reduced transmission intensity with increasing flow. Red blood cells with spherical shape exhibit less shear stress with increasing flow and show little or no orientation effect with flow as measured light transmission changes.

We can thus conclude that the cell orientation of the red blood cells as a function of flow e.g. flexible or inflexible tubes or arteries in humans and mammals is mainly due to their unique bi-concave disc shape and flexibility.

Example 2

A second experimental setup consisted essentially of the following. There were essentially three main parts:

* a cylindrical disc oxygenator which also served as a blood reservoir.
* a flow controlled roller pump (peristaltic pump)
* a rigid flow-through model connected to a light source and photodetectors via optical fibres

The setup is essentially shown in figure 7, but it lacks one photodetector, as both transmission and reflection was measured. A waveform generator regulated the roller pump, which produced a continuous blood flow. A pressure transducer was also part of the circuit for the blood flow. The blood temperature was maintained constant at 37.0° ± 0.1°C, by circulating warm air around the setup.

A gas mixture was lead into the reservoir and mixed with

the blood. The gas exchange was simulated by a disc oxygenator and the gas mixture consisted of 19% oxygen and 5.6 % carbon dioxide in nitrogen. The oxygen saturation was maintained at 98-99%, and the blood gas parameters (pO_2, pCO_2 and pH) were assumed not to deviate from normal physiological values.

Laminar flow-through model was used in order to minimize hemolysis of the red blood cells. The wavelength that was used was 800 nm, an isobestic point where a minimal absorbance of light take place on the red blood cells. The measurements were performed on a tube made of acrylic glass with an inner diameter of 3.0 mm.

Figure 8 shows a diagram with the relative change of the quotient reflection/transmission (%) i.e. AC_R/AC_T, on the y-axis and the hemoglobin concentration in mmol/l on the x-axis. The quotient between reflection/transmission appears to be independent of the blood flow, but appears to vary according to the concentration of hemoglobin. The optically registered hemoglobin (Hb) signal may thus be stated;

$$Hb=AC_R/AC_T$$

and this has been confirmed by analysing in parallel with the method according to the present invention, drawn blood samples from volontary healthy persons and patients on a Hemocue apparatus (Ängelholm, Sweden) in a Clinical Chemistry Laboratory. Thus a calibration curve was obtained. This calibration curve may be stored in a memory of the processor, which preferably is part of a computer, which allows readily the conversion from AC_R/AC_T, obtained when directing light beam and subsequently detecting the reflection and transmission in accordance with the method of the invention, to a hemoglobin value in mmol/l. This curve may be linear at certain conditions.

Figure 9 shows light reflection and transmission vs. hemoglobin concentration. When illuminating intact blood cells in a circular pipe, the light transmission and reflection will follow the concentration of red blood cells. The transmission of light decreases with increased hemoglobin and the reflection of light increases with increased hemoglobin.

Example 3

A thimble-like test device comprising a shell which is one preferred embodiment of the present invention shown in Figure 10 was used. This thimble comprises:

i) two light sources: One Green Light Emitting Diode (LED), essentially of type 110104, 540, diameter ⌀ 5 mm, and one NIR LED , essentially of type SFH 585, 880, diameter ⌀ 4.85 which are interchangable,

ii) two detectors, essentially of type SD 1420-002 and CFD 10 respectively.

For SpO_2 measurements there may preferably be incorporated two additional light sources (red and infrared light) and corresponding detectors for detecting transmitted light, in said thimble construction.

The thimble has one rigid part comprising a stiffer material and one flexible part comprising a flexible material. The rigid part comprises PMMA or any other similar plastic material. The flexible part comprises silicon rubber with black dye (ceramic pigment which is non-conducting). The rigid and flexible parts form a circular ring forming a keyhole-like hole in the middle, with a bend for e.g. a finger or a toe. The rigid and flexible parts may be glued together or held together by other means.

How the thimble is connected to a power source and so on,

is shown in Figure 11 through a block diagram illustrating this schematically. The numbers in the figure has the following explanations:

1. oscillator
2. LED-Driver λ 1
3. LED-Driver λ 2
4. LED λ 1 or 2
5. Photodiode reflection
6. Subject
7. Photodiode transmission
9. Current/Voltage converter
10. Current/Voltage converter
11. Lowpass Filter
12. Lowpass Filter
13. Sample and Hold amplifier
14. Sample and Hold amplifier
15. Band pass Filter
16. Band pass Filter
17. Analog output
18. Analog output
19. μ-controller
20. Read out unit

The oscillator is connected to the Sample and Hold amplifiers and the LED-Driver λ 1 and LED-Driver λ 2. These drivers are connected to one or in this case two LEDs and one photodiode for detecting the reflected light. The photodiode for detecting transmitted light is connected to at least one current/voltage converter in this case two, which in turn are connected to the Sample and Hold amplifiers . The signals then pass to the Band pass Filters and subsequently to the analog outputs or to a μ-

controller which is connected to a Read out unit.

Example 4

A handcuff-like test device comprising a shell which is one preferred embodiment of the present invention shown in Figure 16 was used. This handcuff comprises:

i) six light sources: LEDs, λ=875 nm;

ii) one detector.

At least one of the light sources may preferably have a wavelength different from the other ones.

The handcuff comprises a patch of flexible material and a strap. The flexible material comprises silicon rubber with black dye (ceramic pigment which is non-conducting). The flexible material may form a bend for e.g. a wrist, a finger or a toe. The PPG sensor was especially designed to be used on the wrist. The optical geometry of the sensor was optimized in order to make it possible to monitor blood characteristics, preferably blood flow, deep in the tissue from the radial artery where it passes over the flat portion of the radius bone. The center to center distance between the LEDs and the photodetector is approximately 8-9 mm.

All components are incorporated in the sensor with the electronics on one side of the printed circuit card covered with black-coloured silicone and the optical components on the other side covered with transparent silicone. This ensures electrical isolation, reduction of stray light and the possibility for sterilization.

For SpO_2 determination, the above handcuff construction may preferably comprise two LEDs with wavelengths within the red and infrared range, respectively. The handcuff preferably also comprises two detectors for appearing on the opposite side

of the wrist and detecting the transmitted SpO_2 light intensities, red/infrared.

How the handcuff is connected to a power source, a battery eliminator, is shown in Figure 16 through a block diagram illustrating this schematically. The handcuff is further connected to a laptop computer where all measured signals were stored.

Measurement was performed by using the above probe fastened on the wrist (see figure 16) of a subject. The probe was placed on the wrist over the radial artery. Saline was injected in the flow direction close to the probe. The artery needle was inserted 10 cm from the hand into the radial artery with the needle in the flow direction. The distance between the sensor and the tip of the needle was approximately 5 cm. Physiological saline was injected during 1-5 seconds at different volumes. The PPG signal was recorded in order to confirm the monitoring depth.

In clinical measurements the PPG signal was recorded in heart failure patients simultaneously with ECG recording. Only the intensity of the reflected light was recorded and the change in signal corresponded to the dilution effect in the blood. The result, i.e. the PPG signal which consists of two components namely a pulsatile component (AC) synchronous with the heart rate and a slowly varying component (DC), can be seen in figure 17, where the light reflection showed in change in both AC and DC signals corresponding to dilution effect in the blood after a delay of approximately 0.5 seconds. This proves the ability to extract information from the radial artery itself using the apparatus according to the present invention. The two diagrams in the bottom of figure 17 shows a recording on a patient with atrial fibrillation. The AC PPG signal (upper

curve) is in accordance with the irregular appearance of the QRS complex in the electrocardiogram. The DC component reflects total blood volume changes of different physiological features in the circulation, e.g. vasomotion, temperature regulation and respiration.

The apparatus according to the present invention thus is useful for e.g. central related blood flow monitoring together with SpO_2 on the wrist. Signal variations in amplitude, curve form and frequency content may further reflect different pathological events in the body corresponding to congestive heart failure and cardiac arythmies. Other telemetrical applications in telemedicine are thinkable for the apparatus and the method according to the present invention.

As with other blood flow monitoring system, the apparatus according to the present invention is susceptible to patient arm movement. An artefact reducing loop may further be incorporated in the apparatus. Besides the blood flow parameter described above there may be incorporated in the apparatus means for monitoring blood pressure, heart rate and respiratory rate together with the oxygen saturation, SpO_2.

Another measurement was performed by using an apparatus according to present invention. The relative pressure was monitored and the results can be seen in figure 13. The diagram in figure 13 shows the intensity of the reflected pulsative light versus increasing systolic pressure. The diastolic pressure was kept constant. This exemplifies the central measurement of blood characteristics including Hb, as represented in larger vessels such as arteries. This is acheived by compensating for the influence of blood pressure and blood flow, by using a quotient of the transmitted/reflected, reflected/transmitted or

reflected/reflected values for light intensities, on the measured intensities of the reflected and transmitted light. The effect may be used to measure the change in blood characteristics including Hb together with SpO_2 in one individual or in an extracorporeal system when the blood hemoglobin value is constant.

Another measurement was performed by using a probe, where only reflected light was detected, fastened on the wrist (see figure 16) of a subject. The probe was placed on the wrist over the radial artery. Saline was injected in the flow direction close to the probe. The artery needle was inserted 10 cm from the hand into the radial artery with the needle in the flow direction. The distance between the sensor and the tip of the needle was approximately 5 cm. Physiological saline was injected during 1-5 seconds at different volumes. The PPG signal was recorded in order to confirm the monitoring depth. Only the intensity of the reflected light was recorded and the change in signal corresponded to the dilution effect in the blood. The result, i.e. the PPG signal which consists of two components namely a pulsatile component (AC) synchronous with the heart rate and a slowly varying component (DC), can be seen in figure 17, where the light reflection showed in change in both AC and DC signals corresponding to dilution effect in the blood after a delay of approximately 0.5 seconds. The DC component reflects total blood volume changes of different physiological features in the circulation, e.g. vasomotion, temperature regulation and respiration.

Various embodiments of the present invention have been described above but a person skilled in the art realizes further minor alterations which would fall into the scope of

the present invention. The breadth and scope of the present invention should not be limited by any of the above-described exemplary embodiments, but should be defined only in accordance with the following appended claims and their equivalents.

Claims

1. A non-invasive method of determining SpO_2 of a mixture of liquid and blood cells, comprising:
a) directing light beams against the mixture;
b) determining at least one blood characteristic other than SpO_2 including hemoglobin of the mixture by analyzing the intensity of the light reflected from the mixture, or the intensity of the light reflected from the mixture in combination with the intensity of the light transmitted through the mixture;
c) determining oxygen saturation, SpO_2, of the mixture by analyzing the intensity of the light transmitted through the mixture; and optionally
d) based on the result of step b), establishing whether the result of step c) is relevant.

2. A method according to claim 1, wherein (c) is performed by pulse-oximetrically determining oxygen saturation.

3. A method according to claim 1, wherein (a) is performed by directing at least one light beam with a wavelength in the red light range against the mixture, and directing at least one light beam with a wavelength in the infrared light range against the mixture.

4. A method according to claim 3, wherein (c) is performed by detecting the intensities of the red light and infrared light transmitted through the mixture, calculating a quotient of the detected intensities, red/infrared, of the transmitted light,

and determining SpO_2 by analyzing the quotient.

5. A method according to claim 1; wherein (b) is performed by:
i) detecting the intensity of the light of the light beams reflected from the mixture and the intensity of the light of the light beams transmitted through the mixture;
ii) calculating a quotient of the detected intensity of the transmitted light and detected intensity of the reflected light or a quotient of the detected intensity of the reflected light and detected intensity of the transmitted light; and
iii) analyzing the quotient to determine the blood characteristic.

6. A method according to claim 1, wherein (a) is performed by directing at least two light beams with different wavelengths against the mixture.

7. A method according to claim 6, wherein (b) is performed by:
i) detecting the intensities of the light of the light beams reflected from the mixture;
ii) calculating a quotient of the detected intensities of the reflected lights; and
iii) analyzing the quotient to determine the blood characteristic.

8. The method according to claim 1 wherein one or more of the values of the detected intensity of the light of the light beam(s) reflected from the mixture and the detected intensity of the light of the light beam(s) transmitted through the mixture, is transmitted over a wireless connection to a unit for performing (b), (c) and (d), preferably using a module for

wireless communication.

9. The method according to claim 8, wherein the wireless communication is performed using a Bluetooth™ standard based communication path.

10. The method according to claim 1, wherein the light beam(s) are directed essentially perpendicular to a measuring area of a vessel containing the mixture.

11. A method according to claim 1, wherein the wavelength of the light beams, when transmitted light also is detected, is from 200 nm to 2000 nm, preferably from 770 nm to 950 nm, most preferred approximately 770, 800, 850, 940 or 950 nm.

12. A method according to claim 1, wherein at least two light beams with different wavelengths are directed against the mixture, wherein one with a wavelength of from 770 to 950 nm and the other with a wavelength of from 480 to 590 nm.

13. A method according to claim 1, wherein the mixture of liquid and blood cells is flowing.

14. A method according to claim 1, wherein the mixture of liquid and blood cells comprises plasma.

15. A method according to claim 1, wherein it is performed on a mammal, preferably on a human being.

16. A method according to claim 15, wherein it is performed on a blood mixture with a diameter greater than 0,1 mm, preferably

a vein, an artery or an arteriol.

17. A method according to claim 15, wherein it is performed on an arm, a toe or a finger, preferably on a wrist or a finger on the third phalanx.

18. A method according to claims 1, wherein it is performed in a dialysis apparatus, or on a blood bag assembly, or on a slaughter house device, or on a blood fractionation device, preferably it is performed on a tube or pipe.

19. A method according to claim 1, wherein in step (b) light is emitted from at least four light sources, preferably six light sources, wherein the light sources being adapted to appear on either side of the detector(s), preferably the light sources are arranged in groups of two, most preferred in groups of three when six light sources are present, most preferred the light sources form an "H" with one detector in the centre.

20. A method according to claim 19, wherein the "H" is tilted approximately 90° during the measurement on preferably a wrist when looking from the direction of the arm.

21. A method according to claim 1, wherein in (b) light is emitted from two light sources, which are positioned and thus appearing on two different opposite sides of a vessel containing the mixture, and detection of reflected light from and transmitted light through the vessel is performed by at least two detectors, preferably by only two detectors.

22. A method according to claim 1, wherein (b) comprises the following steps:

I) sweeping a window over a curve with detected values from transmission and/or reflection, wherein the size of the window preferably is approximately 60 % of the period time, divided equally to the right and to the left;
II) if no value within the window is higher than the middle value, designating the value a maximum point whereupon moving the window by leap half of the window length, or if a value exceeds the middle value moving the window only one step;
III) designating the minimum points in the same manner as in II) but with regards to minimum values instead of maximum values;
IV) obtaining the height of the AC-signal by subtracting from a value on a connection line involving two maximum points, the vertically lying value of an in between lying minimum point;
V) repeating step IV) at least 8 times, and summarizing the values from IV) and dividing the sum with the number of observations, thus obtaining a median AC-value; and
VI) optionally obtaining the DC-signal by adding the total height of the minimum point in IV) to the median AC-signal of step V);
whereby preferably using a computer program for obtaining the AC-signal and optionally the DC-signal.

23. A method according to claim 3, wherein the wavelength in the red light range is approximately 660 nm and the wavelength in the infrared light is approximately 940 nm.

24. A method according to claim 1, wherein the determined SpO_2 and determined blood characteristic including hemoglobin is presented simultaneously.

25. A method according to claim 1, wherein the determined SpO_2 is corrected by using the determined blood characteristic including hemoglobin.

26. An apparatus for accurate determination of SpO_2 from a mixture of liquid and blood cells contained in a light pervious vessel comprising:
- light sources for directing light beams against the vessel,
- means for determining a blood characteristic other than oxygen saturation, SpO_2, including hemoglobin and capable of analyzing the intensity of the light reflected from the vessel, or the intensity of the light reflected from the vessel in combination with the intensity of the light transmitted through the mixture,
- means for determining oxygen saturation, SpO_2, of the mixture, preferably pulse-oximetrically, and of analyzing the intensity of the light transmitted through the mixture; and optionally means for establishing whether the determined value of SpO_2 is relevant with respect to the determined value of the blood characteristic.

27. An apparatus according to claim 26, wherein the light sources comprise a first light source for emitting a first light beam with a wavelength in the red light range against the vessel, and a second light source for emitting a second light beam with a wavelength in the infrared light range against the vessel.

28. An apparatus according to claim 27, further comprising a first detector for detecting the intensity of the light of the red first light beam transmitted through the vessel, and a

second detector for detecting the light of the infrared second light beam transmitted through the vessel.

29. An apparatus according to claim 28, wherein the oxygen saturation determining means comprises a processor adapted to calculate a quotient of the detected intensities of the transmitted red and infrared lights and to determine the value of the oxygen saturation by analyzing the quotient.

30. An apparatus according to claim 26, wherein the light sources comprise a third light source for emitting a third light beam against the vessel, and further comprising a third detector for detecting the intensity of the light of the third light beam reflected from the vessel and a fourth detector for detecting the intensity of the light of the third light beam transmitted through the vessel.

31. An apparatus according to claim 30, wherein the blood characteristic determining means comprises a processor adapted to calculate a quotient of the detected intensities of the reflected and transmitted lights of the third light beam and to determine the value of the blood characteristic by analyzing the quotient.

32. An apparatus according to claim 26, further comprising registration means for storing the determined blood characteristics and SpO_2.

33. An apparatus according to claim 26, further comprising means for visualization of the determined blood characteristic and SpO_2.

34. An apparatus according to claim 26, wherein the light sources direct at least two light beams on the same side of the vessel, preferably one of the light sources emits a light of a wavelength in the range of 770 to 950 nm and the other a wavelength in the range of 480 to 590 nm.

35. An apparatus according to claim 26, wherein at least two of the components of the apparatus communicate with each other over a wireless connection, preferably over a module for wireless communication.

36. An apparatus according to claim 35, wherein the module for wireless communication comprises at least one transmitter and one receiver.

37. An apparatus according to claim 31, wherein there is one module for wireless communication between at least three components of the apparatus, i.e. light sources, detectors, and the processor.

38. An apparatus according to claim 35, wherein the wireless communication is performed using a Bluetooth™ standard based communication path.

39. An apparatus according to claim 26 wherein the light sources are positioned essentially perpendicular to a measuring area of the vessel.

40. An apparatus according to claim 26, wherein the wavelength of at least one of the light beams is from 200 nm to 2000 nm,

preferably from 770 nm to 950 nm, most preferred approximately 770, 800, 850, 940 or 950 nm.

41. An apparatus according to claim 26, wherein two of the light sources direct two light beams on the same side of the vessel, one of the light beams having a wavelength of from 800 nm to 940 nm and the other light beam having a wavelength of from 480 to 590 nm.

42. An apparatus according to claim 30, wherein the light sources are at least four, preferably at least six, the light sources being adapted to appear on either side of the detector(s), preferably the light sources are arranged in groups of two , preferably groups of three, wherein the light sources preferably form an "H" with one detector in the centre.

43. An apparatus according to claim 26, further comprising a test device having the shape of a wrist, finger or toe fitting device equipped with the light source(s) and at least one light detector.

44. An apparatus according to claim 43, wherein the test device comprises a thimble-like shell to be applied on a finger or toe, the light source and detector being arranged to direct the light beam and detect the light intensity within the shell.

45. An apparatus according to claim 44, wherein at least one light source and the detector are positioned in the shell comprising a constriction whereby the light source and detector are positioned and thus appearing in the constriction, whereby the shell preferably is a part of a thimble design for covering

a finger or a toe.

46. An apparatus according to claim 26, wherein the light sources comprise at least four light emitting diodes, preferably at least six light emitting diodes, and further comprising one light detector which together form an "H" with the detector in the centre, fixed on a patch which in turn is making part of a handcuff construction suitable for wrist measurements, wherein the distance between the light sources and the detector preferably is for determining blood characteristics including Hb from 4 to 12 mm when referring from the centres of respective component, most preferred the distance is approximately from 8 to 9 mm.

47. An apparatus according to claim 46, wherein the light sources and the detectors, which are arranged for detecting reflected light, are fixed at the edge of the patch, which may house a finger, a toe or wrist, preferably a wrist, wherein preferably the patch is a flexible plastic patch anchored to a strap for fastening to the wrist wherein the strap preferaby has a locking device.

48. An apparatus according to claim 47, wherein the light sources and detectors are incorporated in the patch whereby the electric components are fixed on one side of a printed circuit card covered with black-coloured silicone and the optical components are fixed on the other side covered with transparent silicone.

49. An apparatus according to claim 47, wherein the patch is rectangular with a size of 51 x 35 mm, and the

light sources and detector arranged as an "H" are fixed in a corner of the patch.

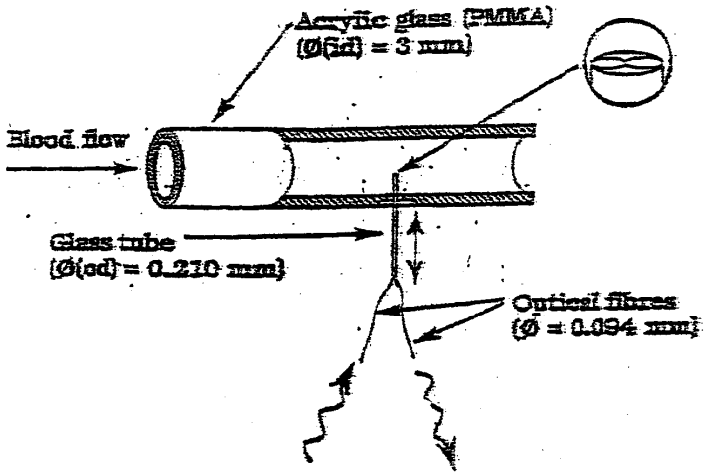
50. An apparatus according to claim 31, wherein the processor is adapted to convert the reflection values to a concentration value of the determined blood characteristic.

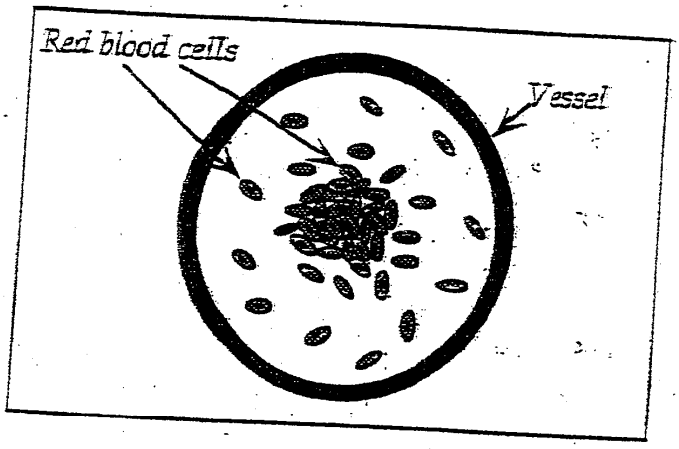
51. An apparatus according to claim 26, further comprising a processor having a computer program for performing the method according to any of claims 1 to 20.

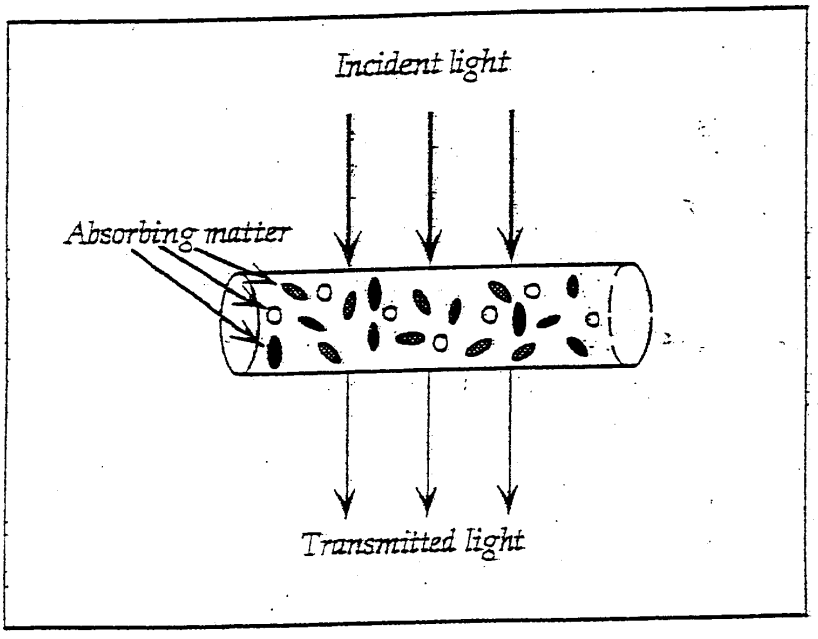
52. An apparatus according to claim 27, wherein the wavelength of the red light is approximately 660 nm and the wavelength of the infrared light is approximately 940 nm.

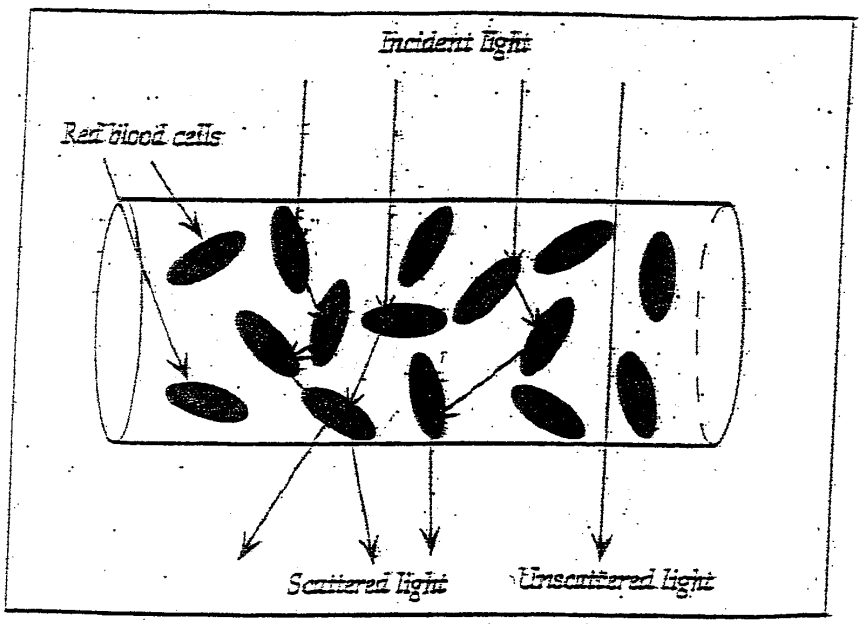
53. A computer program stored on a data carrier for performing the method according to any one of claims 1 to 25.

54. Use of an apparatus according to any of claims 26 to 52 in a dialysis apparatus.

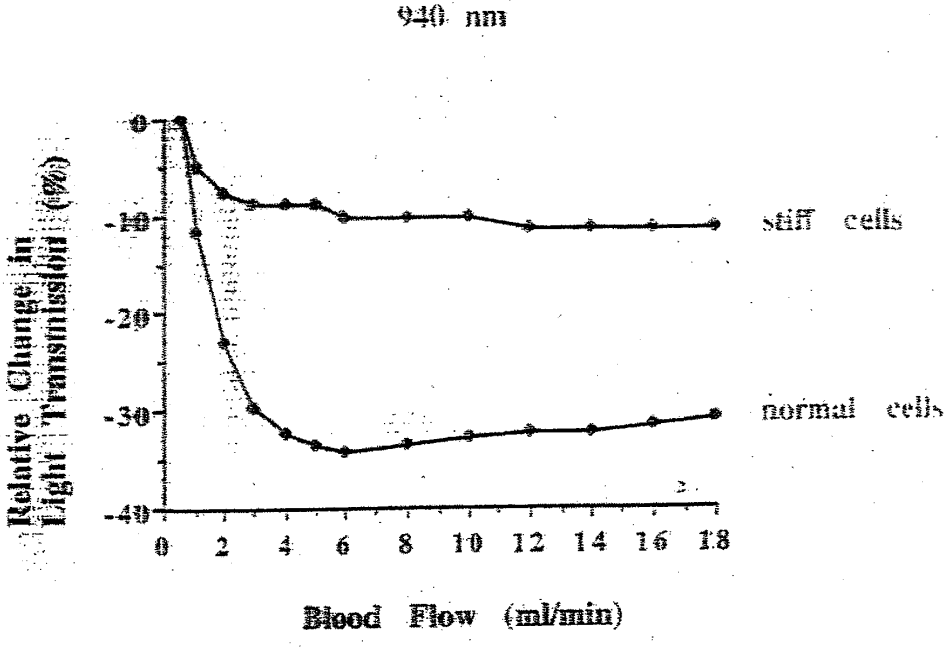

Acrylic glass (PMMA)
(Ø(id) = 3 mm)
Blood flow
Glass tube
(Ø(od) = 0.210 mm)
Optical fibres
(Ø = 0.094 mm)

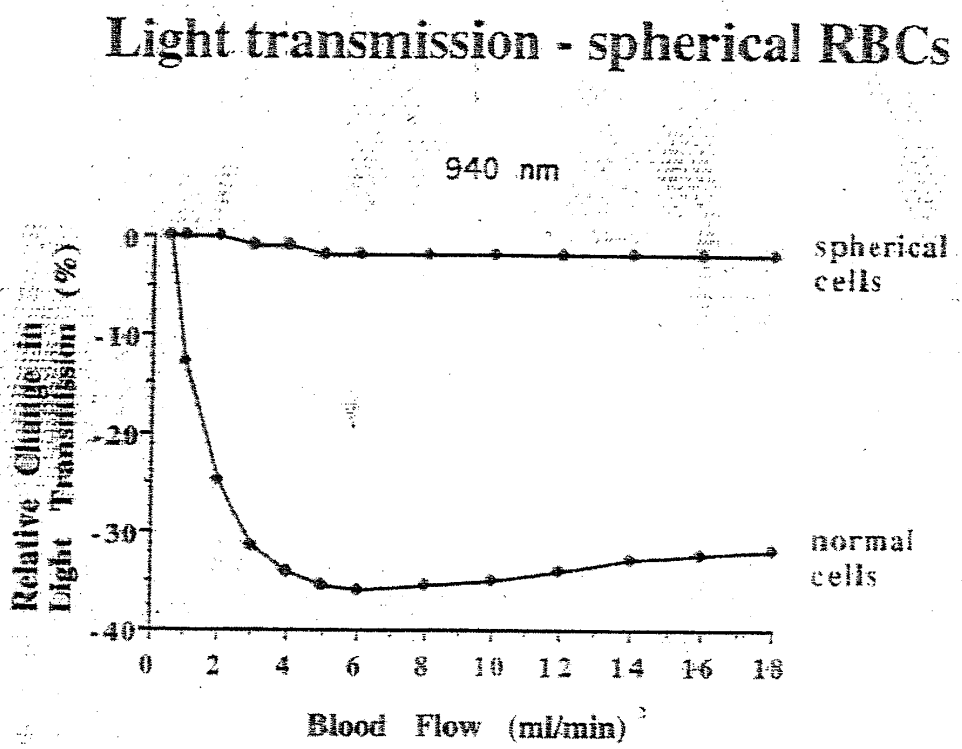

Red blood cells
Vessel

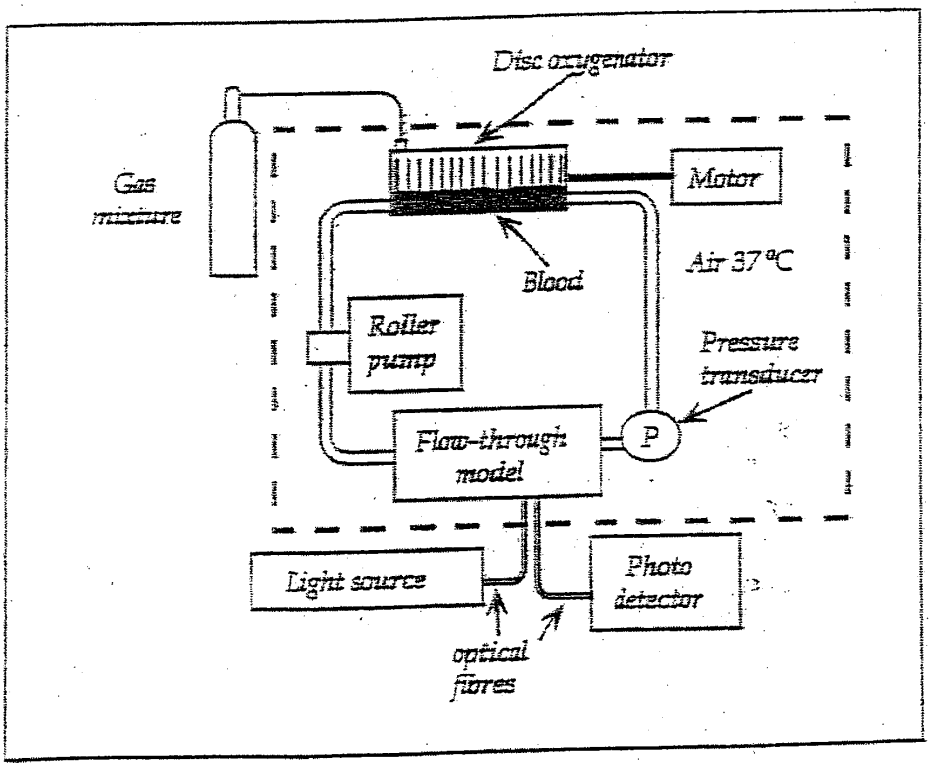

Incident light
Absorbing matter
Transmitted light

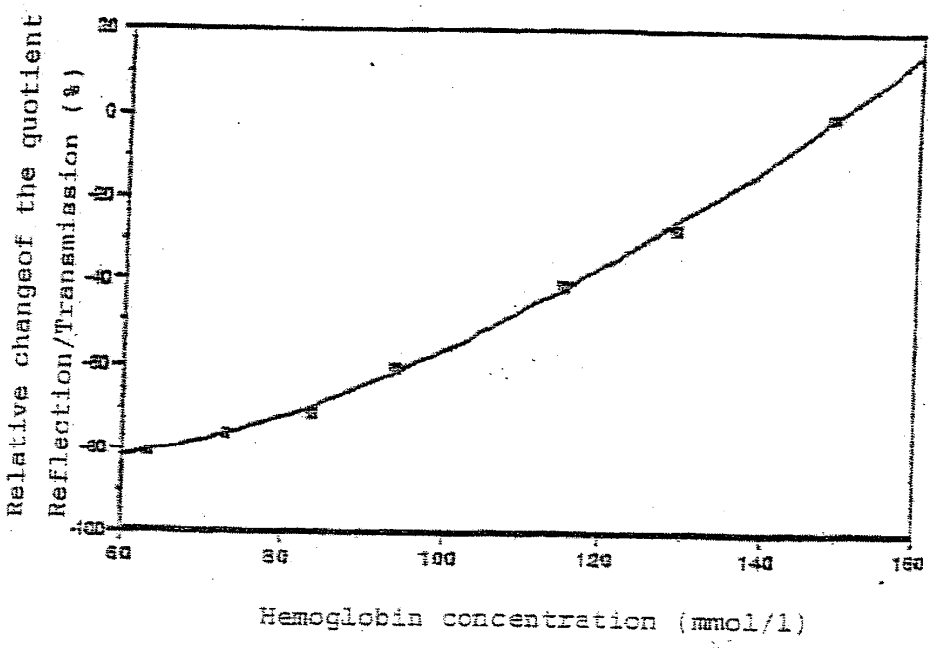

Incident light
Red blood cells
Scattered light
Unscattered light

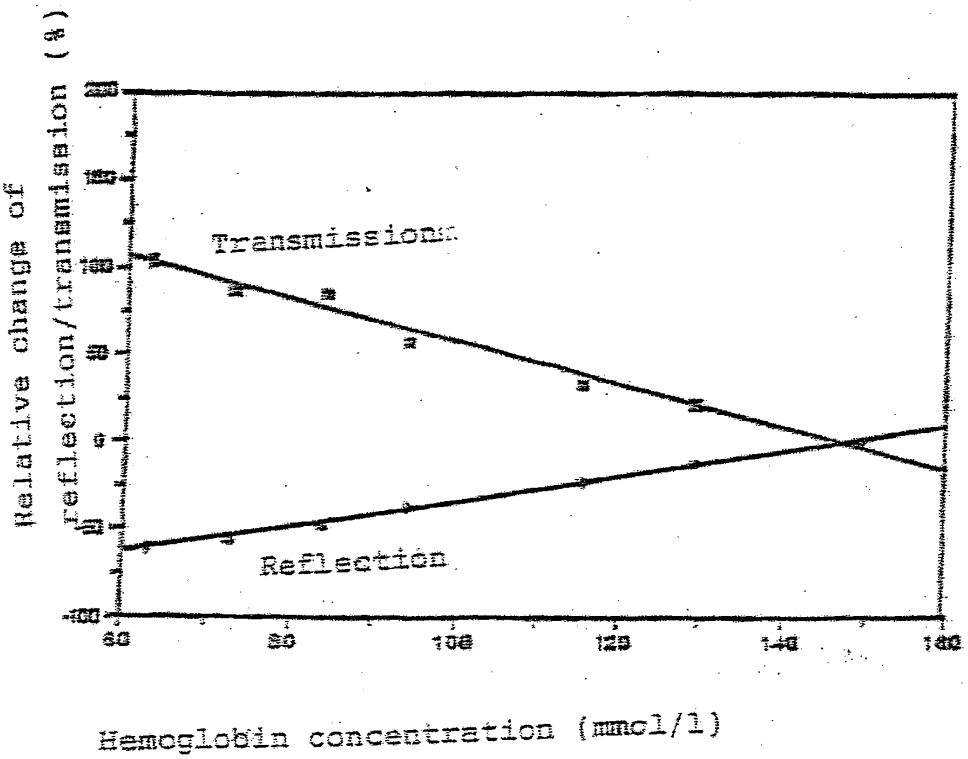
Light transmission - stiff RBCs

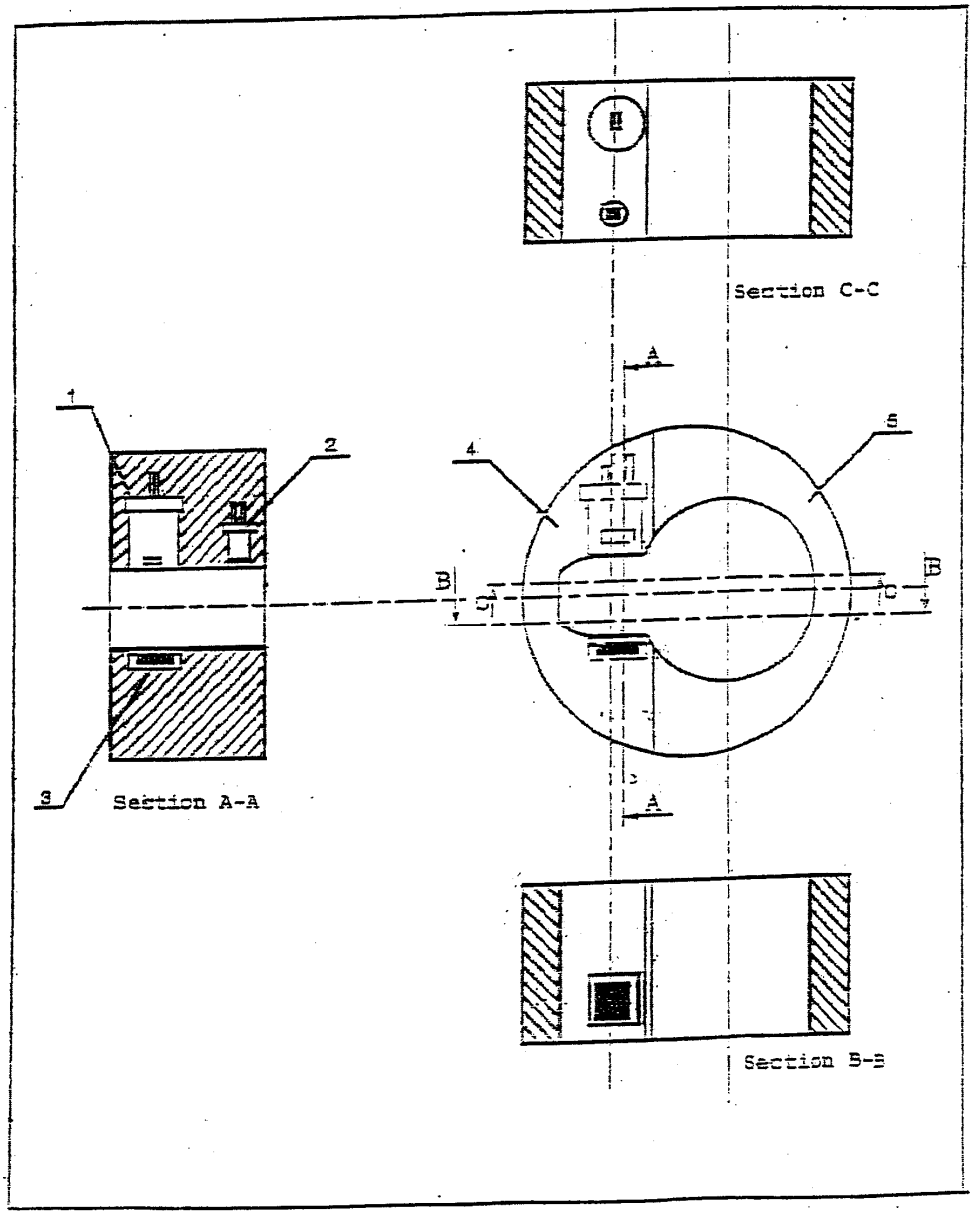


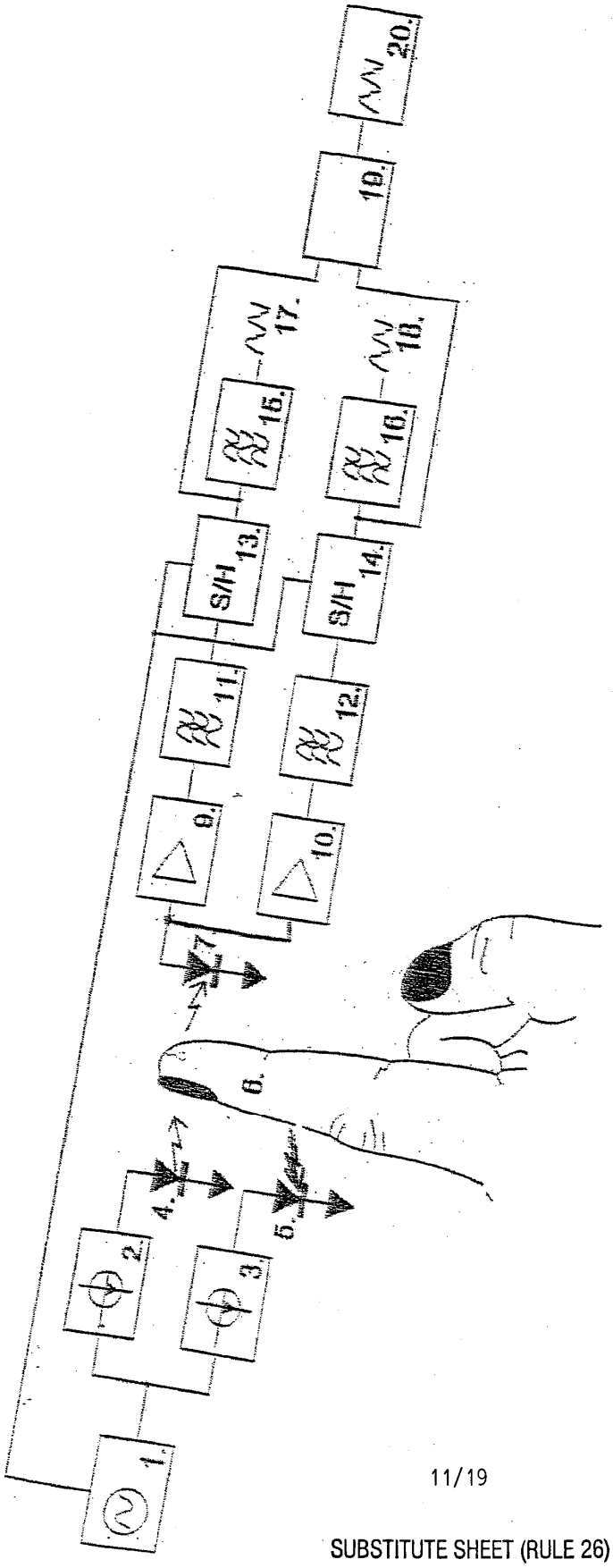

Light transmission - spherical RBCs
940 nm
Relative Change in Light Transmission (%)
0
-10
-20
-30
-40
0
2
4
6
8
10
12
14
16
18
Blood Flow (ml/min)
spherical cells
normal cells


Disc oxygenator
Gas mixture
Motor
Blood
Air 37 °C
Roller pump
Pressure transducer
Flow-through model
P
Light source
Photo detector
optical fibres

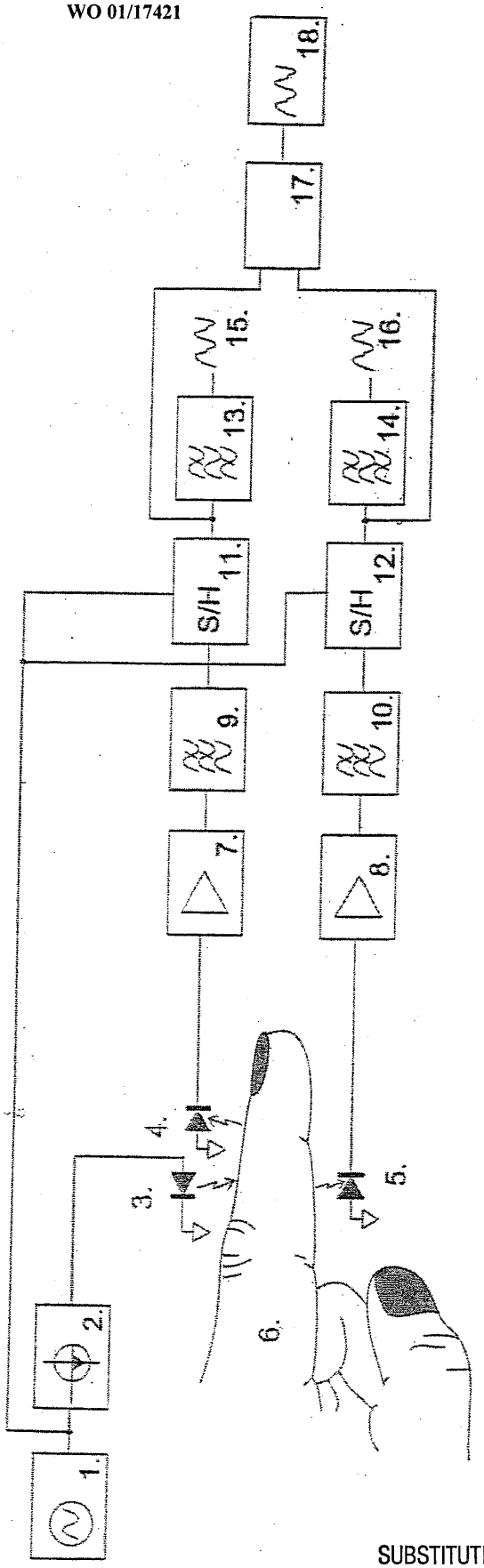

Relative changeof the quotient
Reflection/Transmission (%)
12
8
4
0
-4
-8
-12
60
80
100
120
140
160
Hemoglobin concentration (mmol/l)


Relative change of reflection/transmission (%)
Transmission
Reflection
60
80
100
120
140
160
Hemoglobin concentration (mmol/l)


Section C-C
A
1
2
4
5
B
B
C
3
Section A-A
A
Section B-B

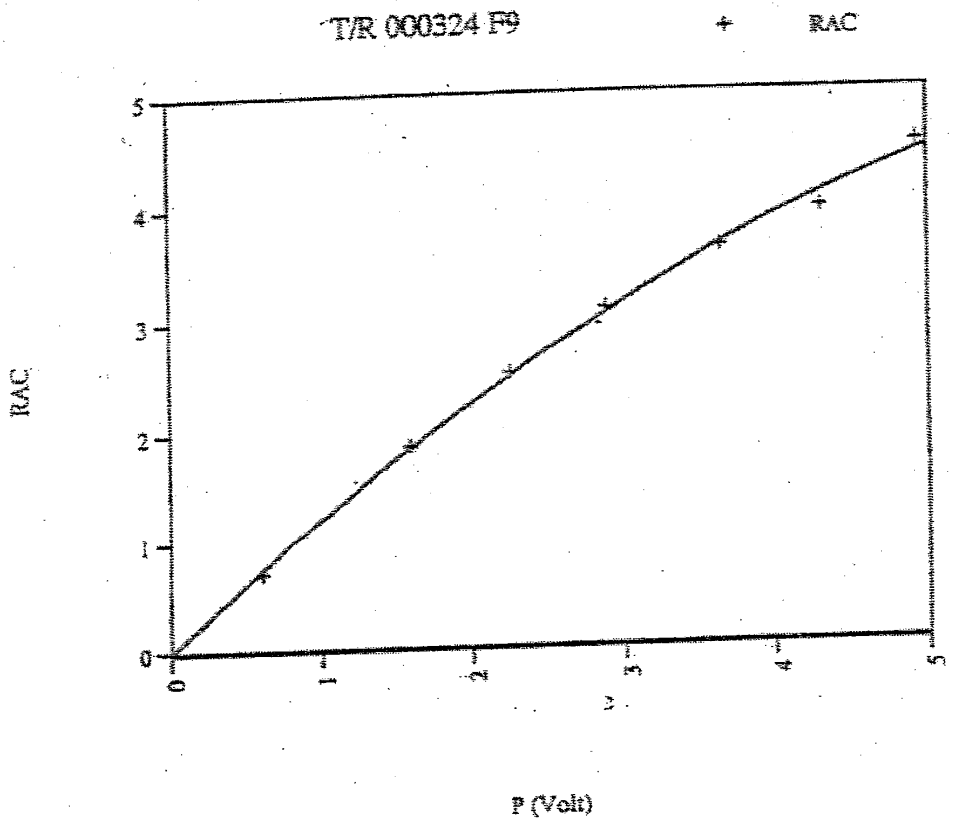


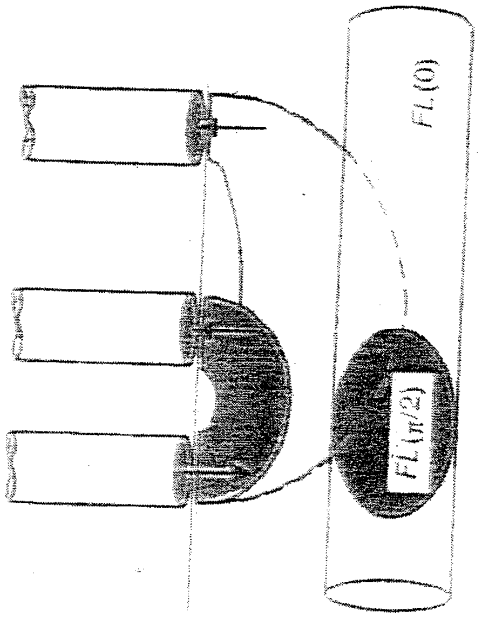
SUBSTITUTE SHEET (RULE 26)

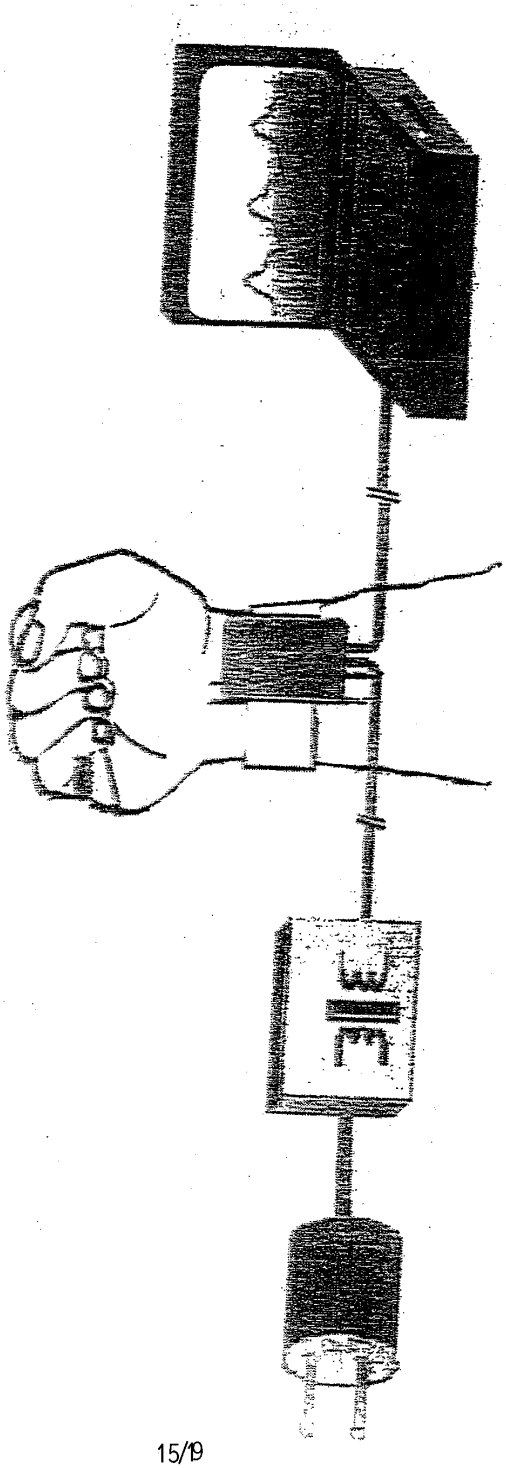


12/19

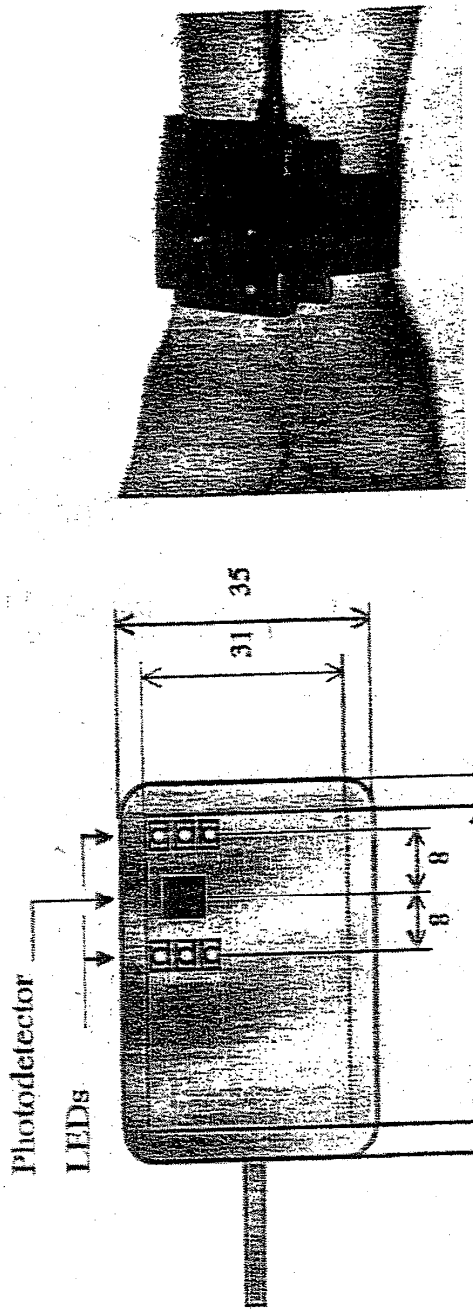
SUBSTITUTE SHEET (RULE 26)


T/R 000324 F9
RAC
RAC
P (Volt)
0
1
2
3
4
5

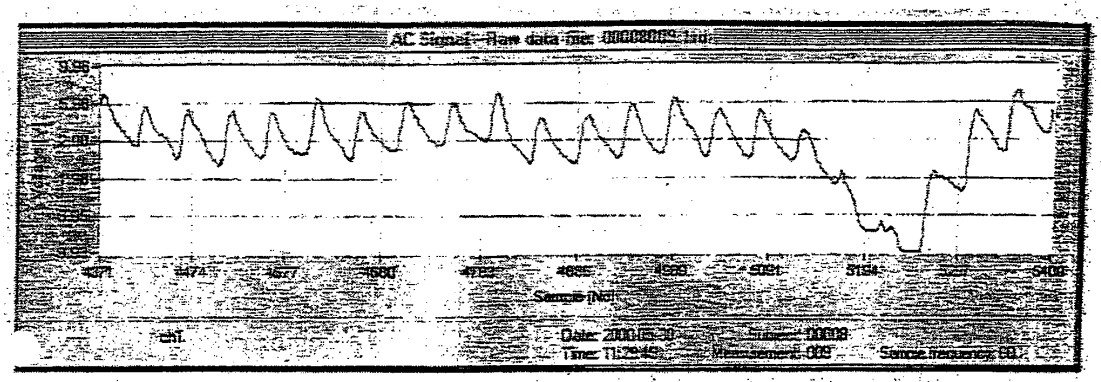

FL(0)
FL(π/2)



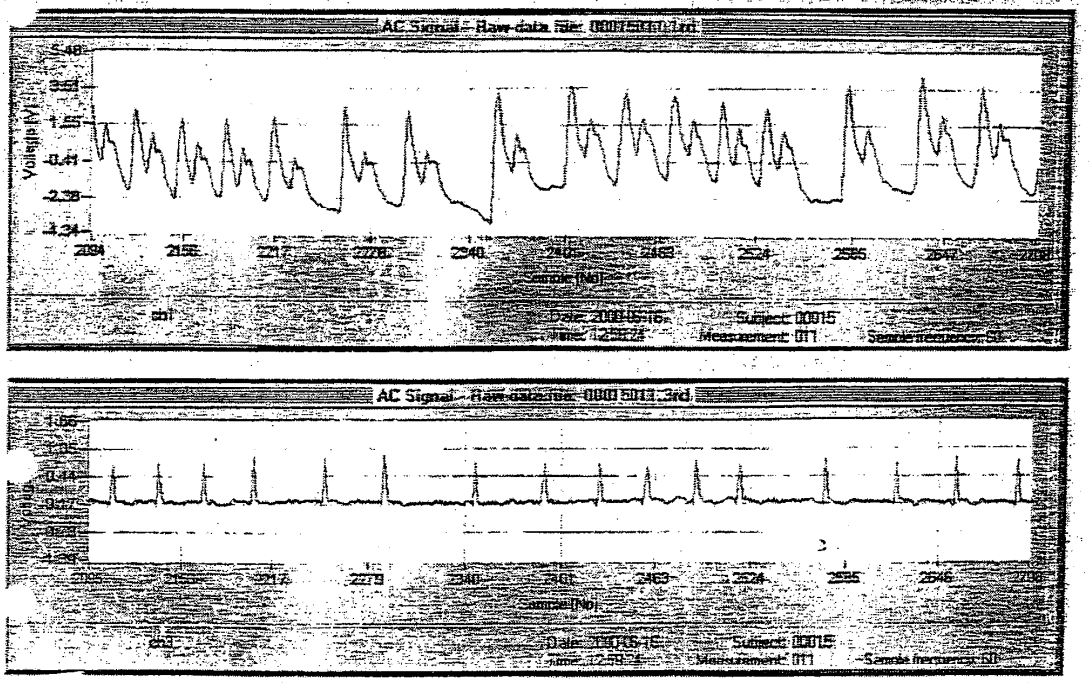
Experimental set-up.



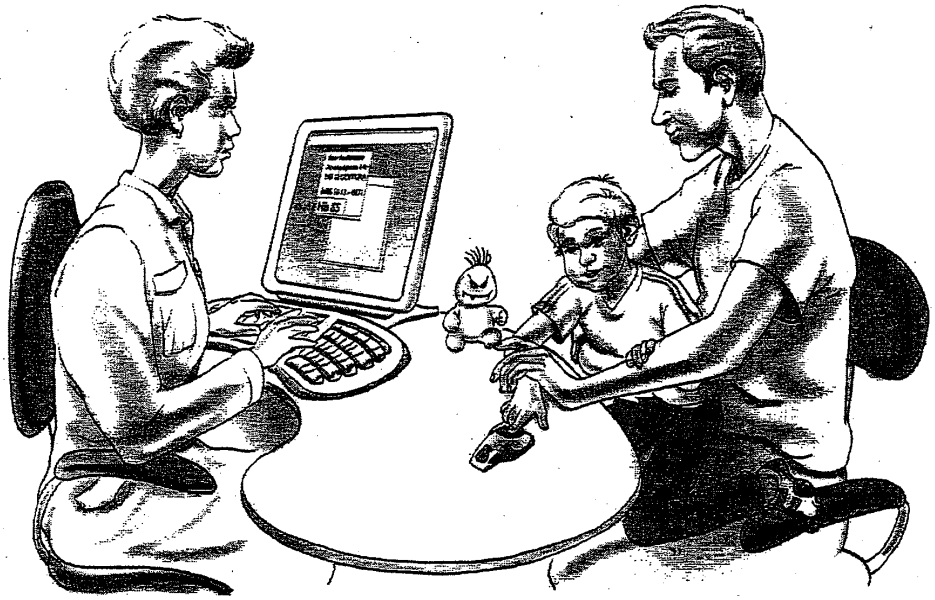
The optical sensor (all numbers are in mm).

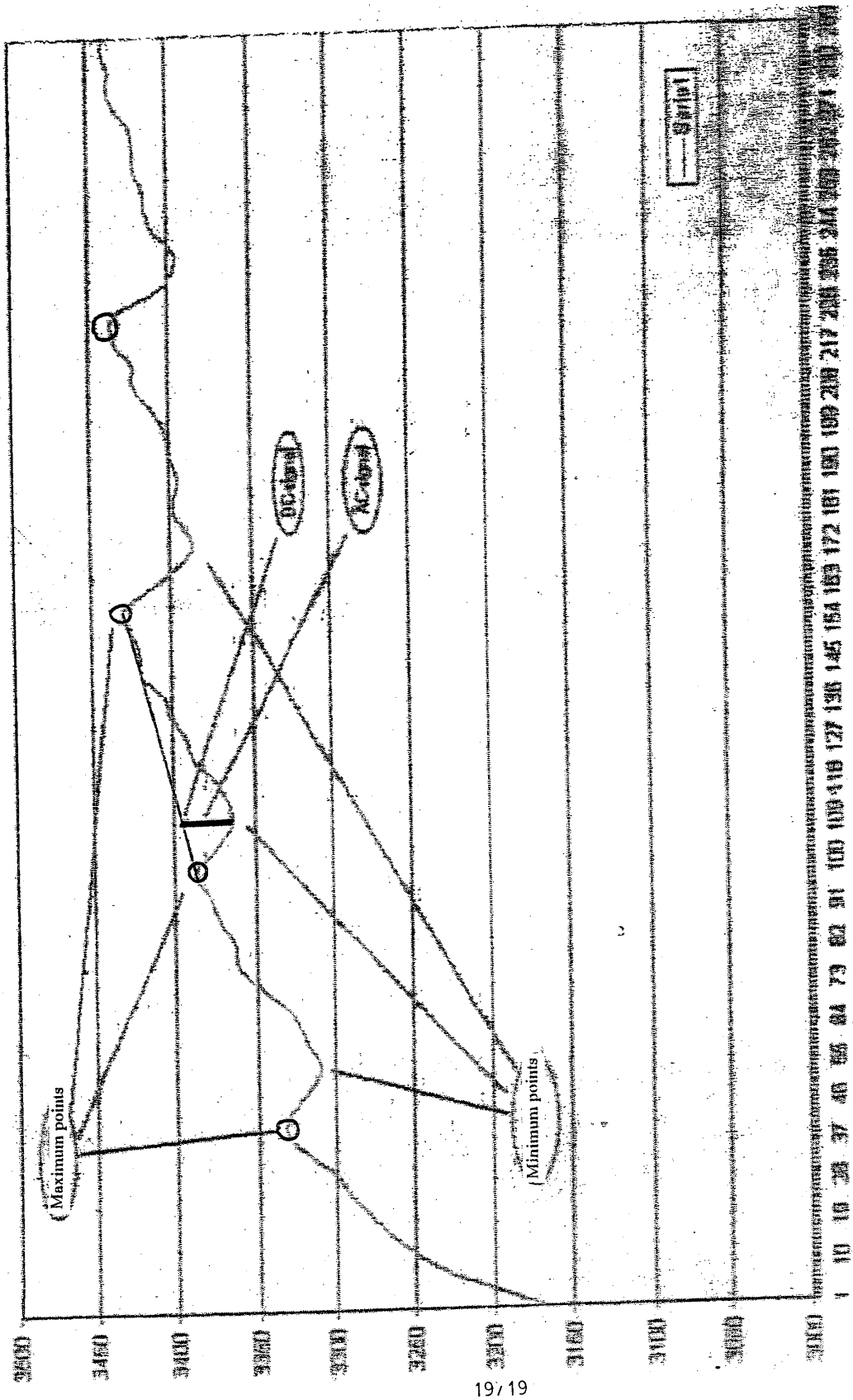


.The PPG signal during blood dilution in the radial artery.



The PPG and ECG signals in a patient with arterial fibrillation.





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SUBSTITUTE SHEET (RULE 26)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 00/01740

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: A61B 5/00, G01N 33/49, G01N 21/55
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)

IPC7: A61B, G01N

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

SE,DK,FI,NO classes as above

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5499627 A (ROBERT R. STEUER ET AL), 19 March 1996 (19.03.96) --	1-4,6-54
A	WO 9111136 A1 (BOSTON ADVANCED TECHNOLOGIES, INC.), 8 August 1991 (08.08.91) --	6-7
A	WO 8901758 A1 (VANDER CORPORATION), 9 March 1989 (09.03.89) --	1-5
A	US 5720284 A (TAKUO AOYAGI ET AL), 24 February 1998 (24.02.98) --	1-5

[X] Further documents are listed in the continuation of Box C. [X] 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
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"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
22 January 2001	29 -01- 2001
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Carolina Palmcrantz/ELY Telephone No. +46 8 782 25 00

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 00/01740

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 9637259 A1 (DOMJÁN, GYULA ET AL), 28 November 1996 (28.11.96) --	1-5
A	EP 0762108 A2 (KYOTO DAI-ICHI KAGAKU CO., LTD.), 12 March 1997 (12.03.97) --	1-5

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INTERNATIONAL SEARCH REPORT

Information on patent family members

27/12/00

International application No.
PCT/SE 00/01740

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		US 5239180 A	24/08/93
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