US 20060224053A1

(19) United States

(12) Patent Application Publication (10) Pub. No.: US 2006/0224053 A1

Black et al. (43) Pub. Date: Oct. 5, 2006

(54) APPARATUS AND METHOD FOR NON-INVASIVE AND MINIMALLY-INVASIVE SENSING OF VENOUS OXYGEN SATURATION AND PH LEVELS

(75) Inventors: **John F. Black**, San Mateo, CA (US); **Daniel Hwan Kim**, Mountain View, CA (US); **Butrus T. Khuri-Yakub**, Palo Alto, CA (US)

Correspondence Address:
JOSHUA D. ISENBERG
JDI PATENT
809 CORPORATE WAY
FREMONT, CA 94539 (US)

(73) Assignee: **Skyline Biomedical, Inc.**, San Mateo, CA

(21) Appl. No.: **11/095,091**

(22) Filed: **Mar. 30, 2005**

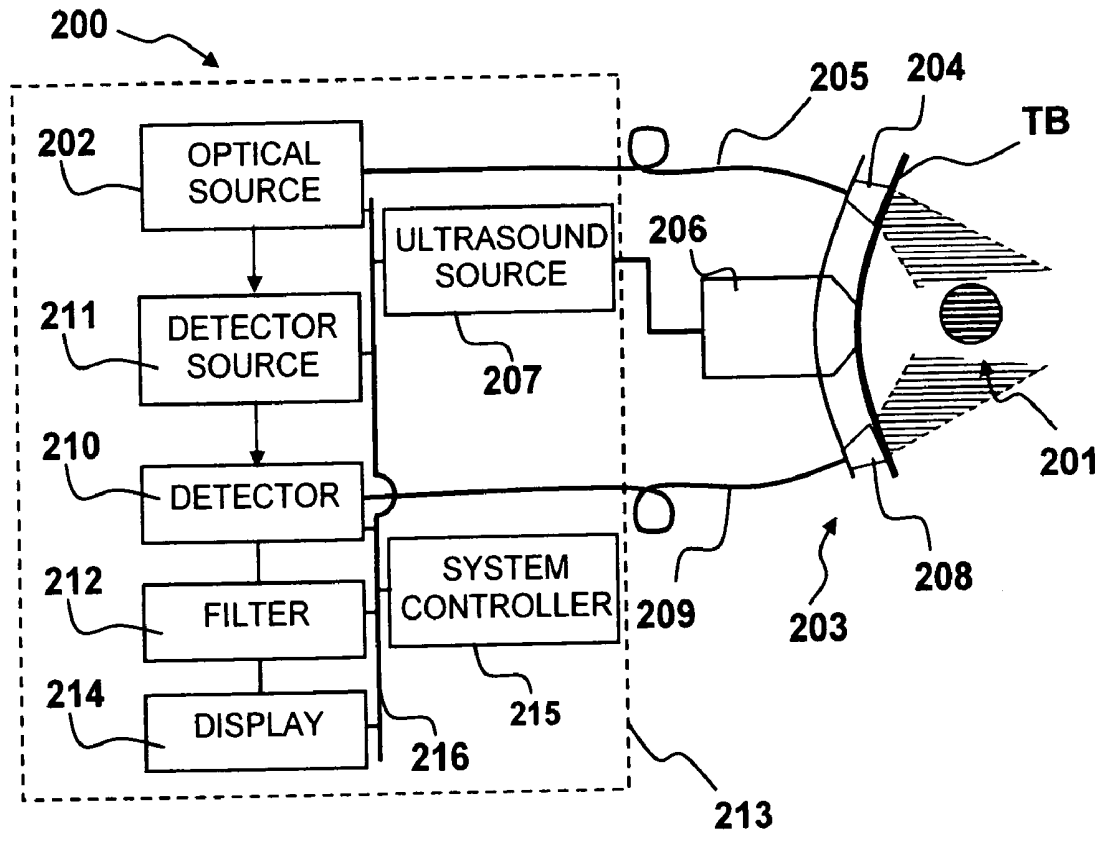
Publication Classification

(51) **Int. Cl.**
A61B 5/00 (2006.01)

(52) **U.S. Cl.** **600/310**; 600/326; 600/323

(57) **ABSTRACT**

Medical diagnostic apparatus and methods are disclosed. Ultrasound radiation pressure selectively modulates a target area within a body. One or more pulses of radiation containing temporally correlated groups of photons are generated. The photons are characterized by two or more different wavelengths that are selected to have specific interaction with a target chromophore. The two or more different wavelengths are also selected to have substantially similar scattering cross-sections and anisotropy parameters in the target and its surroundings. The pulses of radiation are injected into the body proximate the target area being modulated by the radiation pressure field. Photon groups at each of the different wavelengths that are backscattered from the target area are detected in temporal coincidence. Time-gated background-free amplification of the return signal is used to exclude photons which could not by virtue of their arrival time have interacted with the radiation-pressure-modulated target. Photon groups are selected with a modulation component at the modulation frequency of the radiation pressure modulation field, or at a harmonic of the modulation frequency. From the arrival rate of the detected temporally correlated photon pairs or multiplets, chemical information about the target area, such as an oxygenation or pH level can be inferred. Cardiac output may be computed from measurements of venous and/or arterial oxygenation using this technique.



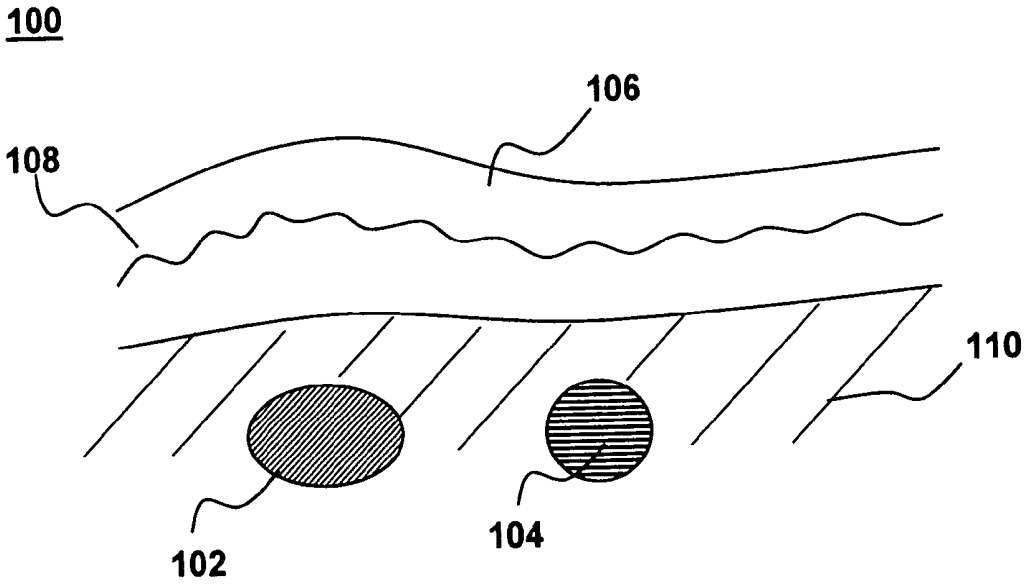

100
106
108
110
102
104

FIG. 1

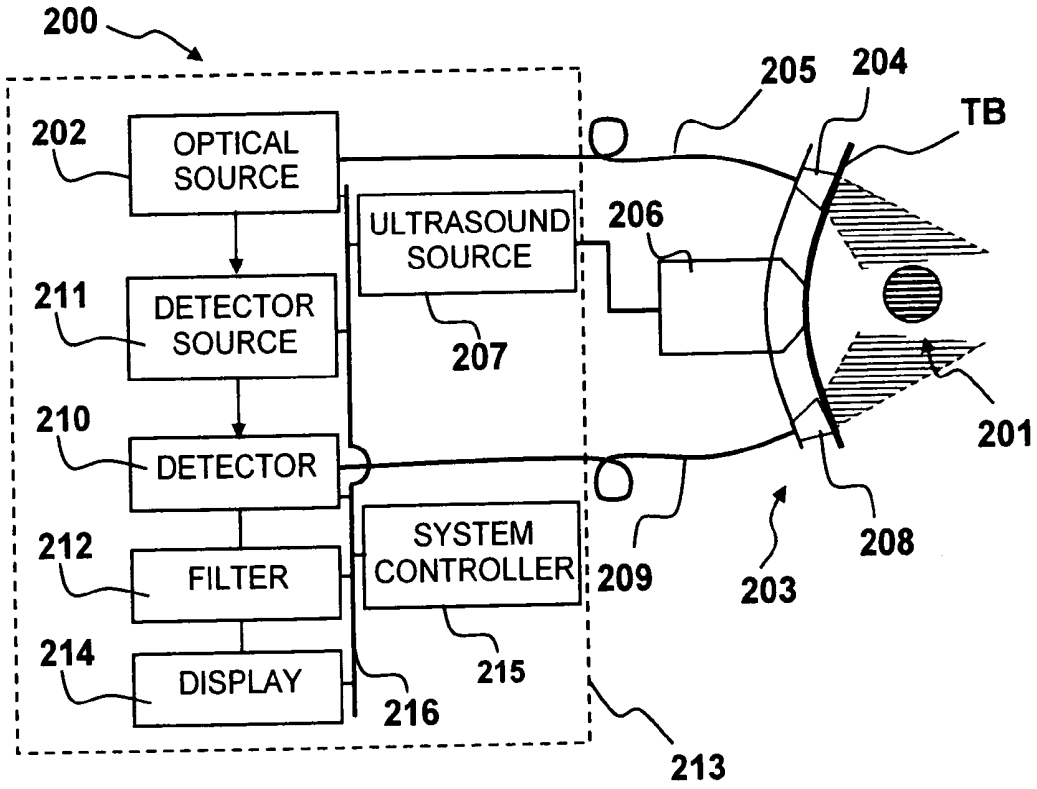

200
202
OPTICAL SOURCE
211
DETECTOR SOURCE
210
DETECTOR
212
FILTER
214
DISPLAY
ULTRASOUND SOURCE
207
SYSTEM CONTROLLER
215
216
213
205
204
TB
206
201
208
209
203

FIG. 2A

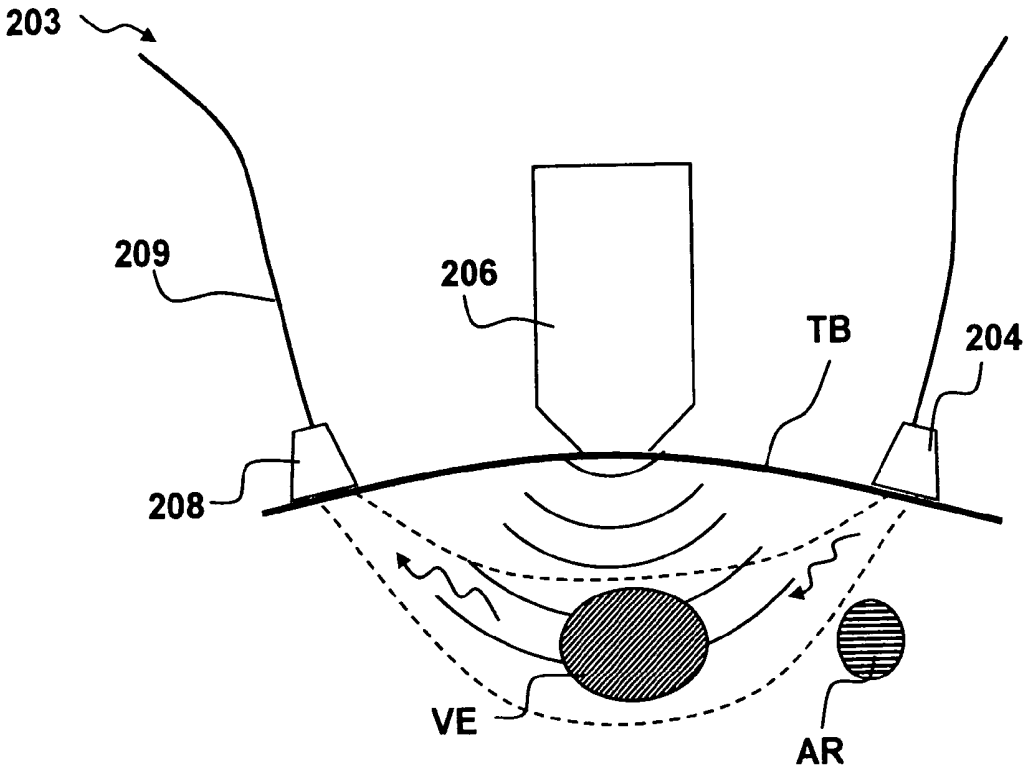

203
209
206
TB
204
208
VE
AR

FIG. 2B

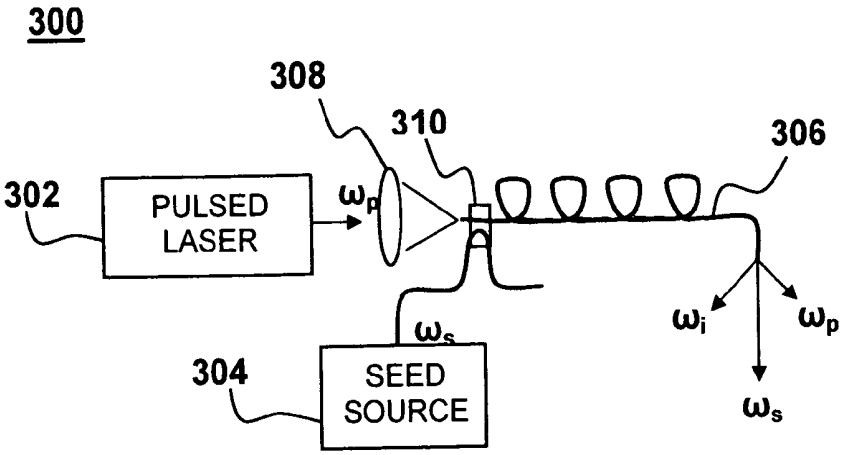

300
308
310
306
302
PULSED LASER
ω_p
ω_s
304
SEED SOURCE
ω_i
ω_p
ω_s

FIG. 3

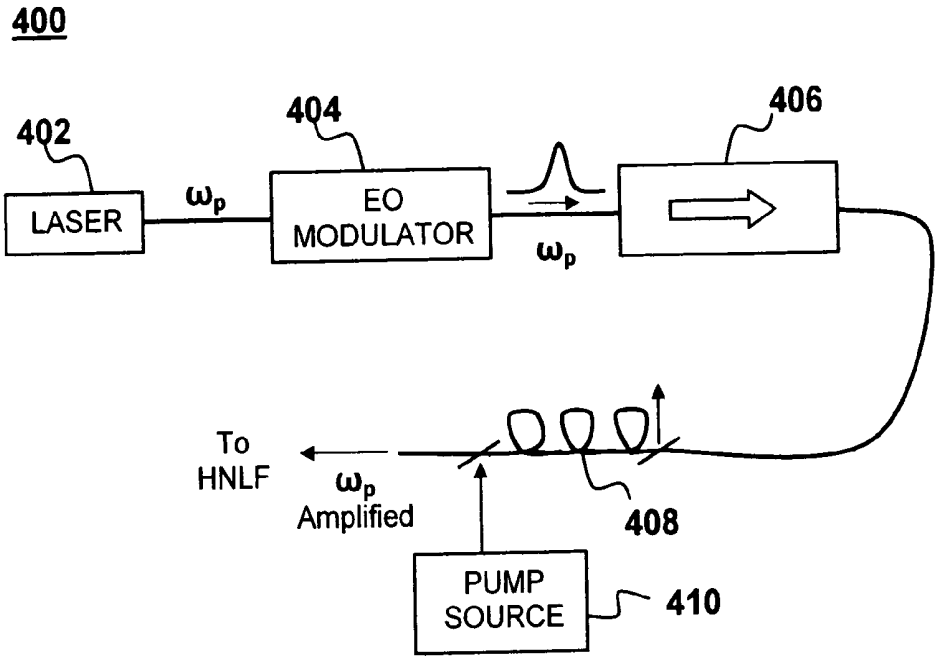

400
402
LASER
ω_p
404
EO
MODULATOR
ω_p
406
To
HNLF
ω_p
Amplified
408
PUMP
SOURCE
410

FIG. 4

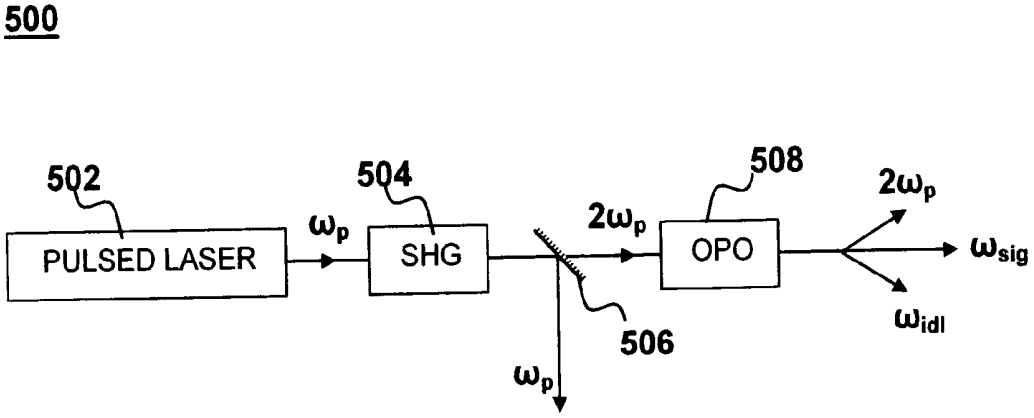

500
502
PULSED LASER
ω_p
504
SHG
$2\omega_p$
508
OPO
$2\omega_p$
ω_{sig}
ω_{idl}
506
ω_p

FIG. 5

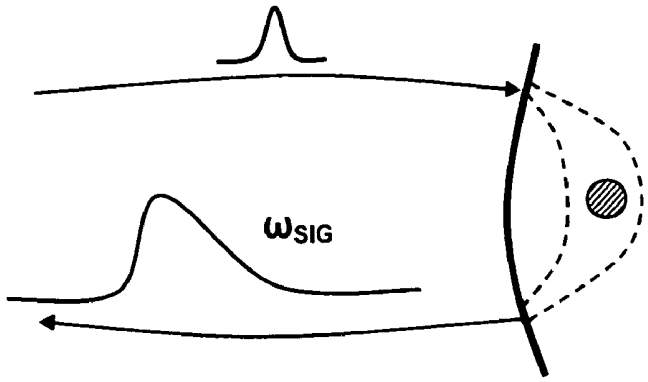


FIG. 6

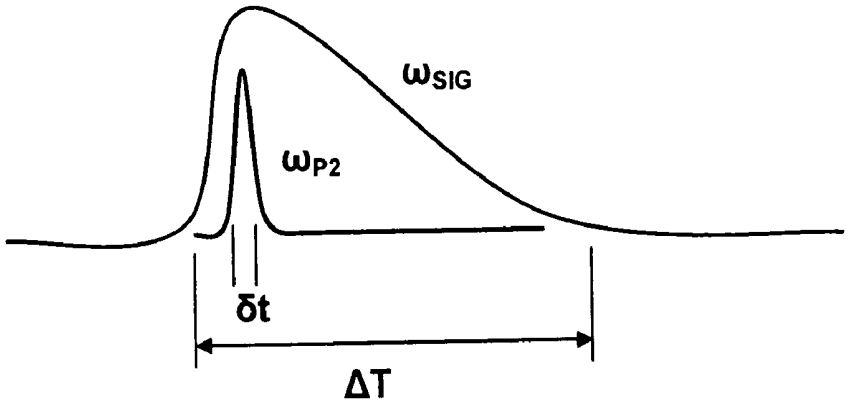


FIG. 7

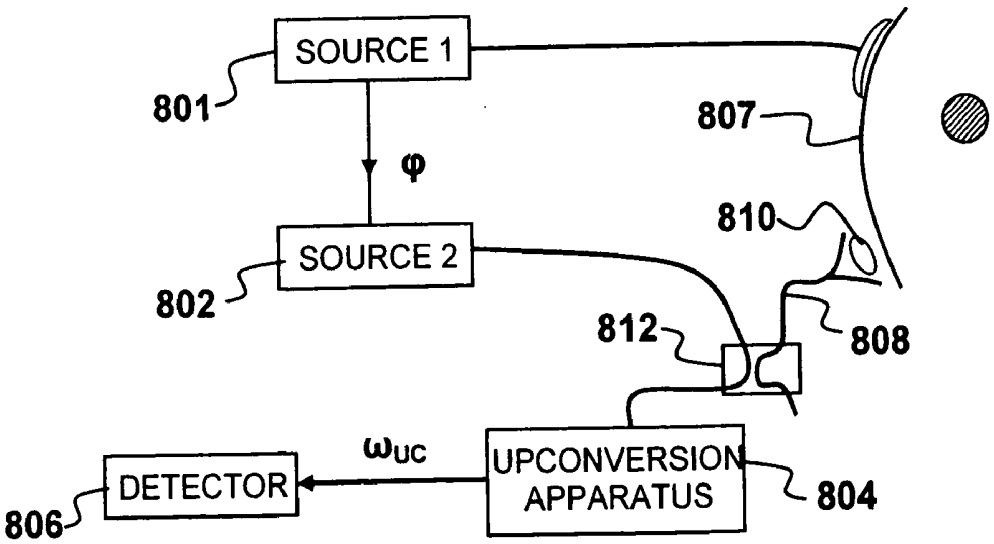


FIG. 8

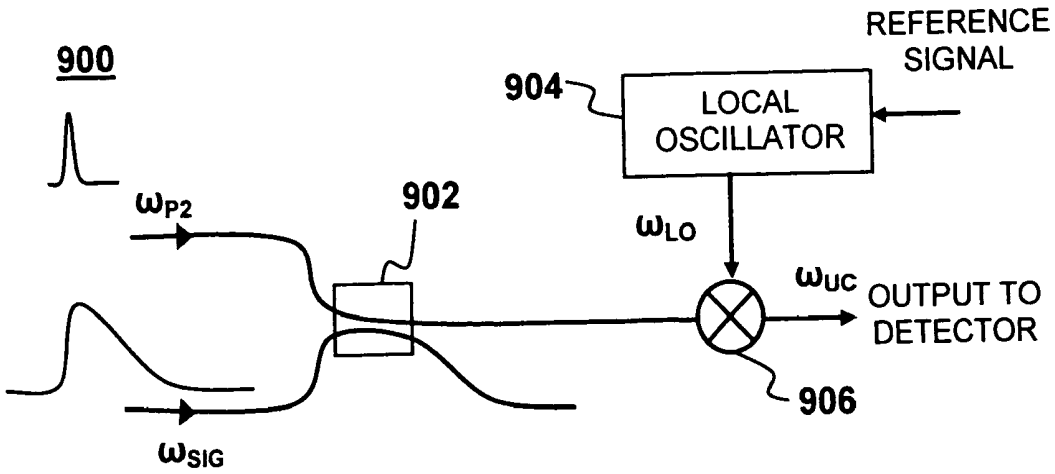


FIG. 9A

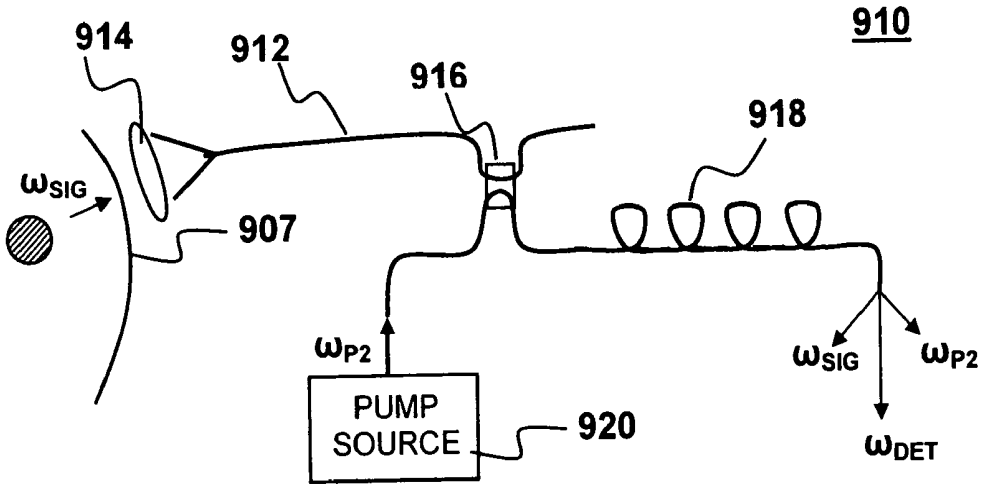


FIG. 9B

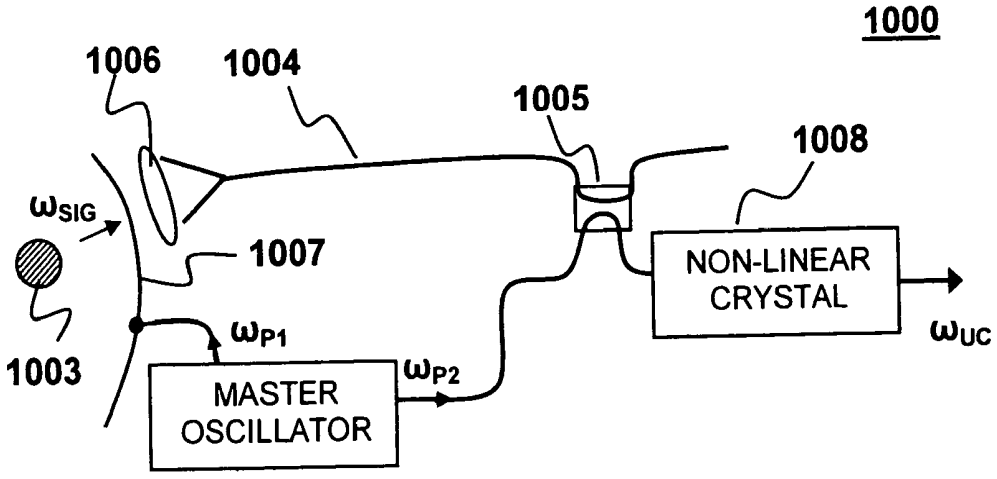


FIG. 10

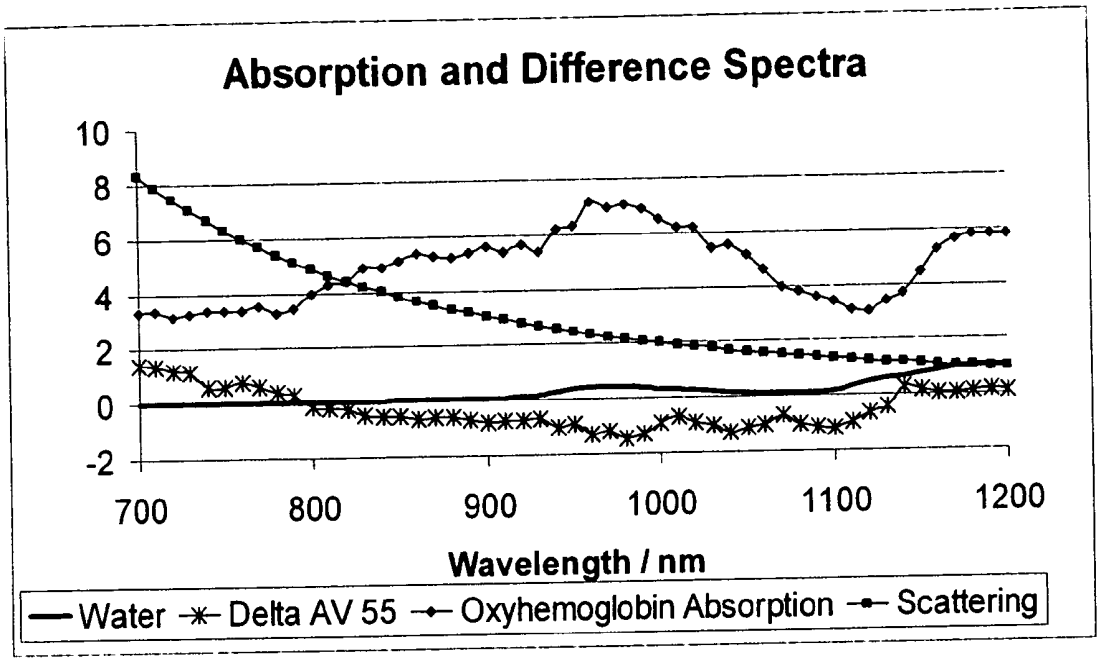

Absorption and Difference Spectra
10
8
6
4
2
0
-2
700
800
900
1000
1100
1200
Wavelength / nm
Water
Delta AV 55
Oxyhemoglobin Absorption
Scattering

FIG. 11

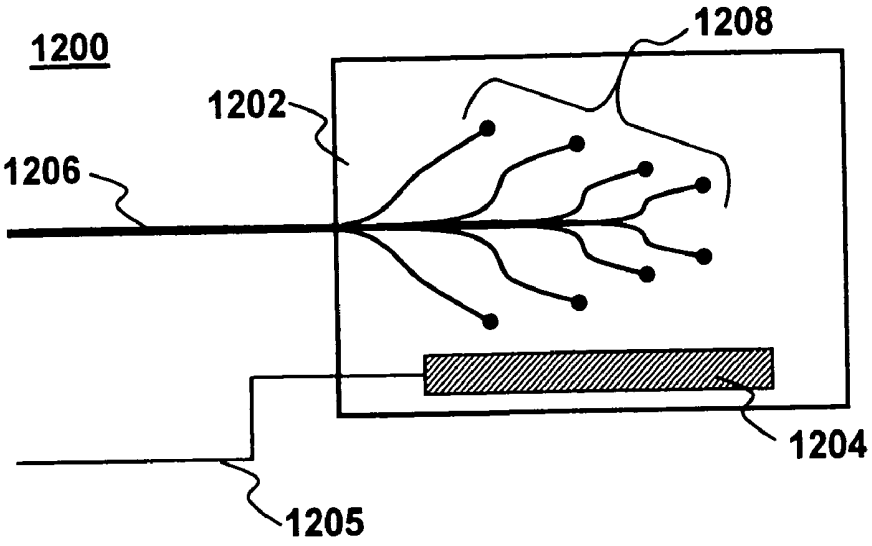


FIG. 12A

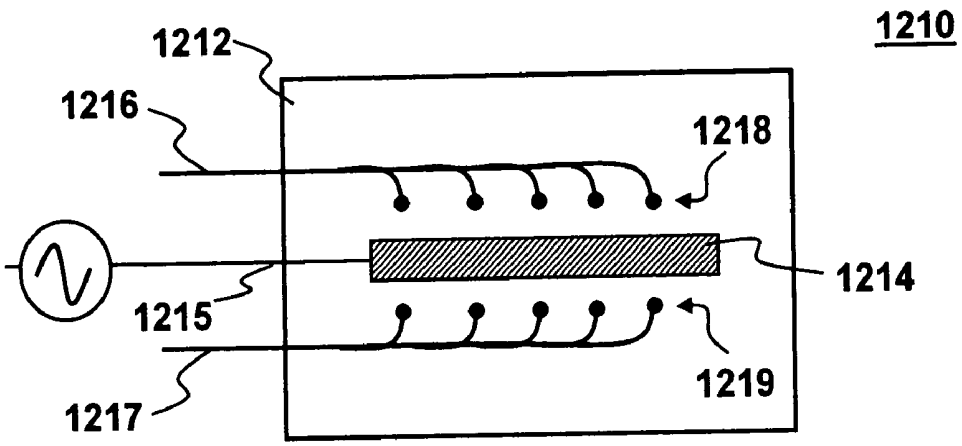


FIG. 12B

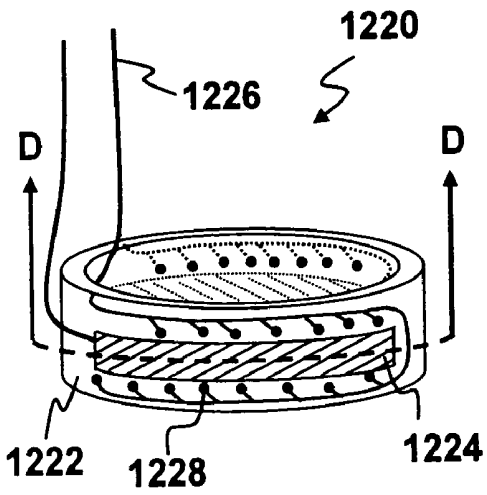


FIG. 12C

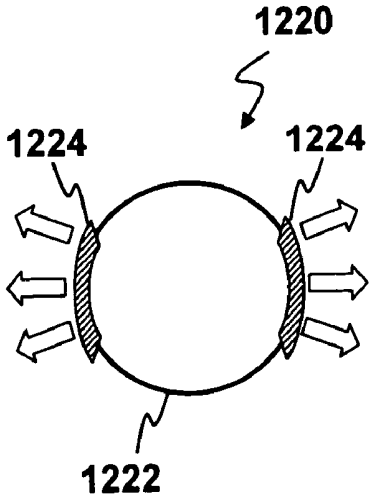


FIG. 12D

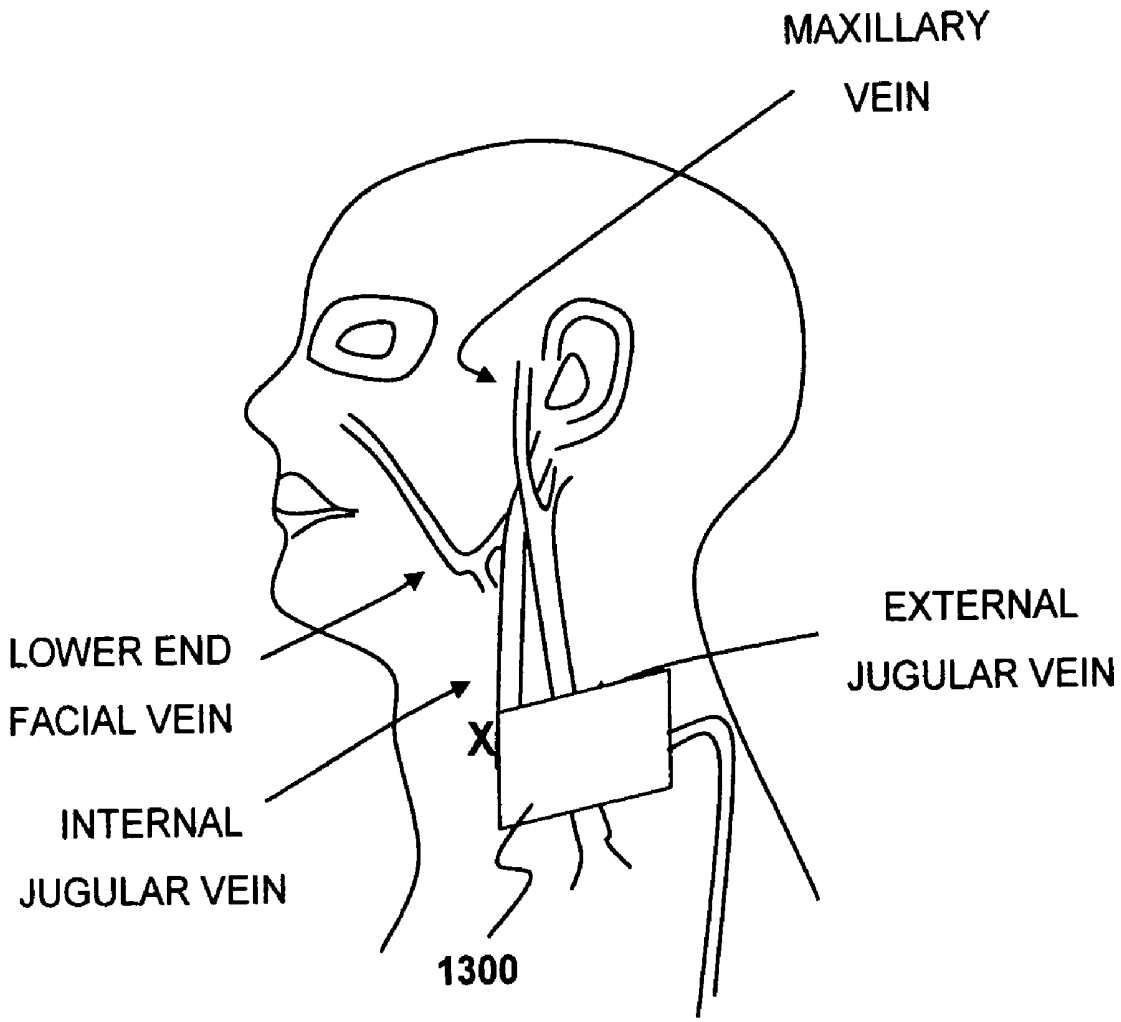

MAXILLARY
VEIN
EXTERNAL
JUGULAR VEIN
LOWER END
FACIAL VEIN
X
INTERNAL
JUGULAR VEIN
1300

FIG. 13

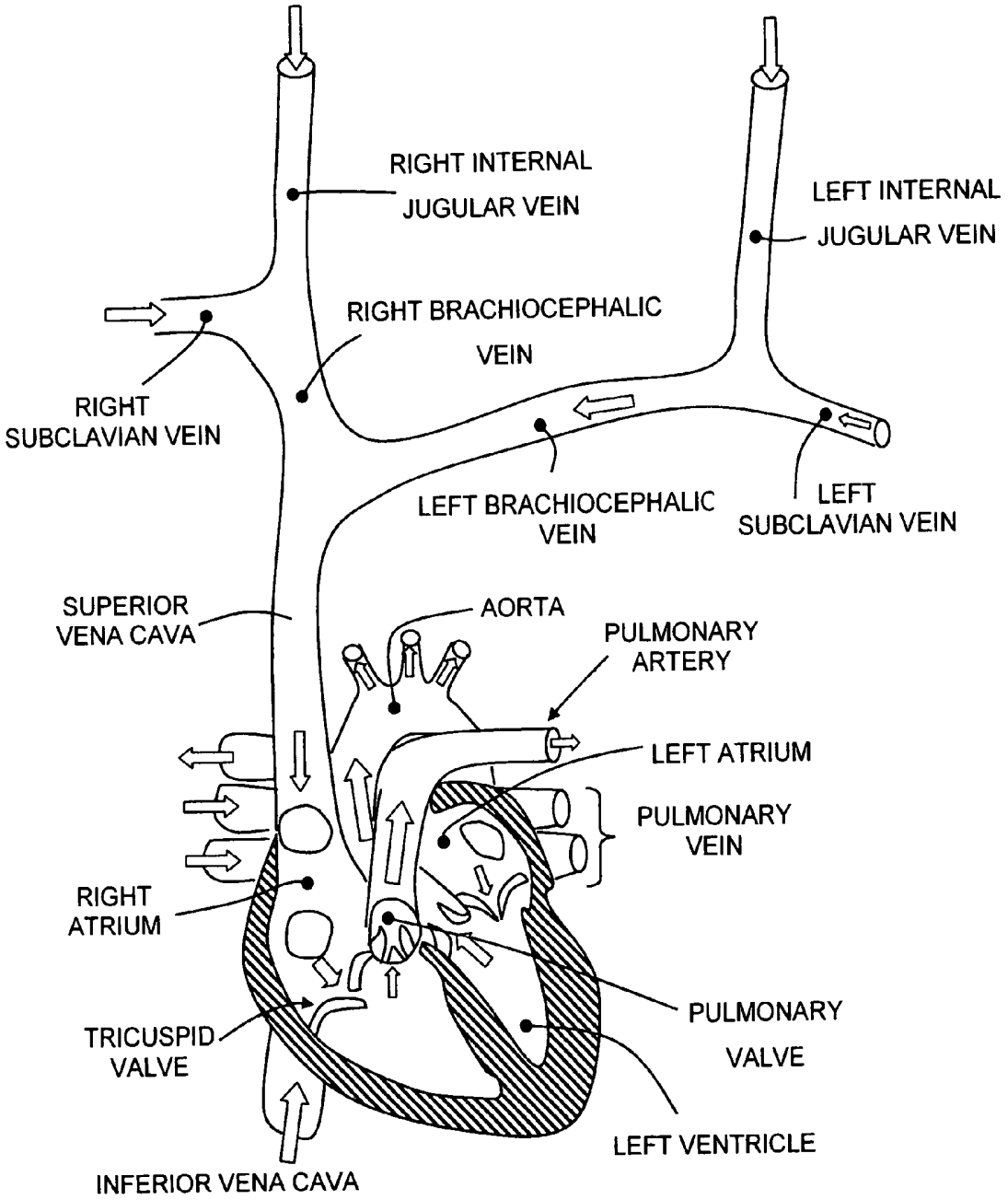

RIGHT INTERNAL
JUGULAR VEIN
LEFT INTERNAL
JUGULAR VEIN
RIGHT BRACHIOCEPHALIC
VEIN
RIGHT
SUBCLAVIAN VEIN
LEFT BRACHIOCEPHALIC
VEIN
LEFT
SUBCLAVIAN VEIN
SUPERIOR
VENA CAVA
AORTA
PULMONARY
ARTERY
LEFT ATRIUM
PULMONARY
VEIN
RIGHT
ATRIUM
PULMONARY
VALVE
TRICUSPID
VALVE
LEFT VENTRICLE
INFERIOR VENA CAVA

FIG. 14

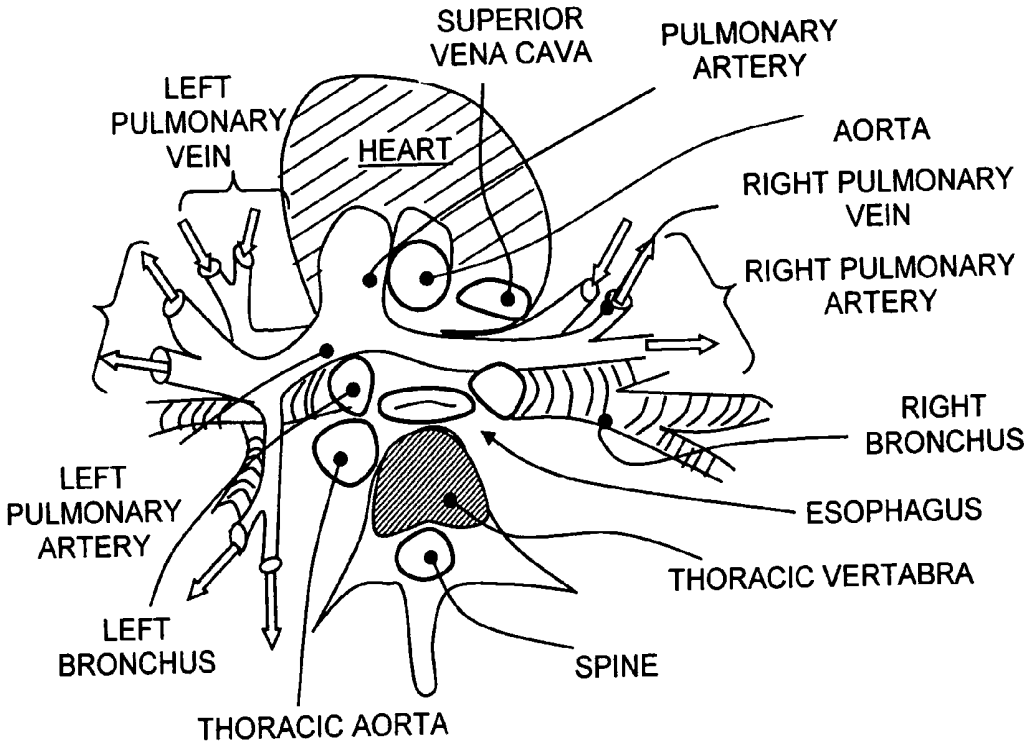

SUPERIOR
VENA CAVA
PULMONARY
ARTERY
LEFT
PULMONARY
VEIN
HEART
AORTA
RIGHT PULMONARY
VEIN
RIGHT PULMONARY
ARTERY
RIGHT
BRONCHUS
ESOPHAGUS
LEFT
PULMONARY
ARTERY
THORACIC VERTABRA
LEFT
BRONCHUS
SPINE
THORACIC AORTA

FIG. 15

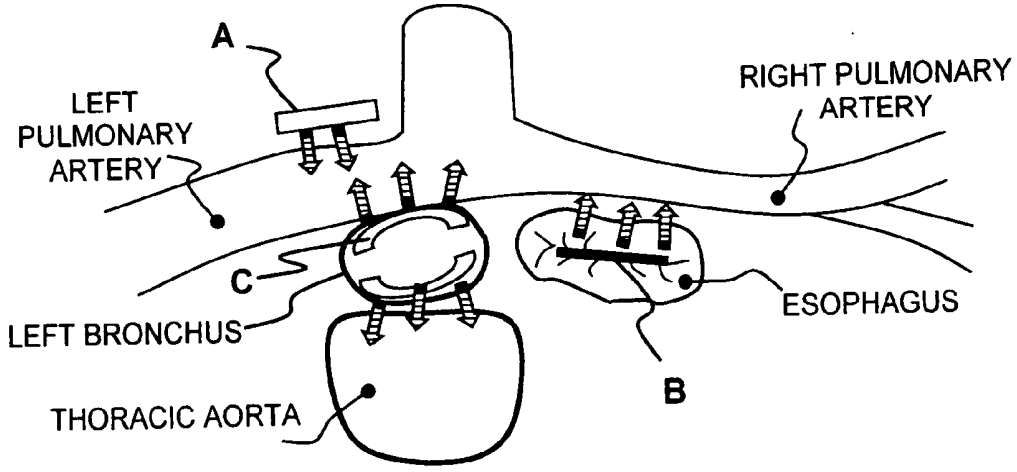

A
LEFT
PULMONARY
ARTERY
RIGHT PULMONARY
ARTERY
C
ESOPHAGUS
LEFT BRONCHUS
B
THORACIC AORTA

FIG. 16

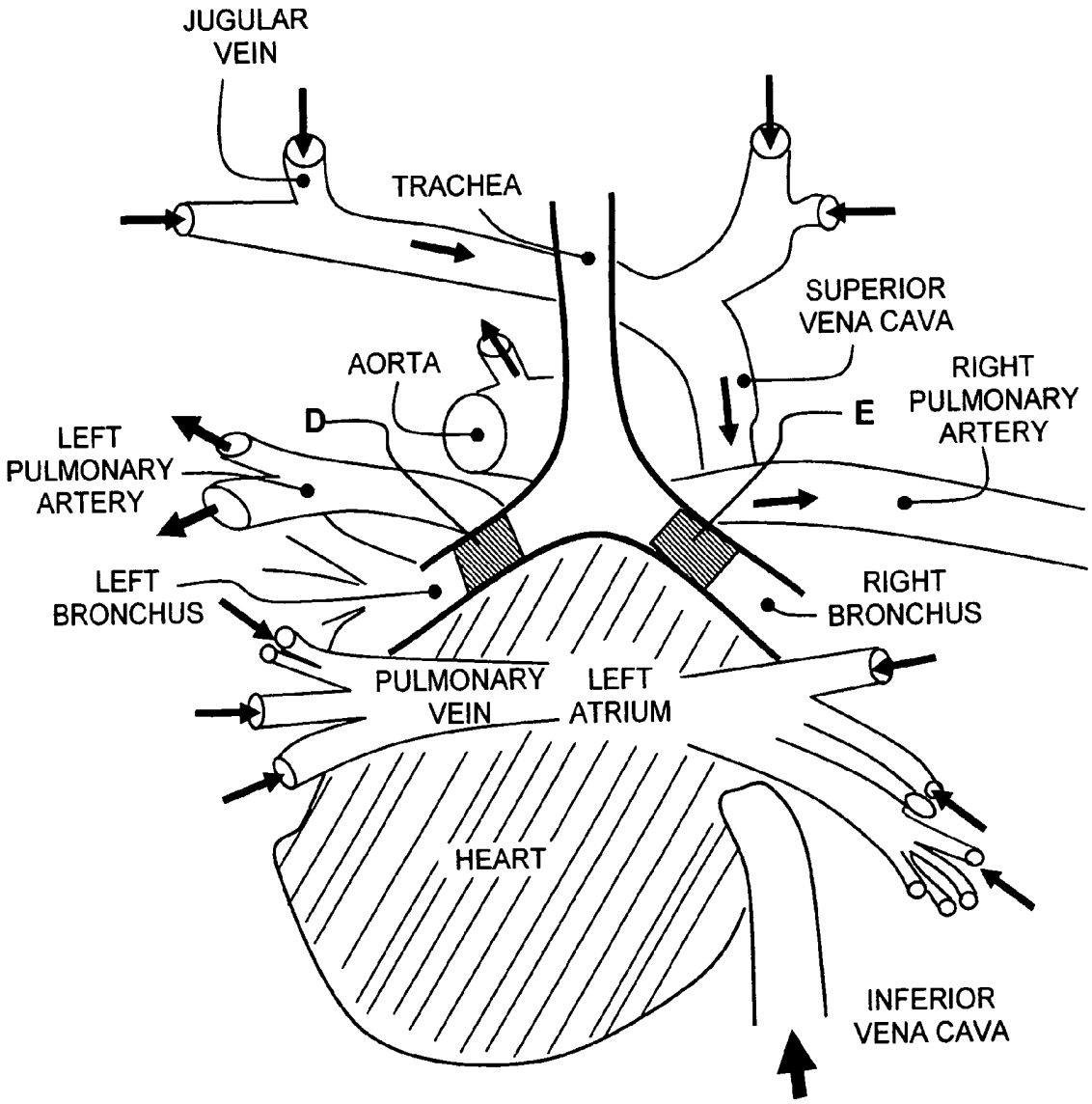

JUGULAR VEIN
TRACHEA
SUPERIOR VENA CAVA
AORTA
RIGHT PULMONARY ARTERY
D
E
LEFT PULMONARY ARTERY
LEFT BRONCHUS
RIGHT BRONCHUS
PULMONARY VEIN
LEFT ATRIUM
HEART
INFERIOR VENA CAVA

FIG. 17

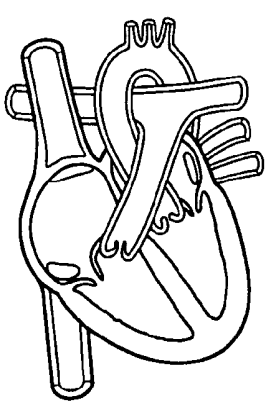


FIG. 18A

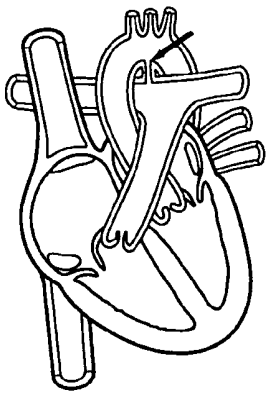


FIG. 18B

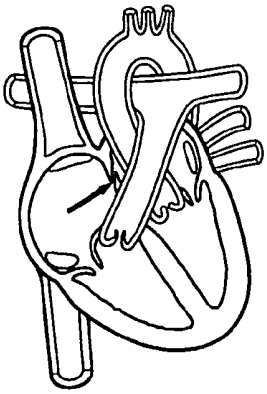


FIG. 18C

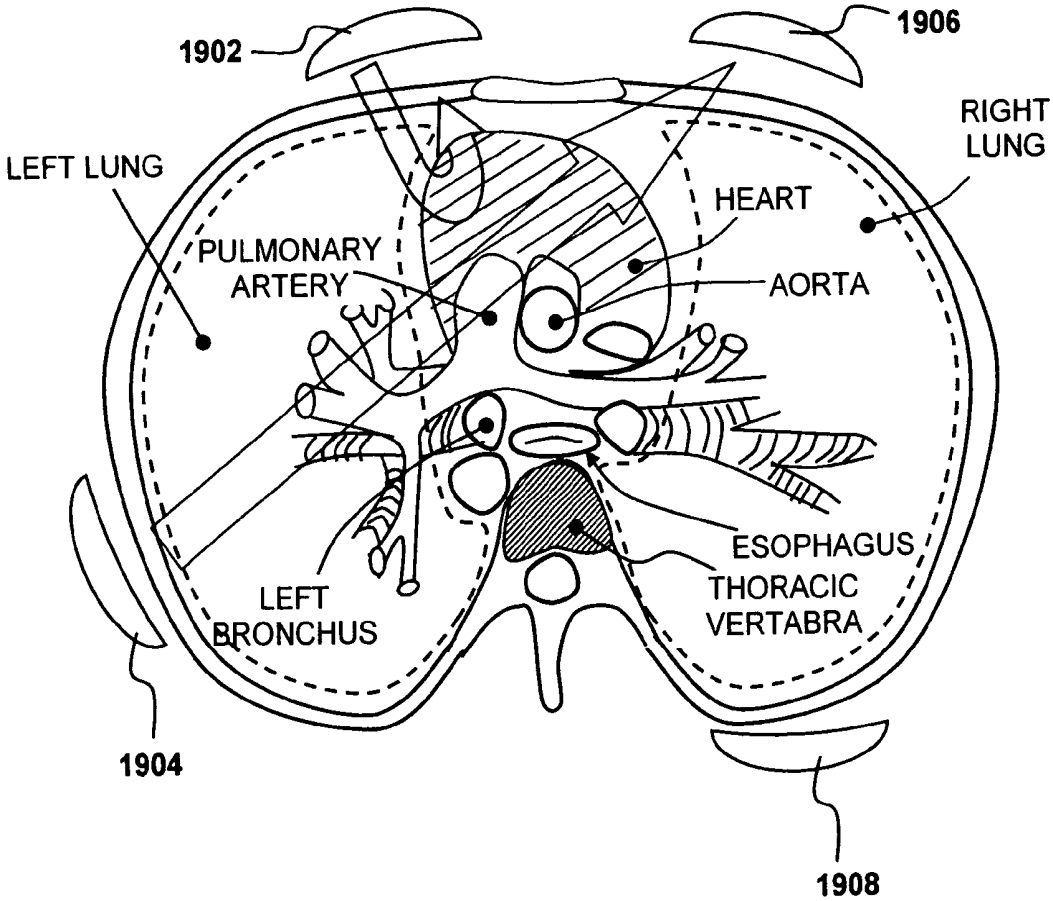


FIG. 19

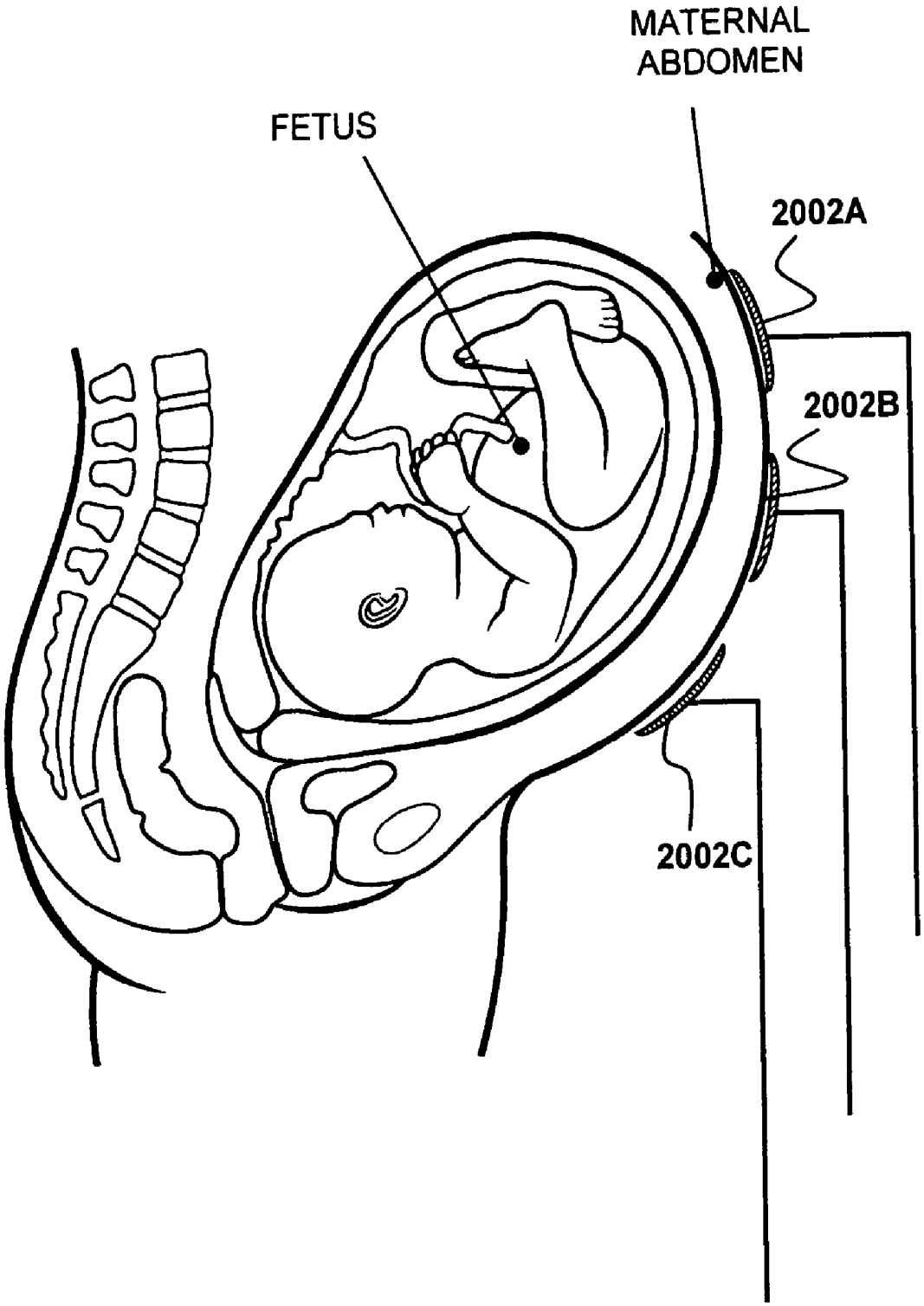


FIG. 20

APPARATUS AND METHOD FOR NON-INVASIVE AND MINIMALLY-INVASIVE SENSING OF VENOUS OXYGEN SATURATION AND PH LEVELS

FIELD OF THE INVENTION

[0001] This invention is related to techniques for monitoring vital bodily functions, including cardiac output. It relates in particular to methods and apparatus for non-invasive and minimally-invasive real-time monitoring of the venous oxygenation saturation in a vessel, an organ or tissue containing blood, and pH monitoring of blood in a vessel or organ.

BACKGROUND OF THE INVENTION

[0002] Cardiac output is defined as the volume of blood circulated per minute. It is equal to the heart rate multiplied by the stroke volume (the amount ejected by the heart with each contraction). Cardiac output averages approximately 5 liters per minute for an average adult at rest, although it may reach up to 30 liters/minute during extreme exercise.

[0003] Cardiac output is of central importance in the monitoring of cardiovascular health, as discussed by Conway "Clinical assessment of cardiac output", Eur. Heart J. 11, 148-150 (1990). Accurate clinical assessment of the circulatory status is particular desirable in critically ill patients in the ICU and patients undergoing cardiac, thoracic, or vascular interventions, and has proven valuable in long term follow-up of outpatient therapies. As the patient's hemodynamic status may change rapidly, continuous monitoring of cardiac output will provide information allowing rapid adjustment of therapy. Measurements of cardiac output and blood pressure can also be used to calculate peripheral resistance.

[0004] A recent review of the various techniques for measuring cardiac output is given in Linton and Gilon, "Advances in non-invasive cardiac output monitoring", Annals of Cardiac Anaesthesia, 2002, volume 5, p 141-148. This article lists both non/minimally invasive and invasive methods and compares the advantages and disadvantages of each.

[0005] The pulmonary artery catheter (PAC) thermodilution method is generally accepted as the clinical standard for monitoring cardiac output, to which all other methods are compared as discussed by Conway and Lund-Johansen ("Thermodilution method for measuring cardiac output", Europ. Heart J. 11(Suppl 1), 17-20 (1990)). The long history of use has defined the technology, suitable clinical applications, and its inadequacies. Many new methods have attempted to replace the thermodilution technique, but none have so far gained acceptance.

[0006] Jansen (J. R. C. Jansen, "Novel methods of invasive/non-invasive cardiac output monitoring", Abstracts of the 7th annual meeting of the European Society for Intravenous Anesthesia, Lisbon **2004**) describes eight desirable characteristics for cardiac output monitoring techniques; accuracy, reproducibility or precision, fast response time, operator independency, ease of use, continuous use, cost effectiveness, and no increased mortality and morbidity. A brief description of some of these techniques follows.

[0007] Indicator dilution techniques. There are several indicator dilution techniques including transpulmonary thermodilution (also known as PiCCO technology, from Pulsion Medical Technologies of Munich, Germany), transpulmonary lithium dilution method (LiDCO Group plc of London, UK), PAC based thermodilution and other methods (Vigilance, Baxter; Opti-Q, Abbott; and TruCCOMS, AorTech). U.S. Pat. No. 6,757,544 to Rubinstein et al. teaches the technique of optically monitoring indicator dilution in a non-invasive manner for the purpose of computation of cardiac output, cardiac index, and blood volume. Transpulmonary indicator dilution methods with bolus injections are variations on the conventional bolus thermodilution method. CO is calculated with use of the Steward-Hamilton equation (Geddes, "Cardiac output using the saline dilution impedance technique", IEEE Engineering in Medicine and Biology magazine March 1989, 22-26). Application of this equation assumes three major conditions; complete mixing of blood and indicator, no loss of indicator between place of injection and place of detection, and constant blood flow. The errors associated with indicator dilution techniques are primarily related to the violation of these conditions, as discussed by Lund-Johansen ("The dye dilution method for measurement of cardiac output", Europ. Heart J. 11 (Suppl 1), 6-12 (1990)) and de Leeuw and Birkenhager ("Some comments of the usefulness of measuring cardiac output by dye dilution", Europ. Heart J. 11 (Suppl 1), 13-16 (1990)). Of the mentioned methods the transpulmonary indicator dilution methods as well as the so-called 'continuous cardiac output' thermodilution methods have been partially accepted in clinical practice as described in, for example, Rödig et al. "Continuous cardiac output measurement: pulse contour versus thermodilution technique in cardiac surgical patients". Br J Anaesth 1999; 50: 525.

[0008] Fick principle. The direct oxygen Fick approach is currently the standard reference technique for cardiac output measurement, as discussed by Keinanen et al., "Continuous measurement of cardiac output by the Fick principle: Clinical validation in intensive care", Crit Care Med 20(3), 360-365 (1992), and Doi et al., "Frequently repeated Fick cardiac output measurements during anesthesia", J. Clin. Monit. 6, 107-112 (1990). It is generally considered the most accurate method currently available, although there are many possibilities of introducing errors, and considerable care is needed. However when using the Fick method to trend cardiac output over a short time interval, i.e. during an operation or in an intensive care unit stay, many of these sources of errors are no longer pertinent. The NICO (Novametrix) system is a non-invasive device that applies Fick's principle on CO_2 and relies solely on airway gas measurement as described by Botero et al., "Measurement of cardiac output before and after cardiopulmonary bypass: Comparison among aortic transit-time ultrasound, thermodilution, and noninvasive partial CO_2 rebreathing", J. Cardiothoracic. Vasc. Anesth. 18(5) 563-572 (2004). The method calculates effective lung perfusion, i.e. that part of the pulmonary capillary blood flow that has passed through the ventilated parts of the lung. The effects of unknown ventilation/perfusion inequality in patients may explain why the performance of this method shows a lack of agreement between thermodilution and CO_2-rebreathing cardiac output as described in Nielsson et al. al "Lack of agreement between thermodilution and CO_2-rebreathing cardiac output" Acta Anaesthesiol Scand 2001; 45:680.

[0009] Bio-Impedance and conduction techniques. The bio-impedance method was developed as a simple, low-cost

method that gives information about the cardiovascular system and/or (de)-hydration status of the body in a non-invasive way. Over the years, a diversity of thoracic impedance measurement systems have also appeared. These systems determine CO on a beat-to-beat time base. Studies have been reported with mostly poor results, but in exceptional cases good correlations compared to a reference method. Many of these studies refer to the poor physical principles of the thoracic impedance method as described in Patterson "Fundamentals of impedance cardiography", IEEE Engineering in Medicine and Biology 1989; 35 to explain the discrepancies. The accuracy of this technique is increased when the electrodes are placed directly in the left ventricle, rather than on the chest, however this also increases its invasiveness.

[0010] Echo-Doppler ultrasound. This technique uses ultrasound and the Doppler effect to measure cardiac output. The blood velocity through the aorta causes a 'Doppler shift' in the frequency of the returning ultrasound waves. Echo-Doppler probes positioned inside the esophagus with their echo window on the thoracic aorta may be used for measuring aortic flow velocity, as discussed by Schmidlin et al, "Transoesophageal echocardiography in cardiac and vascular surgery: implications and observer variability", Brit. J. Anaesth. 86(4), 497-505 (2001). Aortic cross sectional area is assumed in devices such as the CardioQ, made by Deltex Medical PLC, Chichester, UK) or measured simultaneously as for example in the HemoSonic device made by Arrow International. With these minimally invasive techniques what is measured is aortic blood flow, not cardiac output. A fixed relationship between aortic blood flow and cardiac output is assumed. CO can therefore be calculated using this relationship. Abrupt changes in cardiac output are better followed with Doppler systems than with the PAC based continuous cardiac output systems as described in Roeck et al. "Change in stroke volume in response to fluid challenge: assessment using esophageal Doppler", Intensive Care Med 2003; 29:1729. This measurement requires an above average level of skill on the part of the operator of the ultrasound machine to get accurate reliable results.

[0011] Arterial pulse contour analysis. The estimation of cardiac output based on pulse contour analysis is an indirect method, since cardiac output is not measured directly but is computed from a pressure pulsation on basis of a criterion or model. The origin of the pulse contour method for estimation of beat-to-beat stroke volume goes back to the Windkessel model as described in, for example, Manning et al. "Validity and reliability of diastolic pulse contour analysis (Windkessel model) in humans", Hypertension. 2002 May; 39(5):963-8. Most pulse contour methods are based on this model explicitly or implicitly as described in Rauch et al. "Pulse contour analysis versus thermodilution in cardiac surgery", Acta Anaesthesiol Scand 2002; 46:424, Linton et al. "Estimation of changes in cardiac output from arterial blood pressure waveform in the upper limb", Br J Anaesth 2001; 86:486 and Jansen et al. "A comparison of cardiac output derived from the arterial pressure wave against thermodilution in cardiac surgery patients" Br J Anaesth 2001; 87:212.

[0012] Arterial pulse contour analysis techniques relate an arterial pressure or pressure difference to a flow or volume change. Three pulse contour methods are currently available; PiCCO (Pulsion), PulseCO (LiDCO) and Modelflow (TNO/BMI). All three of these pulse contour methods use an invasively measured arterial blood pressure and they need to be calibrated. PiCCO is calibrated by transpulmonary thermodilution, LiDCO by transpulmonary lithium dilution and Modelflow by the mean of 3 or 4 conventional thermodilution measurements equally spread over the ventilatory cycle. Output of these pulse contour systems is calculated on a beat-to-beat basis, but presentation of the data is typically within a 30-second window. A non-invasive pulse contour development is the combination of non-invasively measured arterial finger blood pressure with Modelflow as described in Hirschl et al. "Noninvasive assessment of cardiac output in critically ill patients by analysis of finger blood pressure waveform", Crit Care Med 1997; 25:1909.

[0013] None of the above-mentioned CO techniques combines all of the eight "Jansen" criteria mentioned above. With respect to accuracy and precision, a number of methods may approach the thermodilution method with a precision of 15%. None of these new techniques has displaced conventional thermodilution based on the averaged result of 3 or 4 measurements done equally spread over the ventilatory cycle as described in Jansen et al. "An adequate strategy for the thermodilution technique in patients during mechanical ventilation", Intensive Care Med 1990; 16:422. Under research conditions the use of this conventional thermodilution method remains the method of choice. However, in clinical settings, the lower precision of the continuous cardiac output techniques may be outweighed by their advantages of being automatic and continuous.

[0014] In addition to measuring cardiac output, it is also desirable in many critical care situations to continuously monitor a patient's blood oxygen level. Currently, hospitals routinely monitor blood oxygenation by pulse oximetry with a monitor attached to the patient's finger or earlobe as described for example in Silva et al., "Near-infrared transmittance pulse oximetry with laser diodes", J. Biomed. Opt. 8(3), 525-533 (2003). Typically the oxygen monitor is a pair of light-emitting diodes (LED) and photodiodes on a probe clipped to a part of the patient's body. Red light from the LED reflects from the blood in a part of the patient's body, such as an ear-lobe or finger-tip. As a patent's oxygenation level drops, the blood becomes more blue, reflecting less red light to the photodiode. Such blood-oxygen monitors customarily measure percent of normal. Reassuring (normal) ranges are from 95 to 100 percent. For a patient breathing room air, at not far above sea level, an estimate of arterial oxygenation can be made from the blood-oxygen monitor reading. Unfortunately, measurements from such oxygen monitors cannot be reliably correlated to oxygenation in the patient's venous blood. Venous oxygen saturation is also a valuable parameter in the diagnosis of septic and cardiogenic shock as described below.

[0015] Other methods of measuring oxygenation: Diffuse optical tomography methods as described for example in Boas et al., Method for monitoring venous oxygen saturation", US Patent application 20040122300 are conceptually appealing but are useful only where the vessels in the vicinity of the diffusing photon field are isolated veins. The presence of mixed arterial and venous blood complicates the problem to as described by Wolf et al., "Continuous noninvasive measurement of cerebral arterial and venous oxygen saturation at the bedside in mechanically ventilated neonates", Crit. Care. Med 25(9), 1579-1582 (1997).

[0016] Ultrasound-tagged optical spectroscopy involves overlapping an ultrasound wave and a diffusing optical field, and modulating the frequency of the probe photons or their trajectories. A number of different technologies have been developed that utilize some interaction between ultrasound radiation and electromagnetic radiation. U.S. Pat. No. 5,212,667 to Tomlinson et al. and U.S. Pat. No. 5,174,298 to Dolfi et al. teach the technique of ultrasound tagged frequency-modulated imaging. Other patents teaching variations on the theme of frequency-modulated ultrasound tagging techniques include U.S. Pat. No. 6,815,694 to Sfez et al., U.S. Pat. No. 6,738,653 to Sfez et al., U.S. Pat. No. 6,041,248, to Wang, U.S. Pat. No. 6,002,958 to Godik, U.S. Pat. No. 5,951,481 to Evans, U.S. Pat. No. 5,293,873 to Fang. Trajectory modulation is detected by monitoring the speckle pattern of the photons emerging form the target. Image reconstruction techniques are then used to recreate a map of the path the photons followed in the medium. Imaging the speckle resulting from trajectory changes requires significant computation power and post-processing to yield an image. The technique has limited resolution, and is not yet capable of yielding functional (oxygenation) information in a fast flowing vessel.

[0017] Some variations of ultrasound-tagged frequency-modulated imaging rely on observing the frequency shift induced by the photoacoustic effect when an electromagnetic wave interacts in a medium with a sound wave. The electromagnetic wave (having a characteristic frequency ω_{OPT}) receives a frequency shift at the ultrasound frequency ω_{US} to either the + or − side of the carrier wave WOPT. Frequency modulation is detected by measuring the frequency shifted photons by for example using a Fabry-Perot etalon as described by Sakadzic and Wang, "High resolution ultrasound modulated optical tomography in biological tissues", Opt. Lett. 29(23) 2004, p 2770-2772. Since the Doppler shifts induced by the ultrasound wave are very small compared to the probe photon carrier wave frequency, the detection system must be extremely sensitive to small frequency shifts. In addition, the frequency shift can be to both larger and smaller frequency of the initial carrier wave, and therefore some self-cancellation may result.

[0018] There is accordingly a need in the art to be able to measure venous oxygen saturation levels in various vascular structures in the body, and from this be able to calculate cardiac output. There is a need to make these measurements non-invasively. There is a need to be able to make these measurements in an MRI-/CT/X-Ray instrument compatible manner, thus preferably not using ferromagnetic materials in construction, and using designs such that the probe on/in the body may be remotely coupled to the control system away from the magnetic field or ionizing radiation sources generated by the MRI instrument or CT/X-Ray. There is a need in the art to make these measurements in a manner that does not depend on the melanin content of the skin. There is a need to make these measurements in a manner such that the result may be arrived at in a short time period, i.e. such that extensive post-processing of the data is not required, so that the physician may make accurate timely diagnostic and therapeutic decisions.

SUMMARY OF THE INVENTION

[0019] The disadvantages associated with the prior art are overcome by embodiments of the present invention are directed to apparatus and methods that combine ultrasound and optical signals.

[0020] According to an embodiment of the present invention an apparatus generally comprises an ultrasound transducer, an optical source, launch optics, an optical detector and a filter coupled to the optical detector. The ultrasound transducer is configured to provide an ultrasound radiation pressure field to selectively modulate (mechanically vibrate) a target area within a body at a modulation frequency. The optical source is configured to generate one or more pulses of radiation containing temporally correlated groups of photons. The photons in each group are characterized by two or more different wavelengths that are selected to have specific interaction with a target chromophore. The different wavelengths are also selected to have substantially similar scattering cross-sections and anisotropy parameters in the target and its surroundings.

[0021] The launch optics are configured to transmit the pulses of radiation from the optical source to the target area being modulated by the radiation pressure field and inject the pulses of radiation into the body in close proximity to the target area. The optical detector is configured to detect in temporal coincidence photon groups at each of the different wavelengths that are backscattered from the target area so as to select groups of photons that have traveled approximately the same physical pathlength in the tissue. The optical detector uses time-gated amplification and preferably background-free time-gated amplification of the return signal so as to exclude photons which could not by virtue of their arrival time have interacted with the radiation-pressure-modulated target. The filter is configured to select those detected photon groups with a modulation component at the same frequency as the modulation frequency of the radiation pressure modulation field, or at a harmonic of the modulation frequency.

[0022] With such an apparatus, a method for detecting venous oxygen saturation and/or pH of blood in an identified physiological target area in a non-invasive or minimally invasive manner may be implemented according to another embodiment of the present invention. The launch optics are placed such that a light emitting aperture of the launch optics is placed in close proximity to a blood vessel. Radiation pressure from the ultrasound transducer mechanically modulates a target area of the blood vessel. The optical source generates one or more pulses of radiation containing temporally correlated groups of photons characterized by different wavelengths as described above. The pulses of radiation are transmitted from the optical source and injected into the body in close proximity to the target area being modulated by the radiation pressure field.

[0023] Photon groups backscattered from the target area are detected with the optical detector using time-gated background-free amplification of the return signal so as to exclude photons which could not by virtue of their arrival time have interacted with the radiation-pressure-modulated target. The detection occurs in a manner so as to detect photons at each of the different injected wavelengths in temporal coincidence such that detected photons of the two or more different wavelengths have traveled substantially

the same pathlength in tissue of the target area. The detected photon groups are filtered so as to detect those photon groups having a modulation component characterized by the same frequency as the radiation pressure modulation field, or a harmonic of said radiation pressure modulation frequency. From the arrival rate of the detected temporally correlated photon pairs (or higher multiplets), an oxygenation level or pH of the target area can be inferred. For example, the wavelengths can be selected to provide information about the oxygenation level of the blood by targeting oxyhemoglobin and deoxyhemoglobin. Cardiac output can then be computed from a measurement of venous oxygenation using the apparatus and a measurement of arterial oxygenation, e.g., using the present technique or a standard blood oxygen monitor such as pulse oximetry.

[0024] The launch optics, ultrasound transducer and optical detector (or collecting optics coupled to the optical detector) can be placed on the skin of a patient's neck to measure oxygen content in the jugular vein transdermally. Alternatively, the launch optics, ultrasound transducer, and optical detector (or collecting optics) can be placed transtracheally, trans-esophageally, or in direct contact with the pulmonary artery or aorta using a bronchoscope inserted through an intercostal incision.

[0025] Such embodiments allow clinical monitoring of venous oxygen and cardiac output in a minimally invasive or non-invasive manner. Such monitoring can be accurate, reproducible, precise, fast, operator-independent, easy to use, continuous, cost effective, and substantially free of increased mortality and morbidity.

BRIEF DESCRIPTION OF THE DRAWINGS

[0026] The teachings of the present invention can be readily understood by considering the following detailed description in conjunction with the accompanying drawings, in which:

[0027] **FIG. 1** is a schematic view of an embedded vascular structure that is an example of a suitable target for measurement with embodiments of the present invention.

[0028] **FIG. 2A** is a schematic diagram of an apparatus according to an embodiment of the present invention.

[0029] **FIG. 2B** is a close-up cross-sectional schematic diagram illustrating an example of use of the apparatus of **FIG. 2A**

[0030] **FIG. 3** is a schematic diagram of a three-wavelength pulsed optical source for use in embodiments of the present invention.

[0031] **FIG. 4** is a schematic diagram of an all-electronic optical source for use in embodiments of the present invention.

[0032] **FIG. 5** is an example of a source of three wavelengths using an Optical Parametric Oscillator for use with embodiments of the present invention.

[0033] **FIG. 6** is a schematic diagram illustrating an example of signal broadening expected at a tissue boundary.

[0034] **FIG. 7** is a schematic diagram of an apparatus using the principle of time gated upconversion according an alternative embodiment of the present invention.

[0035] **FIG. 8** is a schematic diagram of an apparatus having two pulsed optical sources according another alternative embodiment of the present invention proposed implementation of the present invention.

[0036] **FIG. 9A** is a schematic diagram depicting time-gated upconversion detector that can be used in the apparatus of **FIG. 8**.

[0037] **FIG. 9B** is a schematic diagram depicting an alternative time-gated upconversion detector that can be used in the apparatus of **FIG. 8**.

[0038] **FIG. 10** is a schematic diagram depicting a second apparatus having a background-free time-gated upconversion detector according to another embodiment of the present invention.

[0039] **FIG. 11** is a graph of the absorption of oxyhemoglobin and water in the range 700-1200 nm, an expected variation of the scattering coefficient as a function of wavelength, and an expected difference between an artery with fully oxygen-saturated blood and a vein where the oxygen saturation is 55%.

[0040] **FIGS. 12A-12B** are schematic diagrams of sensors that can be used with embodiments of the present invention.

[0041] **FIG. 12C** is a three-dimensional diagram of an alternative sensor according to an embodiment of the present invention.

[0042] **FIG. 12D** is a cross-sectional diagram taken along line D-D of **FIG. 12C**.

[0043] **FIG. 13** is a schematic diagram illustrating an example of trans-dermal measurement of oxygenation of blood the internal or external jugular veins.

[0044] **FIG. 14** is a schematic diagram of a portion of the circulatory system showing examples of locations that may be probed for blood oxygenation using embodiments of the present invention.

[0045] **FIG. 15** is a horizontal cross-section through the chest showing examples of showing examples of locations that may be probed for blood oxygenation using embodiments of the present invention.

[0046] **FIG. 16** is a close-up vertical thoracic cross-section illustrating a sensor placed in the left bronchus to probe oxygenation of the left pulmonary artery and descending thoracic aorta.

[0047] **FIG. 17** is a schematic thoracic diagram illustrating an example of trans-tracheal placement of a sensor according to an embodiment of the present invention.

[0048] **FIG. 18A** is sagittal cross-sectional schematic diagram illustrating a normal heart.

[0049] **FIG. 18B** is a sagittal cross-sectional schematic diagram illustrating a heart exhibiting Patent Ductus Arteriosus (PDA).

[0050] **FIG. 18C** is a sagittal cross-sectional schematic diagram illustrating a heart exhibiting Patent Foramen Ovale (PFO).

[0051] **FIG. 19** is a thoracic axial cross-sectional schematic diagram illustrating examples of sensor placement for cardiac mapping in newborn infants according to an embodiment of the invention.

[0052] **FIG. 20** is a sagittal cross-sectional schematic diagram illustrating examples of sensor placement for monitoring of fetal blood oxygenation.

DESCRIPTION OF THE SPECIFIC EMBODIMENTS

[0053] Although the following detailed description contains many specific details for the purposes of illustration, anyone of ordinary skill in the art will appreciate that many variations and alterations to the following details are within the scope of the invention. Accordingly, the exemplary embodiments of the invention described below are set forth without any loss of generality to, and without imposing limitations upon, the claimed invention.

Glossary:

[0054] As used herein, the following terms have the following meanings:

[0055] Continuous wave (CW) laser: A laser that emits radiation continuously rather than in short bursts, as in a pulsed laser.

[0056] Diode Laser: Refers to a light-emitting diode designed to use stimulated emission to generate a coherent light output. Diode lasers are also known as laser diodes or semiconductor lasers. A diode-pumped laser refers to a laser having a gain medium that is pumped by a diode laser.

[0057] Mode locked laser: A laser that emits radiation in short bursts, as in a pulsed laser. Typically these pulses are on the order of 0.1-100 picoseconds in temporal length and preferably 1-50 picoseconds.

[0058] Highly Non-linear Fiber: A fiber characterized by having a guiding core with properties that can be used to convert electromagnetic radiation at one frequency to another provided there is sufficient intensity at the originating frequency and the fiber has sufficient length.

[0059] Upconversion Process: A process by which photons of a given frequency are converted to photons of shorter wavelength (higher frequency). This technique may be used, e.g., to bring infra-red photons into the detection range of silicon detectors for example, or may be used in a pulsed configuration to give temporal selectivity in which photons are upconverted and hence detected.

[0060] Non-Linear Crystal: A crystal made of a material having special optical properties allowing the frequency of an incoming electromagnetic wave to be shifted according to predictable rules and conditions.

[0061] Optical Parametric Oscillator: A process by which a photon at a pump frequency ω_p is converted in a material inside a resonator to two photons of lower frequency, typically called the signal and idler photons with the relationship:

$$\omega_P=\omega_{SIG}+\omega_{IDL}$$

[0062] Optical Parametric Amplifier: A process by which a photon at a pump frequency ω_p is converted in a material (but without the need for an external resonator) to two photons of lower frequency, typically called the signal and idler photons with the relationship:

$$\omega_p=\omega_{sig}+\omega_{idl}$$

Theoretical

[0063] As stated above, there are eight desirable characteristics for cardiac output (CO) monitoring techniques: accuracy, reproducibility or precision, fast response time, operator independency, ease of use, continuous use, cost effectiveness, and no increased mortality and morbidity associated with its use. None of the present CO monitoring techniques satisfactorily combines all eight criteria mentioned above.

[0064] The Fick principle involves measuring the oxygen consumption (VO_2) per minute (e.g., using a spirometer), measuring the oxygen saturation of arterial blood using for example standard pulse oximetry on the finger, and measuring venous oxygen saturation in the pulmonary artery or superior vena cava.

From these values, one can calculate:

$$\text{Cardiac Output} = \frac{\text{Oxygen\_Consumption}}{(ArterialSaO_2 - VenousSaO_2)\times[Hb]\times 1.36}$$

where Arterial SaO_2 and Venous SaO_2 are respectively the arterial and venous oxygen saturation, [Hb] is the blood hemoglobin concentration and 1.36 is a factor subsuming the oxygen carrying capacity of the hemoglobin. [Hb] can be related simply to the hematocrit (Hct), a routinely measured parameter defined as the percent of whole blood that is composed of red blood cells (erythrocyte volume to total volume expressed as a percentage). The range for Hct is 32-50% in "normal""healthy" people. Hct does not tend to change dramatically and quickly (unless the patient is bleeding severely), so it is sufficient to take a sample every 4-6-8 hours for example and update the Fick calculation periodically. Hematocrit (hct) can be measured, e.g., by taking a sample of blood and spinning it down in a centrifuge and calculating the volumes.

The Fick principle relies on the observation that the total uptake of (or release of) a substance by the peripheral tissues is equal to the product of the blood flow to the peripheral tissues and the arterial-venous concentration difference (gradient) of the substance. In the determination of cardiac output, the substance most commonly measured is the oxygen content of blood, and the venous saturation is measured in the pulmonary artery using a catheter as for example described by Powelson et al., "Continuous monitoring of mixed venous oxygen saturation during aortic operations", Crit. Care Med. 20(3), 332-336 (1992). This gives a simple way to calculate the cardiac output. The drawback of drift associated with this type of catheter has been discussed by Souter et al., "Jugular venous desaturation following cardiac surgery", Brit. J. Anaesth. 81, 239-241 (1998). It is also highly invasive, incompatible with ambulatory measurement, and poses risks of infection due to vascular system breach (femoral or jugular vessel insertion). The nature of the challenge is illustrated schematically in **FIG. 1**. An embedded vascular structure of a body **100** includes an artery **102** and vein **104**, for example the internal jugular vein and artery in the neck. The vein **102** and artery **104** are located beneath the epidermis **106** and dermis **108** of the body **100**. The vein and artery are embedded in and around subcutaneous structures **110**, e.g., fat, muscle, tendon, etc.

[0065] Assuming there are no shunts across the cardiac or pulmonary system, the pulmonary blood flow equals the systemic blood flow. Measurement of the arterial and venous oxygen content of blood involves the sampling of blood from the pulmonary artery (low oxygen content) and from the pulmonary vein (high oxygen content). In practice, sampling of peripheral arterial blood is a surrogate for pulmonary venous blood.

[0066] Embodiments of the present invention allow non-invasive or minimally invasive measurement of venous oxygen saturation at a point where the value trends correctly with a direct pulmonary artery catheter measurement. One can apply the above-described Fick principle to such a measurement thereby enabling measurement of cardiac output in a non- or minimally invasive manner.

[0067] Embodiments of the present invention for measuring venous oxygen saturation can also be made insensitive to the presence of shunts in the heart, such as for example acquired ventricular septal defects, and as such offer valuable adjunct information if PAC thermodilution or Fick data are already available. This is the case when the sensor is placed on the internal jugular vein.

[0068] The value of the venous oxygen saturation is also a useful adjunct diagnostic parameter in its own right. Patients with low cardiac output tend to have low venous oxygen saturation, for example around 50. This low value results from the increased extraction of oxygen in the body tissues due to the poor perfusion resulting from low flow. However high mixed venous oxygen saturation with low cardiac output can indicate a significant left-to-right shunt across the heart, such as an acquired ventricular septal defect. Embodiments of the present invention where the sensor is placed on the internal jugular will allow a measurement of venous oxygen saturation before the heart and pulmonary system, and thus will in insensitive to the presence of these shunts.

[0069] Also by way of example a presentation of high cardiac output, high venous oxygen saturation, narrow arterio-venous difference and low peripheral resistance might suggest to the physician to test for septic shock. On the other hand cardiogenic shock is associated with high peripheral resistance. Thus measurement of cardiac output can help guide and monitor the administration of drugs such as vasodilators/vasoconstrictors and inotropes.

[0070] A number of different technologies have been developed that utilize some interaction between ultrasound radiation and electromagnetic radiation. However, these prior art technologies are all distinguishable from the techniques described herein. For example, embodiments of the present invention are superior to standard ultrasound-tagged photon techniques in that they are not limited by the ability of the apparatus to detect very small frequency shifts on the detected photons. U.S. Pat. No. 5,212,667 to Tomlinson et al. and U.S. Pat. No. 5,174,298 to Dolfi et al. teach the technique of ultrasound tagged frequency-modulated imaging. Other patents teaching variations on the theme of frequency-modulated ultrasound tagging techniques include U.S. Pat. No. 6,815,694 to Sfez et al., U.S. Pat. No. 6,738,653 to Sfez et al., U.S. Pat. No. 6,041,248, to Wang, U.S. Pat. No. 6,002,958 to Godik, U.S. Pat. No. 5,951,481 to Evans, U.S. Pat. No. 5,293,873 to Fang.

[0071] Ultrasound-tagged frequency modulated imaging relies on observing the frequency shift induced by the photoacoustic effect when an electromagnetic wave interacts in a medium with a sound wave. The electromagnetic wave (having a characteristic frequency ω_{OPT}) receives a frequency shift at the ultrasound frequency ω_{US} to either the + or − side of the carrier wave ω_{OPT}. Heterodyne or interferometric techniques are then used to decouple the frequency shifted wave from the carrier wave. Implementation of the technique requires sophisticated lasers with narrow linewidths and concomitantly long coherence lengths in order to resolve the two frequencies. U.S. Pat. No. 6,002,958 to Godik teaches the study of the amplitude modulation induced on an electromagnetic wave by the ultrasound beam and scanning the ultrasound beam in order to form an image of the absorber.

[0072] U.S. Pat. No. 6,264,610 to Zhu teaches the use of ultrasound and near-IR imaging as adjunctive imaging techniques, but does not attempt a physical link between the two techniques.

[0073] U.S. Pat. No. 5,452,716 to Clift teaches the use of two-wavelength probing using one wavelength specific to the substance being probed and a reference field characterized by another wavelength. This patent does not teach any form of temporal gating, any form of targeting a structure, or any form of depth control using co-located optical and ultrasound fields.

[0074] U.S. Pat. No. 6,445,491 to Sucha et al. and U.S. Pat. No. 5,936,739 to Cameron et al. teach the use of optical parametric processes to amplify signals in imaging systems. Neither of these patents teaches the use of upconversion to produce a signal which is necessarily free from background contamination from for example fluorescence processes or Raman scattering. Neither of the patents teaches the use of the very fast non-linearities found in fiber Optical Parametric Amplifiers to yield time-gated information in a straightforward manner.

[0075] U.S. Pat. No. 5,451,785 to Faris teaches the use of upconversion processes in a transillumination imaging system.

[0076] U.S. Pat. No. 6,665,557 to Alfano et al. teaches spectroscopic and time-resolved optical methods for imaging tumors in turbid media where time gating of the ballistic and near-ballistic photons is used to improve the reconstruction of the image. The more diffusely scattered photons are rejected in this technique and no attempt is made to localize the interaction using ultrasound.

[0077] US Pat. Appl. No. 2004/0122300 A1 Boas et al., US Pat. Appl. No. 2004/0116789 to Boas et al., U.S. Pat. No. 6,332,093 to Painchaud et al., U.S. Pat. No. 5,630,423 to Wang et al., U.S. Pat. No. 5,424,843 to Tromberg et al. and U.S. Pat. No. 5,293,873 to Fang teach variations on the theme of Photon Migration Spectroscopy, Photon Migration Imaging (PMI), Diffuse Optical Tomography (DOT), or Diffuse Imaging, where photons from a source diffuse through the target and are detected using detectors placed at various distances from the source launch point. The characteristics of the diffusing photons are interpreted to yield functional and structural information about the medium they have diffused through. No attempt is made to "tag" these photons to localize the region of interaction. No attempt is made to time-gate the detected signal. Embodiments of the present invention are superior to Photon Migration Imaging

(PMI, DOT etc) in that they allow accurate depth and location localization of the target.

[0078] Embodiments of the present invention are also superior to speckle based imaging techniques because they are insensitive to the speckle decorrelation time of the tissue being probed. This speckle decorrelation is very fast in larger vascular structures with flowing blood inside, preventing use of speckle-based techniques in the types of vessels the current invention aims to address.

[0079] Embodiments of the present invention can also be designed in such a way as to be insensitive to the presence of epidermal melanin (unlike many of the wavelengths used in PMI/DOT and ultrasound tagged spectroscopy and imaging). Embodiments of the present invention can also be designed in a manner that will not suffer from significant solar or environmental background light contamination.

[0080] Embodiments of the present invention do not require the development of sophisticated single frequency lasers and interferometric detection techniques. As a result embodiments of the present invention will be simpler to implement and more technologically robust in a clinical setting. Apparatus according to embodiments of the present invention can use proven telecommunication-based fiber-based technology to yield a robust, small, and efficient product.

[0081] Embodiments of the present invention do not require 2-D imaging arrays or cameras (for example CCD cameras), and in particular do not require infra-red detector arrays such as InGaAs CCDs. These devices need to be cooled to achieve low noise conditions, further complicating the experimental/clinical implementation. Apparatus according to embodiments of the present invention can use proven single element silicon detectors which do not need to be cooled and which do not need extensive computational support.

[0082] **FIG. 2A** is a schematic block diagram of a diagnostic apparatus **200** according to an embodiment of the present invention. The apparatus **200** generally includes an optical source **202**, launch optics **204**, an ultrasound transducer **206**, collection optics **208**, an optical detector **210**, associated electronics such as a filter **212** and an optional display **214**. The optical source **202** provides pulsed electromagnetic radiation. The launch optics **204** may include one or more optical fibers **205** that couple the electromagnetic radiation from the optical source **202** to a body **201**. Similarly the collecting optics **208** collect optical signals reflected from within the body **201**. The collecting optics **208** may also include one or more optical fibers **209** that couple signals scattered electromagnetic radiation to the optical detector **210**. The optical source **202** may supply a timing signal (which may be either optical or electronic) to trigger a detector source **211** that provides an optical signal used in detection of the scattered radiation.

[0083] In some embodiments the launch optics **205**, ultrasound transducer **206**, and collecting optics may be mounted together in a handpiece to form a combined ultrasound optical sensor **203**. In other embodiments, the detector **210** may be part of the sensor **203** without the need for collecting optics. In some embodiments, the optical source **202**, optical detector **210**, detector source **211**, filter **212**, display **214** and an ultrasound generator **207** may be part of a remote unit **213** coupled to the sensor **203** by fiberoptics **205**, **209** and electrical cables. The remote unit **213** may include a system controller **215**. The system controller **215** may include a central processor unit (CPU) and a memory (e.g., RAM, DRAM, ROM, and the like). The controller **215** may also include well-known support circuits, such as input/output (I/O) circuits, power supplies (P/S), a clock (CLK), Field Programmable Gate Arrays (FPGAs) and cache. The controller **215** may optionally include a mass storage device such as a disk drive, CD-ROM drive, tape drive, or the like to store programs and/or data. The controller may also optionally include a user interface unit to facilitate interaction between the controller **215** and a user. The user interface may include a keyboard, mouse, joystick, light pen or other device. The preceding components may exchange signals with each other via a controller bus. In addition, the optical source **210**, detector source **211**, filter **212**, display **214** and an ultrasound generator **207** may exchange signals with the controller **215** via the system bus **216**.

[0084] The controller **215** typically operates the optical source, **202**, ultrasound generator **207**, optical detector **210**, detector source **211** detector, filter **212** and display **214** through the I/O circuits in response to data and program code instructions stored and retrieved by the memory and executed by the processor. The program code instructions may implement embodiments of the diagnostic technique described herein. The code may conform to any one of a number of different programming languages such as Assembly, C++, JAVA, Embedded Linux, or a number of other languages. The CPU forms a general-purpose computer that becomes a specific purpose computer when executing program code. Although the program code is described herein as being implemented in software and executed upon a general purpose computer, those skilled in the art will realize that the method of pulsed pumping could alternatively be implemented using hardware such as an application specific integrated circuit (ASIC) or FPGA or other hardware circuitry. As such, it should be understood that embodiments of the invention can be implemented, in whole or in part, in software, hardware or some combination of both.

[0085] Operation of the apparatus **200** may be understood with respect to the close-up schematic diagram depicted in **FIG. 2B**. An embedded target structure within the body **201** such as an artery AR or vein VE can be identified by ultrasound imaging.

[0086] The ultrasound generator **207** and transducer **206** can be used to do both the ultrasound imaging and the target modulation. Once a target has been located, the apparatus **200** switches between a regular ultrasound mode (imaging) and a radiation pressure modulation mode, firing tone bursts to modulate the target. The basic approach is first to image to choose a location to deliver radiation pressure and then to apply the appropriate phase to the array elements of the transducer **206** to have a focus at the location of interest. The radiation pressure is supplied by applying a tone burst (many cycles of electrical signal at the frequency of operation of the array) from the ultrasound generator **207** to the elements of the array in the transducer **206**. The repetition rate at which the tone burst is applied is the frequency at which the radiation pressure is applied. This repetition rate is constrained at the upper end by the fundamental frequency of the ultrasound transducer **206**, i.e. the tone burst cannot have a higher repetition rate than the fundamental frequency of

the transducer itself. By way of example, the ultrasound transducer **206** can operate at fundamental frequencies in the range 2-50 MHz, and preferably from 2-15 MHz. The tone bursts may produce radiation pressure modulation occurring at frequencies between 50 Hz and 750 kHz.

[**0087**] The sensor **203** is then placed proximate to a tissue boundary TB of the boundary **201**. The target structure is then vibrated using radiation pressure from the transducer **206** and illuminated with a diffuse photon field with a characteristic frequency WINJ delivered from the optical source **202** via the launch optics **204**. The radiation-pressure modulation of the target is detected by its effect on the emerging photon field at the detector (e.g., via the collecting optics **208**). In the example depicted in **FIGS. 1 and 2**A, it may be possible to measure both venous and arterial oxygenation separately by illuminating and modulating the vein and then separately illuminating and modulating the artery. In the case where the target is the internal jugular vein, the corresponding arterial structure is the carotid artery. This method, when it can be used, will implicitly provide a calibration signal. Cardiac output can then be calculated from the Fick Principle, as described above.

[**0088**] To make the measurement a biological structure within the body **201**, such as the pulmonary artery, descending branch of the aorta, internal jugular, or external jugular, is located in a standard manner with medical imaging. Once found the combined ultrasound/optical sensor **203** can be positioned proximate to the targeted structure. This can either be external dermal placement, e.g., on the neck in the case of the internal jugular vein, or an inserted catheter, either endotracheally for direct access to the left pulmonary artery and thoracic aorta, or trans-esophageally for access to the right pulmonary artery. The sensor **203** is preferably positioned such that the distance between the emitting tip of the launch optics **204** and the lumen of the targeted vessel is approximately minimized.

[**0089**] The ultrasound transducer **206** is used to physically modulate (vibrate) the selected target using ultrasound radiation pressure. The ultrasound transducer **206** is designed to focus its acoustic output into the target at various modulation frequencies. Examples of ultrasound transceivers that can provide such focused output include phased array ultrasound transceivers and single element ultrasound transducers with imaging designs. Phased array transducers typically have an array of ultrasound transducer elements that are narrow and have a wide acceptance angle so that energy from various angles is collected, and so that several elements (if not all) in the array contribute to the focusing at a certain location. To generate a beam, the various transducer elements are pulsed at slightly different times. By precisely controlling the delays between the transducer elements, beams of various angles, focal distance, and focal spot size can be produced. Furthermore, for a given point within the targeted tissue a unique set of delays will maximize the constructive interference of acoustic signals from each of the transducer elements. Such transducers can therefore selectively modulate particular structures within the target without modulating surrounding structures. Beam forming in ultrasound refers to the signal processing scheme used to focus the signals from various transducers. The energy is preferentially deposited using focusing to allow the application of radiation pressure at the location of interest with a relatively low level of input signal.

[**0090**] Examples of suitable ultrasound transducers include, for example, the GE Logiq 7 BT03 made by General Electric of Fairfield, Conn., or the Aspen® Echocardiography System made by Siemens (Acuson) of Mountain View, Calif. Other suitable array transducers are made by Philips (The Netherlands), or Hitachi (Japan). It is best to choose an instrument that is used commonly in hospitals say to image the heart.

[**0091**] An ultrasound imaging system can also be used in association with the ultrasound generator **207** and transducer **206** to locate the blood vessels in order to orient the delivery of the pulsed radiation from the optical source **202**. The imaging system can be incorporated into the system controller **215**. The transducer **206** can be a piezo type transducer as used in the above-described commercially-available ultrasound machines or a cMUT (capacitative Micromachined Ultrasonic Transducer), see X. Jin, I. Ladabaum, B. T. Khuri-Yakub. "The Microfabrication of Capacitive Ultrasonic Transducers", J. Microelectromechanical Systems vol. 7, pp. 295-302, September 1998. and U.S. Pat. No. 6,262,946 to Khuri-Yakub et al, both of which are incorporated herein by reference. Using the cMUT will allow a very compact 2-D array to be made. Such compact arrays are very important for ring-shaped transducers such as that shown in **FIGS. 12C-12D** for the trans-tracheal/trans-esophageal applications.

[**0092**] Using an array or other beam-forming transducer one can steer the ultrasound from artery to vein using phase, and alternately modulate each one, allowing a direct calibration of the optical signal. For example one can steer the beam from internal jugular to carotid artery, alternatively sampling 100% oxygen saturated blood and the venous blood with reduced saturation. The ultrasound imaging system can also be used to derive the width of the arteries and veins, and the blood flow velocity using Doppler shift of the scattered ultrasound. Such a measurement can provide an estimate of the cardiac output that can be compared to cardiac output as derived from the use of the apparatus **200**. This adjunct measurement will have additional diagnostic value as discussed above for the diagnosis of shunts, septic and cardiogenic shock etc.

[**0093**] Once the ultrasound transducer **206** and launch optics **204** are aligned with respect to the targeted vessels, the array of transducers in the ultrasound imaging system will all be fired, with appropriate phase delays, with a burst of energy to deliver radiation pressure at the focus as determined by the phase delays. The focus of the acoustic signal can be chosen to be inside the vessel acting on the blood cells, or on the side walls of arteries. The radiation pressure associated with the acoustic pulse which is equal to the acoustic intensity divided by the speed of sound in the medium, will act to impart a movement on the cells or arterial walls on which it acts. The use of radiation pressure (alternatively "radiation force") to induce motion in a target which is then detected by conventional ultrasound techniques has been described by Nightingale et al "Acoustic Radiation Force Impulse Imaging: In Vivo Demonstration of Clinical Feasibility", *Ultrasound in Medicine and Biology,* 28(2): 227-235, (2002) and in U.S. Pat. No. 6,371,912 to Nightingale et al, both of which are incorporated herein by reference. Embodiments of the present invention are superior to this technique in that they will permit functional (oxygenation) information to be derived from the target,

whereas in the aforementioned prior art only mechanical information (stiffness, elasticity etc) is derived.

[0094] In this fashion, the optical signal, which relates to the oxygen content in the blood cells in the target volume, will be modulated at the frequency at which the radiation pressure pulse is applied, WRPM. For instance, using a 7.5 MHz imaging system, one can use a burst of say 10 cycles at any repetition rate up to around 750 kHz as determined by the physical and mechanical properties of the target and the experimental implementation. It may be possible to tune the interpulse spacing (the repetition rate) in the tone burst to resonantly modulate the target depending on its elastic properties. It may also be possible to tune the ultrasound fundamental frequency to optimize its interaction with the desired target (blood cells, vessel walls etc). In this manner the detector **210** may detect only those photons which have interacted with the desired target **201**.

[0095] The optical source **202** may be configured to deliver the temporally correlated groups of photons at a repetition rate of between about 100 kHz and about 500 MHz, preferably between about 1 MHz and about 250 MHZ, more preferably between about 10 MHz and about 200 MHz. The groups of photons may be in the form of pulses having pulse widths in the range of about 1 picosecond to about 1 nanosecond, preferably, about 1 to 100 picoseconds, more preferably about 5 to 50 picoseconds. The photons may be characterized by wavelengths between about 650 nm and about 1175 nm, preferably between about 650 nm and about 930 nm or between about 1020 nm and about 1150 nm.

[0096] The optical source **202** provides temporally correlated photons at two or more different wavelengths. For example radiation from a pulsed laser may be incident on a device that converts radiation at the fundamental frequency of the laser into a pair of photons at two different predetermined frequencies. Such a device could be a nonlinear crystal causing Spontaneous Parametric Down Conversion (SPDC) as for example described by Shi and Tomita, "Highly efficient generation of pulsed photon pairs with bulk periodically poled potassium titanyl phosphate", J. Opt. Soc. Am. B. 21(12) 2081-2084 (2004), or a highly non-linear fiber source as described by Rarity et al., "Photonic crystal fiber source of correlated photon pairs", Opt. Exp. 13(2), 534-544 (2005).

[0097] Alternatively the optical source **202** may include a non-linear crystal phased matched to act as an optical parametric oscillator (OPO) to provide a temporally correlated photon pair. An OPO takes a fundamental electromagnetic wave at frequency ω_{P1} and converts it to two new frequencies called the signal and idler, ω_{SIG} and ω_{IDL} related by the equation $\omega_{P1}=\omega_{sig}+\omega_{idl}$

where the signal and idler waves are emitted in temporal coincidence.

[0098] The OPO may be driven by the second harmonic of a pulsed laser operating at a fundamental frequency ω_{P1} to create two new frequencies called the signal and idler, ω_{SIG} and ω_{IDL} related by the equation

$$2\omega_{P1}=\omega_{sig}+\omega_{idl}$$

where $2\omega_{P1}$ is the second harmonic of the fundamental frequency. For example the drive laser may be a mode-locked or Q-switched Nd:YAG laser operating at 1064 nm, giving a second harmonic wave at 532 nm. This wave in turn is used to drive the OPO. In this manner three clinically useful, temporally coincident photon waves at 1064 (ω_{P1}), 1030 (ω_{sig}) and 1100 (ω_{idl}) may be generated. The nonlinear crystal may be selected from a variety of substances, for example BBO, LBO, KTP, KTA, RTP, or periodically poled materials such as periodically poled lithium Niobate (PPLN), periodically poled stoichiometric lithium tantalate (PP-SLT) and the like. Such materials are described, e.g., in the freeware program SNLO distributed by Sandia National Laboratories, Albuquerque, N. Mex.

[0099] By way of example, the optical source **202** may include a pulsed solid state laser, for example a picosecond mode-locked laser such as the picoTRAIN™ series compact, all-diode-pumped, solid state picosecond oscillator manufactured by High-Q Lasers of Kaiser-Franz-Josef-Str. 61 A-6845 Hohenems Austria. The source may also be a mode-locked fiber laser, such as the picosecond version of the Femtolite™ D-200 from IMRA America Inc., Ann Arbor Mich. 48105. Alternatively, a picosecond pulsed diode such as the PicoTA amplified picosecond pulsed laser diode heads manufactured by Picoquant, of Berlin, Germany, may be used as the optical source **202**. The optical fibers **205** coupling the optical source **202** to the launch optics **204** may be, e.g., single mode fiber optic, such as the P1-980A-FC-2—Single Mode Fiber Patch Cable, 2 m, FC/PC manufactured by Thorlabs, Inc. of Newton, N.J. Radiation coupled from the optical source **202** to the target **201** via the launch optics **204** is used, e.g., to illuminate the lumen of a selected blood vessel with pulses of radiation at two or more different wavelengths carefully chosen to have deep penetration into tissue, to have differing affinities for oxy- and deoxy-hemoglobin, or for oxy-hemoglobin and met-hemoglobin, but to have substantially similar scattering cross-sections and anisotropy parameters.

[0100] Some of the radiation scatters from the target **201** and is collected by the collecting optics **208** and/or detector **210**. By detecting pairs or multiplets of photons at different wavelengths returning from the target tissue in substantial temporal coincidence, it can be inferred that the coincident photons have traveled approximately the same path length in the tissue. This is the main difference between making measurements in clear transparent media where the Beer-Lambert law may be presumed to apply, and making measurements in turbid media where elastic scattering causes a substantial and generally indeterminate pathlength increase, as discussed by Okui and Okada, "Wavelength dependence of cross-talk in dual-wavelength measurement of oxy- and deoxy-hemoglobin", J. Biomed. Opt. 19(1), 011015 (2005).

[0101] The detector is coupled to a filter **212** that selects coincident photon signals having modulation at the radiation pressure modulation frequency or a harmonic thereof. The filter **212** may be coupled to the display **214**, e.g. a CRT screen, flat panel screen, computer monitor, or the like, that displays the results of the aforementioned process in a manner readily interpretable, e.g., in the form of text, numerals, graphical symbols or images.

[0102] By detecting arrival rates of pairs or multiplets of photons at the frequency of the radiation pressure modulation or a harmonic of the radiation pressure modulation frequency, one can infer that these photons interacted with

the radiation-pressure-modulated target **201**. If the target **201** contains the oxygenated or deoxygenated forms of hemoglobin (Hb), the detected pair or multiplet coincidence rate will be altered depending on how the wavelengths were selected. The extent to which the detection rate is altered can be correlated to the oxygenation level of the target or to the pH in the target. The met-hemoglobin absorption spectrum is dependent on pH as shown in Zijlstra et al., "Visible and Near Infrared Absorption Spectra of Human and Animal Haemoglobin, 1st ed. Utrecht: VSP Publishing; 2000, page 62. Thus a non-invasive probe of met-Hb absorption may be used to probe the pH of the structure being targeted.

[**0103**] There are many possible configurations for the optical source **202** of **FIG. 2A**. For example, **FIG. 3** is a schematic diagram of a three-wavelength pulsed optical source **300** that emits three laser pulses at the three wavelengths with temporal coincidence. This could be the OPO source described above. Alternatively the source **300** generally includes a pulsed laser **302**, a seed source **304**, and a highly non-linear fiber (HNLF) **306**. Optics, **308** such as one or more lenses couple pump radiation at a drive frequency ω_p to the HNLF **306**. A 2×2 coupler **310** couples seed radiation at a frequency ω_s from the seed source **304** into the HNLF **306**. When ω_p and ω_s are properly chosen, the HNLF **306** acts as an optical parametric amplifier (OPA) that produces three temporally correlated electromagnetic waves at three frequencies: pump radiation at ω_p, amplified seed radiation at ω_s and idler radiation at an idler frequency ω_{idl} given by:

$$\omega_{idl}=2\omega_p-\omega_s.$$

[**0104**] For example, if ω_p corresponds to a vacuum wavelength of 1064 nm and ω_s corresponds to a vacuum wavelength of 1100 nm, ω_{idl} corresponds to a vacuum wavelength of about 1030 nm.

[**0105**] The fiber **306** preferably has a non-linearity that is high enough to allow non-linear optical effects to occur efficiently in a reasonable length of fiber, and where the non-linearity is sufficiently fast to create the required temporal synchronization between the pump, seed and idler waves. Such fibers may be obtained from Crystal Fibre of Birkenrød, Denmark, for example the NL-5.0-1065 type. The non-linear optics underlying the conversion have been described by for example, Ho et al., "Narrow-linewidth idler generation in fiber four-wave mixing and parametric amplification by dithering two pumps in opposition of phase", J. Lightwave. Tech. 20(3), 469-476 (2002), which is incorporated herein by reference. The drive frequency ω_p may be provided by a high repetition rate mode-locked picosecond laser, such as the picoTRAIN™ series compact, all-diode-pumped, solid state picosecond oscillator manufactured by High-Q lasers of Kaiser-Franz-Josef-Str. 61 A-6845 Hohenems Austria or a mode-locked fiber laser, such as the picosecond version of the Femtolite™ D-200 from IMRA America Inc., Ann Arbor Mich. 48105.

[**0106**] In the source **300** the seed source **304** may be a distributed feedback (DFB) or DBR (Distributed Bragg Reflector) laser, for example the EYP-DBR-1063-00100-2000-SOT02-0000 diode laser manufactured by Eagleyard Photonics, Berlin Germany. There are a number of different possible configurations for the pulsed laser **302**. Generally, the pulsed laser **302** should be capable of providing picosecond pulses of pump radiation to the HNLF **306**. **FIG. 4** is a schematic diagram of an all-electronic optical source **400** of picosecond pulses which could be used as the pulsed laser **302** of **FIG. 3**. The source **400** generally includes a diode laser **402** an electro-optic modulator (EO) **404** a Faraday isolator **406** and a doped fiber amplifier **408**. The diode laser **402** provides radiation at ω_p which is modulated by the EO modulator **404** to create weak picosecond radiation pulses **401**, which are coupled to the fiber amplifier **408**. The Faraday isolator **406** transmits pulses to the fiber amplifier **408** and blocks radiation from being reflected back towards the EO modulator. A fiber pump source **410** provides fiber pump radiation (e.g., at a vacuum wavelength of 980 nm) to the cladding or core of the fiber amplifier **408**. The fiber amplifier may include a dump for the pump laser so that fiber pump radiation does not oscillate through fiber amplifier **408**. The amplifier **408** amplifies the weak pulses **401** to create amplified pulses **403** that can be fed to the HNLF **306**.

[**0107**] By way of example, the diode laser **402** is a continuous wave (CW) tunable DFB or DBR diode laser, such as the EYP-DBR-1063-00100-2000-SOT02-0000 diode laser manufactured by Eagleyard Photonics, Berlin Germany The EO modulator **404** may be a Model 4853 6.8/9.2-GHz Modulator from New Focus (Bookham) San Jose, Calif. The Faraday isolator **406** may be a model 411055 from Electro-Optic technology, of Traverse City, Mich. The fiber amplifier **408** may be doped with Ytterbium or Neodymium, such as the DC-225-22-Yb made by Crystal Fibre (Birkerod, Denmark).

[**0108**] The fiber pump may for example be a model 4800, 4 W, Uncooled, Multi-Mode pump module from JDS Uniphase, of San Jose, Calif. As discussed above, the optical source **202** may include produce the correlated photons by optical parametric oscillation. **FIG. 5** is an example of such an optical source **500**. The source **500** generally includes a pulsed laser **502**, a second harmonic generator (SHG) **504**, a dichroic mirror **506** and an optical parametric oscillator (OPO) **508**. The pulsed laser produces pump radiation at a frequency ω_p. The second harmonic generator interacts with the pump radiation to produce second harmonic radiation at double the frequency of the pump radiation, i.e., at $2\omega_p$. The SHG **504** may be less than 100% efficient at doubling the frequency of the pump radiation. The dichroic mirror **506** deflects pump radiation that makes it through the SHG **504**. In the OPO **508**, some of the second harmonic radiation is converted to signal and idler radiation, respectively at frequencies ω_{sig} and ω_{idl} that are related by:

$$2\omega_p=\omega_{sig}+\omega_{idl}$$

[**0109**] The pulsed laser **502** may be of any of the types described above. The second harmonic generator may be a non-linear crystal of any of the types described above phased matched for second harmonic generation. The OPO **508** may be a non-linear crystal of any of the types described above phased matched for optical parametric oscillation. The source **500** has the advantage of being tunable by virtue of the OPO phase matching. The phase matching is typically tuned by adjusting e.g., the angle of the non-linear crystal used in the OPO, or by changing its temperature. Alternatively the poling period may be adjusted in periodically poled materials to phase match at different wavelengths.

[**0110**] Radiation pulses from the source **200** may be affected by traveling through tissue. For example, **FIG. 6** is

a schematic diagram of the signal expected at the tissue boundary TB shown in **FIG. 2B**. Injected pulses of radiation at frequency WINJ with a short pulse widths (e.g., about 1 to 50 picoseconds) are delivered into the body **201** at the tissue boundary TB. An injected pulse interacts with tissues in the body and emerges as a signal pulse at an optical frequency WSIG, which may be slightly different from ω_{INJ} as a result of interaction with the ultrasound pulse. However any frequency shift occurring as a result of interaction between the optical pulses and the ultrasound pulses will be insignificant compared to the natural linewidth of the pico-second laser pulse as a result of the time-bandwidth constraint which derives directly from the Heisenberg Uncertainty Principle. Furthermore detection of this ultrasound-induced frequency shift is not required in the proposed embodiments of the invention, distinguishing this technique from those in the prior art. The signal pulse is typically broadened (e.g., to a pulse width of several hundred pico-seconds to several nanoseconds) compared to the injected pulse due to the random-walk nature of photon propagation in turbid media, as shown by Turner et al., "Complete-angle projection diffuse optical tomography by use of early photons", Opt. Lett. 30(4), 409-411 (2005). This random walk increases the effective pathlength considerably. The time at which the photon arrives at the tissue boundary may be related to its approximate pathlength through mathematical relationships, for example the diffusion approximation or the Transport Equation.

[**0111**] The pulse spreading described above must be taken into account in time-gated detection of the signal pulse. One possible approach to taking such pulse spreading into account utilizes a technique referred to herein as time gated upconversion. FIG. **7** is a schematic diagram illustrating the principle of time gated upconversion. The broadened signal pulse at WSIG emerging from the tissue boundary TB with a pulse width ΔT of, e.g., a few nanoseconds, is mixed with a short mixing pulse (e.g., pulse width δt of order several picoseconds) of radiation at an optical frequency ω_{P2}. A master oscillator or a secondary slave oscillator may provide the short mixing pulse at ω_{P2}. The mixing takes place in an upconverter such as a fiber OPA or a mixing crystal. Mixing can only occur when the two pulses are temporally and physically overlapped, so by strobing the mixing pulse through the emerging signal pulse it is possible to time gate the signal that is to be detected. This upconversion process may be accomplished in a manner that is highly efficient as described by Langrock et al., "Sum-frequency generation in a PPLN waveguide for efficient single-photon detection at communication wavelengths", Stanford Photonics Research Center Annual Report (2003) D-19-D-21, which is incorporated herein by reference.

[**0112**] **FIG. 8** is a schematic diagram illustrating of an alternative optical signal generation and detection apparatus **800** for use with embodiments of the present invention. The apparatus **800** includes first and second pulsed optical sources **801**, **802** that respectively produce pulsed optical signals at optical frequencies ω_{P1} and ω_{P2}. The first source **801** serves as a master oscillator for timing purposes and its output is used in one of the aforementioned processes to create two or more pulses of light at two or more wavelengths selected per the criteria described above. A timing signal ϕ is derived from the first source **801** and used to trigger the second source **802**, which operates at substantially the same pulse repetition rate as the first source **801**, but with an adjustable delay (phase angle) between the two pulse trains. The pulse train from the second source **802** is mixed in an upconversion apparatus **804** with the emerging signal at optical frequency ω_{SIG} from a tissue boundary **807** and the time delay between the two sources is adjusted to temporally gate the resulting signal, which is detected at a detector **806**. This permits background-free, time-gated analysis of the emerging signal. The resulting upconverted signal may have an optical frequency ω_{UC} of $\omega_{P2}+\omega_{SIG}$ or $2\omega_{P2}-\omega_{SIG}$ depending on the nature of the upconversion apparatus **804**. The two signals may be mixed, e.g., using a relay fiber **808** coupled to collection optics **810** and a 2×2 coupler **812** coupled to the relay optics and the second source **802**.

[**0113**] In some embodiments, the upconversion apparatus **804** may include a local oscillator, e.g., a laser for time-gated upconversion. For example, as depicted in **FIG. 9A**, the signal pulse at WSIG and mixing pulse at ω_{P2} are combined, e.g., using a 2×2 coupler **902**. Upconversion as described above may then be used to create a new signal photon wave at either $\omega_{P2}+\omega_{SIG}$ or $2\omega_{P2}-\omega_{SIG}$. A local oscillator laser **904** produces a pulsed wave at an optical frequency ω_{LO} and a repetition rate correlated to the ultrasound tone burst that is mixed in a mixing stage **906** with the new signal pulses before detection, generating a composite wave at optical frequency ω_{UC} given by either $(\omega_{P2}+\omega_{SIG}+\omega_{LO})$ or $(2\omega_{P2}-\omega_{SIG}+\omega_{LO})$ that is coupled to the detector **210**. The mixing stage **906** may be a waveguide of for example a PPLN or PP-SLT, or a crystal of KTP or other material with high optical non-linearity. In this manner a signal may be generated that is temporally selected for an effective pathlength in the tissue. Upconverting the signal from the near-IR (around 1 micron) to the visible (400-700 nm) in this manner allows the use of silicon-based detector technology that has several advantages over InGaAs technology as discussed by Langrock et al. For example benefits include greater receiver sensitivity and lower dark counts from the detector.

[**0114**] The signal may be further selected for a temporal relationship to the modulating ultrasound tone burst from the transducer **206** by triggering the local oscillator **904** with an appropriate reference signal from the ultrasound source **207**. For example by triggering the local oscillator **904** at twice the repetition rate of the tone burst, one can make a direct on/off comparison between the signal coming back from the tissue in the presence of, and absent the effect of the mechanical modulation.

[**0115**] Alternatively, the upconversion apparatus **804** may provide background free time gated amplification of the signal pulse. This may alternatively be accomplished using fiber Optical Parametric Amplification, e.g., as depicted in **FIG. 9B**. In an OPA-based background-free time-gated upconversion detector **910**, optical signals at optical frequency ω_{SIG} emerging at a tissue boundary **907** are coupled into a relay fiber **912** by collection optics **914**. The emerging optical signals at ω_{SIG} are then mixed (e.g., using a 2×2 coupler **916**) into a Highly Non-Linear Fiber (HNLF) **918** with a drive pulse at optical frequency ω_{P2} from a pump source **920**. The drive frequency ω_P may be provided by a high repetition rate mode-locked picosecond laser, such as the picoTRAIN™ series compact, all-diode-pumped, solid state picosecond oscillator manufactured by High-Q lasers of Kaiser-Franz-Josef-Str. 61 A-6845 Hohenems Austria or a mode-locked fiber laser, such as the picosecond version of

the Femtolite™ D-200 from IMRA America Inc., Ann Arbor, Mich. 48105. The signal at WSIG is converted to a detected signal at WDET by an Optical Parametric Amplification (OPA) process in the fiber **918**. The OPA process creates the detectable signal WDET, e.g., through a four-wave mixing process described by:

$$\omega_{DET}=2\omega_{P2}-\omega_{SIG}$$

[**0116**] Since the upconversion process only happens when the drive pulse at ω_{P2} is present the upconversion can be time gated. It should be noted that the frequency WDET of the detected signal is higher than either the signal or drive frequencies respectively. This means that the signal detected at frequency ω_{DET} will be substantially free of contaminating signals, e.g., from tissue autofluorescence (which always occurs to longer wavelength than the excitation wavelength), inelastic scattering internal to the fiber (Raman scattering for example) which is also always to longer wavelength than the fundamental, and other non-linear inelastic processes. By delaying the onset of the mixing or upconversion pulse used in the detection stage (**802**, **920**), and then lengthening it in time using for example the all-electronic source shown in **FIG. 4**, we may adjust the detector to:

[**0117**] a) eliminate signal from photons which could not have interacted with the target, and

[**0118**] b) include all possible contributions from photons which could have interacted with the target. This is equivalent to applying a Heaviside (step) function to the detected signal.

[**0119**] The aforementioned detection method may be more efficient compared to slowly moving a short upconversion/mixing pulse through the temporally broadened signal (**FIGS. 6 and 7**) by varying the delay as this latter technique implicitly selects a small subset of the photon trajectories, ignoring other possible contributions.

[**0120**] The detected signal may be amplified in a time gated manner by selecting a delay between the signal at ω_{P1} from the tissue boundary to be amplified and the drive pulse at ω_{P2}. The drive pulse may be part of the beam from a master laser or may preferably be produced by a second pulsed laser operating at similar repetition rate and pulse-width to the master oscillator. The amplification of a particular segment of the returning signal may also be selected by overlapping the two signals in time using a variable delay line. Using this technique, the signal at ω_{P1} will also be amplified by gains of for example 10-60 dB, as described by Ho et al. and references therein, allowing very weak signals to be detected.

[**0121**] Other background-free time-gated upconversion detection schemes can be implemented. For example **FIG. 10** depicts an alternative background-free time-gated upconversion detector **1000**. In the detector **1000** a master oscillator **1002** produces a first master oscillator pulse at an optical frequency ω_{P1}. The first master oscillator pulse is used to generate temporally correlated photons (e.g., as described above) that are scattered from a target tissue **1003** within a body **1001** to provide a signal. Signal photons at an optical frequency WSIG emerging from a tissue boundary **1007** are coupled into a fiber **1004**, e.g., via relay optics **1006**. After amplification in a doped section of the fiber **1004**, the signal photons are mixed (e.g., using a 2×2 coupler **1005**) in a non-linear crystal **1008** with a second time-delayed master oscillator pulse having an optical frequency ω_{P2}. The non-linear crystal **1008** is phase matched for frequency mixing of the signal photons and the second oscillator pulse. The resulting upconverted signal is characterized by an optical frequency ω_{UC} given by:

$$\omega_{UC}=\omega_{P2}+\omega_{SIG}.$$

[**0122**] A temporal delay between the first and second oscillator pulses is adjusted such that the time evolution of the signal emerging from the tissue boundary can be probed. This allows early arrival photons, which could not have interacted with the target by virtue of their arrival time, to be gated out.

[**0123**] It should be understood that the signals referred to above generally include two or more signal photons of different wavelengths that are detected in coincidence. Coincidence detection of the two signal photons can be accomplished by balanced photoreceivers, for example New Focus (Bookham) model 1807 and 1817, San Jose, Calif. The wavelengths of interest can be isolated by interference filters such as the RazorEdge™ and MaxLine™ Laser and Raman filters from Semrock, Inc. of Rochester, N.Y. Alternatively coincident photon pairs or multiplets can be detected using high speed analog and digital electronics, for example time correlated single photon counting equipment such as the SPC-134 from Becker and Hickl GmbH, Berlin, Germany, or boxcar integrators such as the Model SR200 Boxcar from Stanford Research Systems, Sunnyvale, Calif.

[**0124**] The time-gated amplified signal is analyzed to reveal the component being modulated at the radiation-pressure modulation frequency ω_{RPM}. This can be accomplished using lock-in detection using for example a lock-in amplifier (e.g., a Stanford Research Systems SRS Model 844) as the filter **212** in **FIG. 2A**.

[**0125**] The remaining signal by virtue of the above generation and detection techniques must have:

[**0126**] a) Interacted with the target structure being modulated by the radiation pressure field,

[**0127**] b) Been generated by photons at each of the two or more selected wavelengths which traveled approximately the same path length from the launch site, through the target being modulated, and back to the detector.

[**0128**] The two or more wavelengths of the correlated photons provided by the optical source **202** may be selected to have different affinities for the various states of hemoglobin (oxy-Hb, met-Hb, deoxy-Hb). The arrival of correlated photons at the different wavelengths therefore can be interpreted to indicate for example the oxygenation level or pH of the blood in the modulated target structure. For example, if one radiation-pressure modulates a blood vessel and its contents, and illuminates the area with two wavelengths of light, one selectively absorbed by oxy-hemoglobin and one substantially less selectively absorbed, the arrival rate of correlated photon pairs will be higher if they traverse a radiation-pressure-modulated vascularized area containing high levels of deoxy-Hb (because one of the pair will be selectively more absorbed in areas of higher oxygen saturation). By way of example 1030-nm radiation is absorbed more strongly by oxy-hemoglobin than 1064-nm

radiation. Similarly, 1100-nm is more strongly absorbed by oxy-hemoglobin than 1064-nm radiation. These three wavelengths may be conveniently generated as shown above. They also have the added attraction of having substantially similar elastic scattering coefficients, which will lead to a simplification in calculation of the effective pathlength each traverses. They also have substantially similar absorption in water, leading to a simplification in assessing the potential contribution for error in the measurement caused by non-hemoglobin related absorption of the probe wavelengths.

[0129] **FIG. 11** is a graph showing the absorption of oxyhemoglobin (diamonds) and water (solid curve) in the range 700-1200 nm, the nominal variation of the scattering coefficient as a function of wavelength (squares), and the expected difference in absorption between an artery with fully oxygen-saturated blood (SaO_2=100) and a representative vein where the oxygen saturation is 55% (asterisks—Delta AV 55). The points at which the difference curve crosses Y=0 are known as isosbestic points. There are two isosbestic points in the absorption spectra of oxy-hemoglobin and deoxy-hemoglobin, one around 810 nm and one around 1135 nm. At these wavelengths the absorption of blood in the vessel is independent of oxygen saturation. These points are known to be useful for internal reference calibration, for example to exclude the effects of volume changes in the absorption resulting from pulsatile flow from the heart.

[0130] The wavelength range 1025-1135 nm is characterized by having reduced absorption as the venous oxygen saturation decreases. This means that the signal derived as described in the embodiments of the present invention will increase with decreasing saturation in this wavelength range. The gradient of the absorption change with respect to oxygen saturation at the 1135 nm isosbestic point is also very steep, much more so than at 810 nm, making it of significant potential value. Around this wavelength range, we may make sensitive measurements at two or more wavelengths on each side of the isosbestic point. The sign of the absorption change will change from one side of the isosbestic point to the other.

[0131] The scattering function in **FIG. 11** varies as the inverse fourth power of the wavelength. This means that longer wavelengths (for example from 1025 nm-1150 nm are not as affected by scattering as shorter wavelengths from for example 700-930 nm). This translates to a smaller increase in the effective pathlength resulting from elastic scattering. The scattering function in the 1025 nm-1150 nm also does not vary significantly, indicating that if we probe the target using wavelengths in this range we may regard scattering as a secondary effect and model it as a perturbation. This is not true in the 700-930 nm range, where the scattering function varies by more than a factor of three.

[0132] The wavelength range 1025-1150 nm has rich structure in the difference spectrum, has much lower scattering than the visible and near-IR wavelength ranges, and has relatively modest water absorption. This region offers several convenient and readily available laser sources (Nd:YAG, Yb:Fiber lasers) which are known from dermatology to have excellent penetration properties into tissue.

[0133] It is possible to bias the selection of wavelengths to enhance the diagnostic value of the measurement. For example, fetal oxygenation levels are known to be substantially lower than the conjugate maternal levels. Thus, the selection of wavelengths can be biased to probe the fetus preferentially over the mother. Furthermore, if it is desired to detect the pH of the blood in the ultrasound-modulated target, one can inject probe photons at a frequency known to be selective for met-hemoglobin absorption. For example in the wavelength range from 800-1350 nm met-hemoglobin has much stronger absorption than either oxy-hemoglobin or deoxy-hemoglobin as shown in Kuenster J. T and Norris K. H. "Spectrophotometry of human hemoglobin in the near infrared region from 1000 to 2500 nm", J. Near Infrared Spectrosc. 259-65 (1994). The wavelength range 1000-1300 nm and especially from 1100-1250 nm is particularly sensitive to met-hemoglobin absorption. The absorption spectrum of met-hemoglobin is known to be sensitive to pH, as shown for example in Zijlstra et al., "Visible and Near Infrared Absorption Spectra of Human and Animal Haemoglobin, 1st ed. Utrecht: VSP Publishing; 2000, page 62, and one may thus infer the pH of the target from the coincidence arrival rate of appropriately chosen photon pairs or triplets or higher multiplets.

[0134] Embodiments of the present invention are distinguishable from Diffuse Optical Tomography, where the signal detected has subsumed within it all possible absorbers in the path of the field and no attempt is made to localize the absorber location. The present technique is further distinguished from the various practices of ultrasound-tagged optical spectroscopy because it does not detect small frequency shifts or speckles on the emerging photons. Instead, the present technique detects the modulation imparted by physical motion of the target, which in turn affects the optical absorption cross-section. The present invention is insensitive to the very short speckle decorrelation time caused by blood flow in the vessel, which would otherwise severely complicate the detection of modulated photons in interferometric or frequency-domain techniques. The present modulation technique occurs at much higher frequency than other motion artifacts, for example pulsatile flow from the heart beat, allowing it to be decoupled in the signal analysis. This is important when, for example, the technique is used to perform trans-abdominal fetal oxygenation measurements where it is desirable to distinguish the material and fetal oxygenation systems.

[0135] There are many possible designs for sensors that may be used in embodiments of the present invention. For example, **FIG. 12A** depicts an example of a sensor **1200** for transdermal measurements. The sensor **1200** generally includes a substrate **1202**, which may be made of a flexible plastic or similar material. A thin ultrasound transducer **1204** is mounted on or embedded within the substrate. The transducer **1204** receives power from an ultrasound transmitter and sends return signals through a cable **1205**. Optical signals are transmitted and received through an optical fiber bundle **1206** containing launch and receive fibers terminated with coupling optics **1208**. The launch/receive fibers and coupling optics **1208** may be mounted to or embedded with the substrate **1202**, proximate the transducer **1204**. The launch/receive fibers may be used to both transmit and receive optical signals. The fibers and coupling optics **1208** are distributed in a more or less planar fashion. This type of sensor may be used for transdermal measurements.

[0136] **FIG. 12B** depicts an alternative sensor **1210** that is a variation on the sensor shown in **FIG. 12A**. A transducer

1214, launch fibers and optics **1218**, collection fibers and optics **1219** are mounted to or embedded within a substrate **1212** in a more or less planar fashion. In this example, the transducer **1214** is disposed between the launch fibers and the collection fibers. The transducer **1214** receives power from an ultrasound transmitter and sends return signals through a cable **1215**. The launch fibers and optics **1218** receive optical radiation from a source via a fiber bundle **1216**. The collection fibers and optics **1219** transmit signals to a detector via another fiber bundle **1217**.

[**0137**] Other sensor configurations may be useful for trans-esophageal or trans-tracheal measurements. For example, **FIGS. 12C-12D** depict a sensor **1220** that may be inserted into the esophagus or the trachea. The sensor **1220** includes a ring-shaped substrate **1222** made of a bio-compatible material. Two or more ultrasound transducers (or transducer arrays) **1224** are mounted to the substrate **1222**. The transducers are arranged to emit ultrasound in an outward fashion as indicated by the arrows depicted in **FIG. 12D**. The transducers receive and transmit signals through a cable **1225**. Arrays of launch/receive fibers **1228** are disposed on or embedded within the substrate **1222** proximate the transducers **1224**. The launch/receive fibers **1228** receive and/or transmit optical signals via a fiber bundle **1226**. The ring-shaped sensor **1220** may be placed in the esophagus. Alternatively, the sensor **1220** may be placed in the left or right bronchus, through the trachea, e.g., at the end of a tube that provides oxygen to the patient. Alternatively, the sensor **1220** may be implanted into the patient's trachea and providing a read out to small portable monitoring unit for continuous ambulatory monitoring.

[**0138**] Use of the sensors and apparatus described above for monitoring of blood oxygenation can be accomplished in a variety of different ways.

[**0139**] For example, **FIG. 13** illustrates a simple case of transdermal measurements of oxygenation in the interior or exterior jugular vein of a patient. A sensor **1300**, e.g., of the type depicted in **FIG. 12A** or **FIG. 12B** may be placed against the patient's neck in the vicinity of the spot marked with an X. The sensor **1300** may be coupled to a remote unit of the type described above with respect to **FIG. 2A**. Venous oxygen saturation in the jugular vein can be measured using the ultrasound/optical technique described above while arterial oxygenation can be measured using standard pulse oximetry. Cardiac output can then be calculated from the Fick principle as described above. Alternatively arterial saturation may be measured by radiation-pressure modulating the carotid artery instead of the internal jugular vein. Although a single sensor **1300** is depicted on one side of the of the neck, two or more such sensors (or one large sensor) may be placed on the dermis simultaneously on the left and right side of the neck over both internal jugular veins.

[**0140**] There are a number of different targets within the body that are suitable for blood oxygen monitoring using embodiments of the present invention. These can be understood with reference to the anatomical diagrams of **FIG. 14** and **FIG. 15**. For example, both right and left internal jugular veins are potential targets as described above. Measuring both simultaneously would probably be a superior method. **FIG. 16** illustrates three other possible sensor placements that may be used in conjunction with embodiments of the present invention. First, a sensor A may be inserted using a bronchoscope between two ribs (an intercostal space) next to the sternum. In this case the sensor could be positioned right up against the pulmonary artery (probably away from the aorta). This is the optimum place to make the measurement of venous oxygen saturation assuming that there are no defects in the heart. For example, if there is an acquired ventricular septal defect, in which blood is short-circuited from left ventricle to right ventricle, the oxygen saturation of the pulmonary artery is abnormally high (e.g., about 80, whereas the incoming blood from the jugular vein may be around 50). Such a condition would result in a false reading for the cardiac output measured using the Fick principle. However an alternative probe site on the internal jugular vein gives an adjunct measure of the cardiac output independent of heart defects. So the two measurements would be complimentary.

[**0141**] Alternatively, as shown in **FIG. 16**, a sensor B may be placed in the esophagus. The sensor B may be of the planar type depicted in **FIG. 12A** or **FIG. 12B** or the ring type depicted in **FIGS. 12C-12D**. A sensor C may also be placed in the left bronchus via the trachea. These two probes will also sample the pulmonary arteries. The trans-esophageal probe will sample the right pulmonary artery. The trans-tracheal (bronchial) sensor C will potentially be able to simultaneously probe the oxygen saturation in both the left pulmonary artery (the venous saturation) and the descending thoracic aorta (arterial saturation). This would eliminate the need for external pulse oximetry to measure the arterial oxygen saturation. Positioning of a sensor D within the left bronchus or a sensor E within the right bronchus is illustrated in the dorsal pull-away view of **FIG. 17**. Such trans-tracheal sensors may be the ring-shaped sensor of the type depicted in **FIGS. 12C-12D**. The sensors A, B, C, D, E may be coupled to a remote unit of the type described above with respect to **FIG. 2A**. Optical and ultrasound signals can probe the chemistry of the cardiovascular system in the manner described above.

[**0142**] Embodiments of the present invention also have application to monitoring of neonatal blood oxygenation. Monitoring of neonatal blood oxygenation is particularly useful in the cases of neonatal heart defects as illustrated in **FIGS. 18A-18C**. **FIG. 18A** depicts an example of a normal heart. Certain patients exhibit a heart defect known as Patent Ductus Arteriosus (PDA). As illustrated in **FIG. 18B**, PDA is the persistence of a normal fetal structure (indicated by the arrow) between the left pulmonary artery and the descending aorta. Persistence of this fetal structure beyond 10 days of life is considered abnormal. Other patients exhibit a defect known as Patent Foramen Ovale (PFO). As shown in **FIG. 18C**, PFO is a persistent opening in the wall of the heart (indicated by the arrow) which did not close completely after birth. The opening is required before birth for transfer of oxygenated blood via the umbilical cord. This opening can cause a shunt of blood from right to left, but more often there is a movement of blood from the left side of the heart (high pressure) to the right side of the heart (low pressure). Normally this opening closes in the first year of life; however in about 30% of adults a small patent foramen ovale is still present. Diagnosis of both PDA and PFO may be helped by measurement of venous oxygen saturation.

[**0143**] In newborn infants (neonates) the distance across the thorax may be small enough that in addition to trans-esophageal and trans-tracheal, and trans-dermal for the

internal jugular, it may be possible to operate the diagnostic apparatus transdermally with a sensor placed directly on a neonate's chest surface. The sensor, e.g., of the planar type depicted in **FIGS. 12A-12B**, is placed proximate the heart or a blood vessel of interest. The target area is a neonatal cardiovascular system. As illustrated in the cross-sectional diagram of **FIG. 19** the measurement may be made in either a reflection mode or trans-illumination mode (in one side—out the other). In the reflection mode, optical signals are transmitted and received via a common sensor **1902**. In the trans-illumination mode a transmitter unit **1904** sends optical signals through an infant's thorax. Scattered photons of radiation from these signals are collected by one or more sensors **1906**, **1908** that are positioned to probe radiation scattered from particular structures within the neonatal anatomy such as the pulmonary artery. The sensors **1906**, **1908** may be coupled to a remote unit of the type described above with respect to **FIG. 2A**. Optical and ultrasound signals can probe the chemistry of the neonatal cardiovascular system in the manner described above.

[**0144**] Further embodiments of the invention include using diagnostic apparatus of the type described herein for fetal monitoring. For example, as depicted in **FIG. 20**, one or more sensors **2002**A, **2002**B, **2002**C, e.g., planar sensors of the type depicted in **FIGS. 12A-12B**, may be placed on a pregnant woman's abdomen to probe the fetal cardiovascular system. The sensors **2002**A, **2002**B, **2002**C may be coupled to a remote unit of the type described above with respect to **FIG. 2A**. Optical and ultrasound signals can probe the chemistry of the fetal cardiovascular system in the manner described above. In this case, the target area is the fetal oxygen exchange system, including the placenta, placental vasculature, fetal heart and major fetal blood vessels. Such trans-abdominal fetal monitoring can provide information about fetal blood oxygenation levels in a minimally invasive or non-invasive manner. Fetal oxygenation levels are known to be substantially lower than the conjugate maternal levels. The selection of wavelengths used can be biased to probe the fetus preferentially over the mother.

[**0145**] Although the above description emphasizes measurement of blood oxygenation for the purpose of determining venous oxygen saturation, cardiac output and pH, the invention is not limited to such applications. The technique described herein can be adapted to selectively probe tissues within the body to measure the level of a particular target chromophore within those tissues and derive diagnostic information about the tissue from the measurement. These measurements can be made in a manner which is accurate, reproducible, precise, fast, operator independent, easy to use, continuous, cost effective, and substantially free of increased mortality and morbidity. Embodiments of the present invention allow measurements that used to be made in a highly invasive manner to be made in a non-invasive or minimally invasive manner. Applications of the technique include measuring the health of a transplanted organ to check for signs of rejection, measuring the perfusion of a skin graft in, for example a burn victim, to determine the health of the graft, potential ambulatory monitoring of high-risk cardiovascular patients, and ambulatory monitoring of high-risk pregnancies.

[**0146**] The techniques described are not limited to the hospital or medical office setting. Embodiments of the invention could be made portable and simple to use by virtue of its use of rugged telecom components and low power-consumption devices which could in turn allow its use in ambulances. Embodiments of the invention may be useful for real-time monitoring of personnel in high risk situations. For example rescue workers in chemical plants responding to emergencies, or firemen in burning buildings could be monitored remotely for signs of physical distress. Military personnel with ambulatory versions of the sensors could be monitored on the battlefield, and portable versions of the device could be used for first-responder battlefield triage.

[**0147**] While the above is a complete description of the preferred embodiment of the present invention, it is possible to use various alternatives, modifications and equivalents. Therefore, the scope of the present invention should be determined not with reference to the above description but should, instead, be determined with reference to the appended claims, along with their full scope of equivalents. In the claims that follow, the indefinite article "A", or "An" refers to a quantity of one or more of the item following the article, except where expressly stated otherwise. The appended claims are not to be interpreted as including means-plus-function limitations, unless such a limitation is explicitly recited in a given claim using the phrase "means for."

What is claimed is:

1. An apparatus, comprising:

an ultrasound transducer configured to provide an ultrasound radiation pressure field to modulate a target area within a body at a modulation frequency;

an optical source configured to generate one or more pulses of radiation containing temporally correlated groups of photons, wherein the photons in each group are characterized by two or more different wavelengths, the two or more different wavelengths being selected to have specific interaction with a target chromophore, and wherein the two or more different wavelengths being selected to have substantially similar scattering cross-sections and anisotropy parameters in the target and its surroundings;

launch optics configured to transmit the pulses of radiation from the optical source to the target area being modulated by the radiation pressure field and to inject the pulses of radiation into the body in proximity to the target area;

an optical detector configured to detect in temporal coincidence photon groups at each of the different wavelengths that are backscattered from the target area, the optical detector using time-gated amplification or time-gated background-free amplification of the return signal so as to exclude photons which could not by virtue of their arrival time have interacted with the radiation-pressure-modulated target; and

a filter coupled to the optical detector, the filter being configured to select those detected photon groups with a modulation component at the same frequency as the modulation frequency of the radiation pressure modulation field, or at a harmonic of the modulation frequency.

2. The apparatus of claim 1 where the ultrasound transducer and launch optics are contained in a catheter.

3. The apparatus of claim 1 wherein the launch optics include one or more optical fibers coupled between the optical source and a handpiece.

4. The apparatus of claim 3 wherein the handpiece includes detection optics coupled to the optical detector by one or more optical fibers, the detection optics and optical fibers being adapted to relay optical signals, including the temporally coincident photon groups, from the target through the handpiece to optical detector.

5. The apparatus of claim 1 wherein the ultrasound transducer is of a design such that the output energy may be focused, such as the phased-array type.

6. The apparatus of claim 1 wherein the ultrasound transducer operates at fundamental frequencies in the range 2-50 MHz, and preferably from 2-15 MHz.

7. The apparatus of claim 6 wherein the ultrasound transducer operates at fundamental frequencies in the range 2-15 MHz.

8. The apparatus of claim 1 wherein the radiation pressure modulation is occurring at frequencies between 50 Hz and 750 kHz.

9. The apparatus of claim 1 wherein the optical source is configured to deliver the temporally correlated groups of photons at a repetition rate of between about 100 kHz and about 500 MHz.

10. The apparatus of claim 9 wherein the repetition rate is between about 1 MHz and about 250 MHZ.

11. The apparatus of claim 9 wherein the repetition rate is between about 10 MHz and about 200 MHz.

12. The apparatus of claim 1 wherein the optical source is configured to deliver the temporally correlated groups of photons with a pulse width between about 1 picosecond and about 1 nanosecond.

13. The apparatus of claim 12 wherein the pulse width is between about 1 picosecond and about 100 picoseconds.

14. The apparatus of claim 13 wherein the pulse width is between about 5 picoseconds and about 50 picoseconds.

15. The apparatus of claim 1 wherein wavelengths of the temporally correlated pairs of photons fall in the range between 650 and 1175 nm.

16. The apparatus of claim 1 wherein wavelengths of the temporally correlated groups of photons lie in a range between about 650 and about 930 nm.

17. The apparatus of claim 1 wherein wavelengths of the temporally correlated groups of photons lie in the range between about 1020 and about 1150 nm.

18. The apparatus of claim 1 wherein the optical source is configured to generate the temporally correlated groups of photons by Spontaneous Parametric Downconversion (SPDC).

19. The apparatus of claim 1 wherein the optical source includes an optical parametric oscillator pumped by a master laser.

20. The apparatus of claim 1 wherein the optical source includes a fiber Optical Parametric Amplifier.

21. The apparatus of claim 1 wherein the optical detector is configured to perform the time-gated background free amplification of returning photon pairs by upconverting a signal in a fiber Optical Parametric Amplifier (OPA).

22. The apparatus of claim 21 wherein where the fiber OPA is pumped by the same master oscillator as that creating the source of the temporally correlated photon pairs.

23. The apparatus of claim 21 wherein the fiber OPA is pumped by a second pump source slaved temporally to the master oscillator creating the injected source of the temporally correlated photon pairs.

24. The apparatus of claim 1 wherein the time-gated background free amplification of the returning photon groups is performed by upconverting the signal in an optical mixer where it is mixed with a second frequency from the master oscillator or a second slaved oscillator.

25. The apparatus of claim 1 wherein where the wavelengths are selected to provide information about the oxygenation level of the blood by targeting oxy and deoxyhemoglobin.

26. The apparatus of claim 1 wherein where the wavelengths are selected to provide information about the pH level of the blood by targeting met-hemoglobin.

27. The apparatus of claim 1 wherein the ultrasound transducer, launch optics and optical detector (or collecting optics coupled to the optical detector) are configured to be placed on the dermis over the internal jugular vein on the left or right side of the neck.

28. The apparatus of claim 1 wherein the ultrasound transducer, launch optics and optical detector (or collecting optics coupled to the optical detector) are configured to be placed on the dermis simultaneously on the left and right side of the neck over the internal jugular veins.

29. The apparatus of claim 1 wherein the ultrasound transducer, launch optics and optical detector (or collecting optics coupled to the optical detector) are configured to be placed trans-tracheally into the left bronchus of a patient in order to simultaneously probe the patient's left pulmonary artery and descending thoracic aorta.

30. The apparatus of claim 1 wherein the ultrasound transducer, launch optics and optical detector (or collecting optics coupled to the optical detector) are configured to be placed trans-esophageally so as to be in close proximity to a patient's right pulmonary artery.

31. The apparatus of claim 1 wherein the ultrasound transducer, launch optics and optical detector (or collecting optics coupled to the optical detector) are configured to be placed in direct contact with the pulmonary artery and/or aorta by being inserted on a catheter through an intercostal space using an endoscope.

32. The apparatus of claim 1 further comprising a display coupled to the filter wherein the display is configured to present an output of the filter in a manner interpretable by a user of the apparatus.

33. A method for detecting oxygen saturation and/or pH of blood in an identified physiological target area in a non-invasive or minimally invasive manner using the apparatus of claim 1, the method comprising the steps of:

placing the launch optics of the apparatus such that a light emitting aperture of the launch optics is placed in proximity to a blood vessel;

using radiation pressure from the ultrasound transducer to mechanically modulate a target area within the blood vessel;

using the optical source to generate one or more pulses of radiation containing temporally correlated groups of photons, wherein the photons in each group are characterized by two or more different wavelengths, the two or more different wavelengths being selected to have specific interaction with a target chromophore, and

wherein the two or more different wavelengths being selected to have substantially similar scattering cross-sections and anisotropy parameters in the target and its surroundings;

transmitting the pulses of radiation from the optical source to the target area being modulated by the radiation pressure field and injecting the pulses of radiation into the body in close proximity to the target area;

detecting photon groups backscattered from the target area with the optical detector,

said detection occurring using time-gated or time-gated background-free amplification of the return signal so as to exclude photons which could not by virtue of their arrival time have interacted with the radiation-pressure-modulated target,

said detection occurring in a manner so as to detect two or more photons at each of the different injected wavelengths in temporal coincidence such that detected photons of the two or more different wavelengths have traveled substantially the same pathlength in tissue of the target area;

filtering the detected photon groups with the filter so as to detect those photon groups having a modulation component characterized by the same frequency as the radiation pressure modulation field, or a harmonic of said radiation pressure modulation frequency; and

inferring from the arrival rate of the detected temporally correlated photon pairs an oxygenation level or pH of the target area.

34. The method of claim 33, further comprising the step of displaying results of the aforementioned process in a manner readily interpretable.

35. The method according to claim 33 wherein the target area is a fetal oxygen exchange system, including the placenta, placental vasculature, fetal heart and major fetal blood vessels.

36. The method of claim 33 wherein the target area is a neonatal cardiovascular system.

37. The method of claim 33 wherein the physiological target area is an external or internal jugular vein, located transdermally close to the clavicle.

38. The method of claim 33 wherein the physiological target area is a pulmonary artery.

39. The method of claim 33, wherein the oxygenation level is a venous or arterial blood oxygenation level, wherein the method further comprises inferring a cardiac output from the blood oxygenation level using the Fick principle.

40. A method for obtaining diagnostic information about a patient using the apparatus of claim 1, comprising the steps of:

locating a target tissue within the patient's body by ultrasound imaging with the transducer;

placing the launch optics of the apparatus such that a light emitting aperture of the launch optics is placed in proximity to target tissue;

using radiation pressure from the ultrasound transducer to mechanically modulate a target area within the target tissue;

using the optical source to generate one or more pulses of radiation containing temporally correlated groups of photons, wherein the photons in each group are characterized by two or more different wavelengths, the two or more different wavelengths being selected to have specific interaction with a target chromophore, and wherein the two or more different wavelengths being selected to have substantially similar scattering cross-sections and anisotropy parameters in the target and its surroundings;

transmitting the pulses of radiation from the optical source to the target area being modulated by the radiation pressure field and injecting the pulses of radiation into the body in close proximity to the target area;

detecting photon groups backscattered from the target area with the optical detector,

said detection occurring using time-gated or time-gated background-free amplification of the return signal so as to exclude photons which could not by virtue of their arrival time have interacted with the radiation-pressure-modulated target,

said detection occurring in a manner so as to detect two or more photons at each of the different injected wavelengths in temporal coincidence such that detected photons of the two or more different wavelengths have traveled substantially the same pathlength in tissue of the target area;

filtering the detected photon groups with the filter so as to detect those photon groups having a modulation component characterized by the same frequency as the radiation pressure modulation field, or a harmonic of said radiation pressure modulation frequency; and

inferring from the arrival rate of the detected temporally correlated photon pairs diagnostic information about the patient.

* * * * *

专利名称(译)	用于静脉血氧饱和度和pH水平的非侵入性和微创感测的装置和方法		
公开(公告)号	US20060224053A1	公开(公告)日	2006-10-05
申请号	US11/095091	申请日	2005-03-30
[标]申请(专利权)人(译)	SKYLINE生物医学		
申请(专利权)人(译)	SKYLINE生物医学，INC.		
当前申请(专利权)人(译)	SKYLINE生物医学，INC.		
[标]发明人	BLACK JOHN F KIM DANIEL HWAN KHURI YAKUB BUTRUS T		
发明人	BLACK, JOHN F. KIM, DANIEL HWAN KHURI-YAKUB, BUTRUS T.		
IPC分类号	A61B5/00		
CPC分类号	A61B5/0048 A61B5/0261 A61B8/08 A61B5/14551 A61B5/413 A61B5/029		
外部链接	Espacenet USPTO		

摘要(译)

公开了医学诊断设备和方法。超声辐射压力选择性地调节体内的目标区域。产生包含时间相关的光子组的一个或多个辐射脉冲。光子的特征在于两种或更多种不同的波长，选择这些波长以与靶发色团具有特异性相互作用。还选择两种或更多种不同波长以在靶及其周围具有基本相似的散射截面和各向异性参数。辐射脉冲被辐射压力场调制到靠近目标区域的物体中。在时间重合中检测从目标区域反向散射的每个不同波长的光子组。返回信号的时间门控无背景放大用于排除光子，这些光子由于它们的到达时间而不能与辐射压力调制目标相互作用。利用调制分量以辐射压力调制场的调制频率或调制频率的谐波选择光子组。根据检测到的时间相关光子对或多重峰的到达速率，可以推断出关于目标区域的化学信息，例如氧合或pH水平。可以使用该技术通过静脉和/或动脉氧合的测量来计算心输出量。