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(71) Applicant: **ERASMUS UNIVERSITY MEDICAL CENTER ROTTERDAM** [NL/NL]; 's-Gravendijkwal 230, 3015 CE Rotterdam (NL).

(72) Inventors: **GANGARAM-PANDAY, Norani Hridayanand**; Noordeindseweg 1B, 2651 CV Berkel en Rodenrijs (NL). **VAN WETERINGEN, Willem**; Admiraliteitskade 185, 3011 TT Rotterdam (NL). **GOOS, Tomas Gijsbertus**; Cornelis Trompstraat 27, 2628 RN Delft (NL).

(74) Agent: **MÜLLER, Christoph** et al.; Hepp Wenger Ryffel AG, Friedtalweg 5, 9500 Wil (CH).

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(54) Title: DEVICE FOR OBTAINING AN INDICATOR OF A MICROCIRCULATORY CONDITION

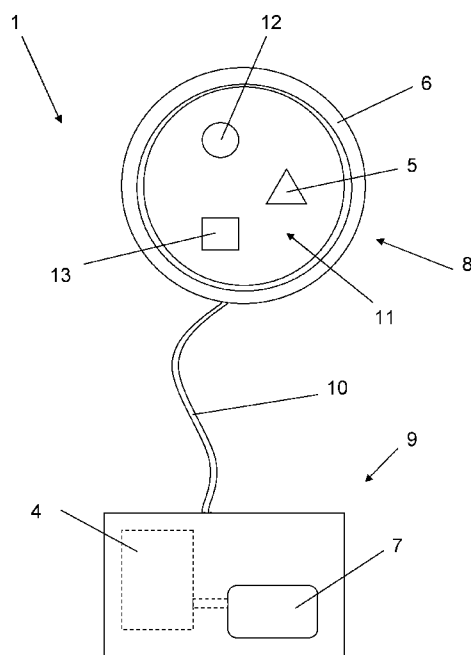


Fig. 1

(57) Abstract: The invention relates to a device (1, 1') and a method for obtaining an indicator of microcirculatory condition of a patient. The device (1, 1') comprises at least one first sensor (13) for measuring data indicative of first carbon dioxide levels, in particular tissue carbon dioxide levels, at least one second sensor (12) for measuring data indicative of second carbon dioxide levels, in particular transcutaneously measured arterial blood carbon dioxide levels, and a control unit (4) for determining a measure of microcirculation, in particular changes in tissue perfusion, preferably in septic patients, on the basis of the tissue carbon dioxide level and the transcutaneously measured arterial blood carbon dioxide level.

Device for Obtaining an Indicator of a Microcirculatory Condition

The invention relates to a device and a method for obtaining an
5 indicator of the microcirculatory condition of a patient.

Several clinical situations, such as sepsis, haemorrhage and
cardiac arrest lead to a decrease in tissue perfusion and affect
even the smallest blood vessels. Prolonged microcirculatory im-
10 pairment eventually leads to dysfunction or even failure of or-
gans, worsening the patient's prognosis.

When bacteria enter the bloodstream and cause a systemic infec-
tion to which the body responds, this is called sepsis. Sepsis
15 is one of the main causes of morbidity and mortality in Inten-
sive Care Units (ICU) for neonates, children and adults. The in-
cidence of sepsis is approximately 25% in high-level neonatal
ICUs. Multiple factors including prematurity, immunological de-
ficiencies and multiple entry points such as lines/intravascular
20 catheters often lead to infiltration of organisms into the
bloodstream.

Clinical monitoring provides continuous surveillance of the pa-
tient. Current monitoring techniques are however unable to accu-
25 rately detect sepsis, in particular the onset. Although there is
a large variety in the actual clinical manifestations of sepsis,
sepsis is currently defined as a combination of clinical symp-
toms, deviating lab values and a positive blood culture.

30 When sepsis is suspected, a blood culture is drawn. Due to the
time which is needed for microbial growth and determination in
the blood culture, antibiotic treatment is started immediately
after withdrawal and the blood culture serves to confirm and as-

sess the specific microbiological profile found in the blood culture and adjust treatment. Unfortunately the clinical condition of the patient may deteriorate severely because of the time delay between blood withdrawal and confirmation of sepsis. Mortality and morbidity are significant despite prompt start of an antibiotic treatment. Early detection of sepsis or even confirming its occurrence remains challenging.

Sepsis is a systemic bloodstream infection by an organism, such as bacteria, causing serious illness. In sepsis, dysfunction of the microcirculation appears in the early stages. Blood flow gets shunted from the arterioles to the venules, leaving the microcirculation hypoxemic and incapable of washing out carbon dioxide. Skin levels of carbon dioxide increase significantly and oxygen levels decrease.

Several studies indicate that sepsis affects the microcirculation at an early stage. Continuous monitoring of the microcirculatory condition would be of added value for detecting potential changes in the microcirculatory condition and relating these changes to sepsis. All cells of the body consume oxygen and produce carbon dioxide. Blood transports oxygen from the lungs to the tissue and stimulates carbon dioxide washout from the tissue which is then exhaled. Due to the lower oxygen and higher carbon dioxide concentrations in peripheral tissues, oxygen diffuses from the circulating blood into the tissue.

Heating of the skin increases blood flow to such an extent that oxygen levels increase and carbon dioxide levels decrease in the heated skin, a process which is called arterialization. When the skin is sufficiently heated and the skin and microcirculatory conditions permit, oxygen and carbon dioxide levels which correspond to arterial oxygen and carbon dioxide levels can be meas-

ured on the skin surface. This principle is applied in transcutaneous blood gas monitoring of patients.

There are various techniques for measuring oxygen and carbon dioxide levels transcutaneously. Currently optical and electrochemical sensors are widely used for transcutaneous oxygen and carbon dioxide measurement.

Typically such sensors house a pH electrode, a reference electrode, an electrolyte solution, a membrane and a heating element. Other technologies for transcutaneous carbon dioxide measurements include optical techniques.

The sensor may be fastened to the skin. The heating element warms the skin to a temperature sufficient to improve perfusion, in particular to a temperature above 40 °C, more particular to a temperature of 42 °C to 45 °C. Oxygen and carbon dioxide diffuse through the epidermis and pass across the sensor's semipermeable membrane into an electrolyte solution-filled sensor chamber.

In the case of an electrochemical sensor, a glass electrode measures the change in pH-value. The electrode's output is converted into a signal indicative of the partial pressure of carbon dioxide. The signal may be read out or displayed.

According to EP2470066 B1 an indicator of tissue perfusion in a patient may be obtained by calculating the difference between the cutaneous partial pressure of carbon dioxide $c\text{PCO}_2$ (here below indicated as PcCO_2) measured with a carbon dioxide sensor without heating of said sensor at a temperature superior to 37.5°C and the arterial pressure of carbon dioxide $a\text{PCO}_2$ below indicated as PaCO_2 , or the end-tidal partial pressure of carbon dioxide EtPCO_2 below indicated as PetCO_2

In patients with a ventilation-perfusion mismatch, the end-tidal partial pressure of carbon dioxide might not be an appropriate reference value. In these cases the end-tidal carbon dioxide pressure is not representative of the arterial carbon dioxide pressure.

In specific patient groups such as neonates the small tidal volumes make end-tidal carbon dioxide measurements more difficult and less accurate.

An objective of this invention is to avoid drawbacks of the state of the art and in particular to provide a device and a method for obtaining an indicator of the microcirculatory condition, in particular for indicating and/or predicting sepsis, which in particular allows a noninvasive and reliable measurement providing results within acceptable response times.

According to the invention this object is accomplished by a device and a method according to the independent claims. In particular the device is suitable for obtaining an indicator of the microcirculatory condition of a patient. The device has at least one first sensor for measuring data indicative of first carbon dioxide levels, in particular tissue carbon dioxide levels and at least one second sensor for measuring data indicative of second carbon dioxide levels, in particular arterial blood carbon dioxide levels.

The first sensor preferably is adapted for a transcutaneous measurement at a first temperature, wherein preferably the measurement area is kept below 38°C.

The second sensor preferably is adapted for a transcutaneous measurement at a second temperature of the measurement area dif-

ferent from the first temperature. The second temperature is typically higher than the first temperature, e.g. higher than 38°C. Preferably the second carbon dioxide levels are measured with a heated transcutaneous sensor.

5

A control unit is provided for the determination of a measure of the microcirculatory condition based on the first carbon dioxide level, in particular tissue carbon dioxide level, and the second carbon dioxide level, in particular transcutaneous blood carbon
10 dioxide level.

In particular changes in tissue perfusion are determined for early detection of sepsis.

15 The control unit has at least one input for receiving a measured or estimated first carbon dioxide level value, in particular a value corresponding to the tissue carbon dioxide level, at least one input for receiving a measured or estimated second carbon dioxide level value, in particular a value corresponding to an
20 arterial blood carbon dioxide level and at least one output interface for submitting an indicator of a microcirculatory condition of a patient based on the received inputs.

Within this application "microcirculatory condition" means the
25 state of the microcirculatory perfusion and gas diffusion.

The sensor for measuring data indicative of arterial blood carbon dioxide levels may be a sensor for indication of a general or systemic condition.

30

The sensor for measuring data indicative of tissue carbon dioxide levels may be a sensor for indicating a local condition existing within a patient, e.g. a sensor for measuring data indicative of a skin carbon dioxide level.

The sensors may detect one measured quantity or more measured quantities at a time or one after the other. The measured data may correspond to one or more parameters and/or to a temporal sequence of measured quantities.

5

A measure of microcirculation provides an indication of the degree of vascularization, blood flow and tissue perfusion and hence of the microcirculatory condition.

10 In particular the control unit is adapted for determining changes in tissue perfusion based on the measurements of the two sensors.

The control unit particularly is adapted for determining a measure of microcirculation in septic patients, where microcirculation deteriorates due to decreased vascularization and blood flow in the skin and other peripheral tissues.

Transcutaneously measured carbon dioxide levels correspond to
20 arterial carbon dioxide levels when the skin is locally heated. This leads to sufficient arterialization to mitigate influences that would affect skin diffusion, even in the presence of sepsis from which it is known that the diffusion of oxygen and carbon dioxide through the skin is affected by factors that influence
25 the microcirculation.

It has been found that even when tissue perfusion is impaired, arterial blood carbon dioxide levels and heated transcutaneous carbon dioxide levels are in good correspondence; i.e.
30 transcutaneously measured carbon dioxide levels at elevated temperatures correspond to arterial partial pressure of carbon dioxide in arterial blood samples, even in septic neonatal patients.

In contrast, a transcutaneous carbon dioxide measurement that applies no or less heating to the skin is sensitive to changes that directly affect skin diffusion, such as sepsis.

5 Without sufficient skin heating the transcutaneous carbon dioxide measurement estimates tissue carbon dioxide values in the absence of arterialization. The combination of transcutaneous measurements, in which carbon dioxide is measured on both heated skin and non-heated skin, hence allows measurement and in particular a monitoring of the status of skin carbon dioxide diffusion.
10 sion.

The device detects a relation between the first and the second carbon dioxide level and signals changes thereto to indicate a change of a microcirculatory condition. Specifically, a difference measurement between carbon dioxide levels measured at a first temperature and carbon dioxide levels measured at a second temperature being higher than the first temperature, is used to detect a degree of microcirculatory impairment, caused for example by sepsis.
15
20

By independent measuring of a heated transcutaneous carbon dioxide level and tissue carbon dioxide level, it is possible to provide a reliable detection of the microcirculatory condition.
25

A change of the microcirculatory condition can be a precursor of a severe disturbance of blood flow, vascularization or tissue perfusion. Depending on the temporal course of the change it may therefore indicate a future likelihood of a problem. Hence, preferably, the control unit is adapted for prediction of a measure of microcirculation, preferably adapted for prediction of sepsis depending on the temporal trend of the measured change.
30

The first sensor and/or the second sensor may comprise a chemical sensor, an opto-chemical sensor, an optical sensor, an electrical sensor, an electro-chemical sensor, an opto-electrical sensor, a pressure sensor and/or a temperature sensor.

5

The first sensor and the second sensor may be formed by the same sensing unit that works under different conditions, in particular that works intermittently under different conditions.

In this case the sensing unit may for example be used as a sensor for measuring data indicative of tissue blood carbon dioxide levels at a first temperature and as a sensor for measuring data indicative of arterial blood carbon dioxide levels at a second temperature higher than the first temperature.

15 The sensing unit may be a temperature-controlled sensing unit, in particular for transcutaneous gas measurement, which may be suitable for being used in temperature cycles, such that during a first time period data indicative of first carbon dioxide levels are acquired and during a second time period data indicative of second carbon dioxide levels may be acquired. In this manner
20 temperatures can be cycled alternating.

The sensing unit may also comprise a combined transcutaneous oxygen and carbon dioxide sensor.

25

In an alternative embodiment of the device, the sensor for measuring data indicative of tissue carbon dioxide levels is a first sensing unit and the sensor for measuring data indicative of arterial blood carbon dioxide levels is a second sensing unit different from the first sensing unit. The first sensing unit
30 and/or the second sensing unit may be temperature-controlled. The degree of heating or heatability may be different for the two sensing units.

The first and/or the second sensing unit may comprise a heating element.

Two or more separate sensing units allow a measurement of different data at the same time. Data measured at the same time or at least in a timely manner allow a reasonable comparison of the data.

In that case the two or more sensing units are preferably placed at a distance of at least 1 cm between each other to reduce disturbance of simultaneous measurements.

There are several alternative methods for determining arterial and tissue carbon dioxide levels.

The first and/or the second sensor may be adapted to analyse a blood sample. A blood sample may be taken from the patient. The sample may be drawn from an artery or capillary vessel. For the second sensor the blood can also be drawn from an arterial catheter. Alternatively, a continuous intra-arterial or intravascular measurement may be performed.

Blood samples may also be taken for calibrating a transcutaneous measurement as explained below.

A first sensing unit with a first sensor may comprise a microneedle. The microneedle may be applied to the tissue, preferably up to a distance of 0.2-1 mm from the skin surface. The microneedle may reach the arterioles and/or capillary loops, such that carbon dioxide reaches the needle tip.

The microneedle may be heated or non-heated. The body region around the measurement site is heated or non-heated.

The microneedle may comprise an optical fibre and/or may use fluoroscopy.

The microneedle may comprise an optical fibre and a chemical
5 sensor or an electrochemical probe, for measuring carbon dioxide concentration in a liquid.

The first sensing unit may also be adapted to use spectroscopy
for estimation of the tissue carbon dioxide level. The spectroscopy
10 may be proceeded in tissue, hence as an invasive procedure.

In a preferred embodiment the second sensor hence comprises a
sensor adapted for transcutaneous measurement of carbon dioxide
levels, in particular adapted for a heated transcutaneous meas-
15 urement.

In the context of this application, "heated" measurement means,
that the measurement area is heated to a temperature above the
normal body temperature, for example to 38°C or above. During a
20 "heated" measurement the measurement area is in particular heated to a temperature which achieves arterialization of the skin to such an extent, such that gas diffusion of carbon dioxide levels are allowed that are measurably closer to blood levels.

25 Preferably the sensing unit comprises a heating element.

The second sensing unit may comprise a pH electrode, a reference
electrode, an electrolyte solution and a membrane. Preferably
the second sensing unit may comprise a heating element.

30 In a preferred embodiment the first sensor comprises a sensor adapted for transcutaneous measurement of the tissue (or cutaneous) partial pressure of carbon dioxide P_{cCO_2} .

Preferably the device comprises a transcutaneous sensor for measuring data indicative of tissue carbon dioxide levels adapted for non-heated or low-heated transcutaneous measurements of dioxide levels.

5 For a "non-heated" measurement, the measurement area may also be heated, but not to a temperature that achieves arterialization of the skin, in particular the measurement area may be heated up to 38°C.

10 The first sensing unit may comprise a pH electrode, a reference electrode, an electrolyte solution and a membrane. Optionally the first sensing unit may comprise a heating element. Stabilizing the temperature of the skin typically provides for reproducible data.

The difference between the cutaneous level of carbon dioxide measured with an unheated transcutaneous sensor, and the cutaneous level of carbon dioxide measured with a heated sensor (as an indicator of the arterial carbon dioxide level) provides information on the carbon dioxide diffusion in the skin. This in turn is a measure of the microcirculatory condition. The microcirculatory condition is impaired in sepsis and can thus be detected with this invention, possibly earlier than current methods.

25 In particular the device may comprise a sensing unit which is used as a heated transcutaneous sensor and as a non-heated or low-heated transcutaneous sensor.

30 Hence, the same sensor unit may be used for measuring data indicative of tissue carbon dioxide levels without heating or with limited heating and for measuring data indicative of arterial blood carbon dioxide levels when heated.

Preferably the device comprises at least one further sensor, additional to the first and the second sensor, for measuring data indicative of a further parameter for determining the patient's condition, such as the temperature, the oxygen level, the pH-value of the blood and/or another blood parameter, in particular for correcting and/or calibrating of the transcutaneous blood carbon dioxide level and/or the tissue carbon dioxide level.

The additional sensor may be adapted for measuring data indicative of an arterial blood oxygen level and/or the tissue oxygen level. The additional sensor for indicating an oxygen level may comprise a transcutaneous electrochemical sensor, chemo-optical sensor, an optical sensor or an invasive sensor comprising a needle.

The additional sensor may be adapted for measurement of the temperature, preferably of the skin.

The additional sensor may also be adapted for measuring the foetal haemoglobin, when the device is used for neonates.

The additional sensor may be adapted for measuring the heart rate and/or the heart rate variability.

The additional sensor may be adapted for measuring the pulse rate and/or the pulse rate variability.

The additional sensor may be adapted for measuring the electrical activity, such as ECG values, and/or muscle activity and/or blood flow and/or respiratory gas flow.

The device may comprise a heating element.

The first sensor and/or the second sensor and/or if applicable, the additional sensor may be adapted for continuous and/or intermittent and/or alternating measurement.

5 A continuous measurement allows analysing parameters over time. For parameters known to change slowly or for which a sudden change is not relevant, a continuous measurement may mean that data are collected in predetermined time intervals, such as every few seconds or minutes.

10 In a preferred embodiment the second sensor and the first sensor are adapted for alternating measurements, preferably with a time lag that ensures the stable presence or absence of arterialization, for example a time lag of at least 10 minutes, to ensure
15 undisturbed measurements, in particular, when measurements are carried out alternating at different temperatures.

In another embodiment of the device the first sensor, and/or the second sensor, and/or if applicable the additional sensor, are
20 arranged in a common housing.

The device may comprise a sensor housing, which may be placed on or in the patient, in particular on the skin. The sensor housing may contain the first sensor, the second sensor and, if applicable,
25 ble, the additional sensors. By placing the sensor housing, all sensors are properly positioned with respect to the patient, in particular all sensors may face the skin.

The sensors may be designed as combined sensors, using and/or
30 sharing the same sensor elements, such as a temperature sensor, and/or using and/or sharing the same heating element.

Beneficially the first sensor and the second sensor are adapted to be placed anywhere on the skin or other peripheral tissue, for example on a part of the skin, in particular on an upper or lower extremity, an earlobe, at a fingertip, on a hand palm, on
5 a foot and/or on the thorax.

Advantageously, the control unit is capable of inducing a measurement of the first carbon dioxide level at a first temperature and of inducing a measurement of the second carbon dioxide level,
10 el, with the measurement area being heated to the second temperature, wherein the second temperature being higher than the first temperature, in particular above 38°C.

Preferably, the control unit is capable of inducing a transcutaneous measurement of the tissue $PcCO_2$ with a first sensor.
15

Preferably, the control unit is capable of inducing a transcutaneous measurement of the arterial $PaCO_2$ with a second sensor.

Preferably, the control unit is capable of controlling the first sensor, the second sensor, and at least one heating element for keeping the measurement site of the skin at a certain temperature.
20

Preferably, the control unit comprises an output for controlling a heating element, the first sensor and/or the second sensor.
25

Advantageously the control unit is adapted for estimation of an arterial partial carbon dioxide pressure $PaCO_2$ based on a
30 transcutaneous partial carbon dioxide pressure, preferably obtained by a measurement by the second sensor, wherein the measurement area is heated above 38°C or to a temperature which causes arterialization of the measurement area.

Advantageously the control unit is adapted for estimation of tissue partial carbon dioxide pressure $PcCO_2$ based on a transcutaneous partial carbon dioxide pressure, preferably obtained by a measurement by the first sensor, wherein the measurement area is kept at a temperature, for example below 38°C, such that arterialization is not achieved in the measurement area.

In a preferred embodiment of the device the control unit is adapted for determining the difference between the first and the second carbon dioxide level, in particular the difference between the tissue carbon dioxide level and the arterial carbon dioxide level, the ratio of the first and the second carbon dioxide level, in particular the ratio of the tissue carbon dioxide level and the arterial carbon dioxide level and/or an index based on the first and the second carbon dioxide level, for example the tissue carbon dioxide level and the arterial carbon dioxide level, wherein preferably the tissue carbon dioxide levels and/or the arterial carbon dioxide levels are measured transcutaneously.

An index may be determined by a calculation based on the first and second carbon dioxide levels, such as the tissue carbon dioxide levels and the transcutaneous carbon dioxide levels, and optionally further measured or predetermined parameters.

The control unit may also be adapted for monitoring and in particular for displaying the first and second carbon dioxide levels, such as the tissue carbon dioxide levels and the transcutaneous carbon dioxide levels, the difference, the ratio and/or the index over time and to determine a change over time.

In particular the control unit is adapted for receiving, collecting, storing and processing, particularly time-dependent data.

- 5 In particular the control unit is adapted for determining changes in tissue perfusion on a predetermined and/or selectable timescale.

Furthermore the control unit may be adapted for extrapolation of
10 time-dependent data and/or for prediction of for example a tissue perfusion state.

The control unit may be adapted to average and/or to filter measured and/or determined values and/or to determine a running
15 average for a predetermined time interval.

The control unit may be adapted for comparing the first and second carbon dioxide levels, such as the tissue carbon dioxide level and the transcutaneous carbon dioxide level, the difference,
20 ence, the ratio, the index and/or a deduced value with a respective nominal value.

The control unit may be adapted for receiving data by an input device, such as a control panel, a console or a data carrier
25 reader.

In particular the control unit may be adapted for receiving, storing and processing algorithms, correction parameters, nominal values and trigger values.

30 Correcting parameters may be used to process measured and/or determined data according to a rule. For example medication, vaso-tonic factors and the chemical drift of a sensor may be taken into account for analysing measured data.

The control unit may be adapted for indicating a disturbance of a sensor, a need for maintenance or a need for a new sensor calibration.

- 5 If the difference of a measured and/or determined value and a respective nominal value exceeds a predetermined trigger value, the control unit may produce a respective output information.

10 The control unit may analyse time courses of tissue carbon dioxide levels, transcutaneous carbon dioxide levels, differences, ratios, indexes and/or deduced values and may detect a critical condition or a likelihood of a critical condition in the microcirculatory condition.

- 15 The control unit may provide an alert signal, if there is a critical condition in the microcirculatory or a likelihood of a critical condition to be expected.

20 The device may provide a result based on a present measured and/or determined value. The device may provide a result based on a time development of a measured and/or determined value.

25 The control unit may be adapted to determine a difference, a ratio and/or an index on the basis of data measured during a time interval. Preferably the control unit may be adapted for a continuous determination on the basis of stored data of a running time interval. For this purpose the device may comprise a storage device for storing measurement data and/or reference data.

- 30 Thus the device allows for a retrospective analysis of the data.

Changes due to sepsis are caused by slow processes. Thus, the result to be determined will take some time, typically a few

minutes to a few hours. However, the device may provide an indicator of the microcirculatory condition and thereby an indicator of sepsis, potentially earlier than clinical symptoms indicate or the clinical manifestation of sepsis.

5

In a preferential embodiment of the device the control unit is connected or connectable to an output device, such as a monitor or a display, preferably for displaying the measure of microcirculation and/or for displaying signals produced by the control unit.

10

The output device may be a part of the device.

The output device may be adapted to emit an acoustic and/or optical signal.

15

The output device may be adapted to display measured and/or determined values and/or a time-dependent representation of measured and/or determined values.

20

The output device may be adapted to indicate a measure of microcirculation. For example the output device may comprise a display being designed to comprise a three-level scale, wherein the first level indicates "no problem", the second level indicates "likelihood of a problem" and the third level indicates "attention: problem".

25

The output device may be adapted to display a measure of the quality of measured and/or determined values, such as an estimated measurement error or a standard deviation of an averaged value.

30

The output device may be adapted to display a measure of the quality of the measure of the microcirculation, such as a confi-

dence index, which may be based on the quantity of data used. The more data used, the more trustworthy the result will be. Such a confidence index may be derived from a deviation of measurement data over a period of time; i.e. if the deviation is
5 relatively low over a sustained period of time, the confidence index will be high.

The values measured by the described sensors may be displayed by the output devices. Thus, the user gets additional information
10 and he can control the quality of the measure of microcirculation.

The device may be a stand-alone device to be placed at the bedside of a patient. The device may also be a hook-up element for
15 an existing system.

The device may be partly formed by components of an existing system and may for example share sensors or an output device with an existing system.
20

The object of the invention is also a device for obtaining an indicator of the microcirculatory condition of a patient, preferably as described above, comprising at least one first sensor for measuring data indicative of first carbon dioxide levels, in
25 particular tissue carbon dioxide levels.

The device further comprises at least one second sensor for measuring data indicative of second carbon dioxide levels, in particular arterial blood carbon dioxide levels.
30

The device further comprises a control unit for determining a measure of microcirculation, in particular changes in tissue perfusion, preferably in septic patients, on the basis of the first carbon dioxide levels, in particular tissue carbon dioxide

levels, and the second carbon dioxide levels, in particular the arterial blood carbon dioxide levels.

The control unit has at least one input for receiving a measured
5 or estimated first carbon dioxide level value, in particular a tissue carbon dioxide level value, at least one input for receiving a measured or estimated second carbon dioxide level value, in particular an arterial blood carbon dioxide level value.

10 The control unit has at least one output interface for outputting an indicator of a microcirculatory condition of a patient based on the received inputs.

There are several possible embodiments for the sensors, as well
15 as for respective sensing units, as described above.

The first sensor may comprise a sensor for transcutaneous measurement, preferably adapted for transcutaneously measuring the tissue partial carbon dioxide pressure $PcCO_2$, more preferably at
20 a first temperature below $38^\circ C$.

The second sensor may comprise a sensor for transcutaneous measurement, preferably adapted for transcutaneously measuring the arterial $PaCO_2$. The second sensor preferably is adapted for a
25 transcutaneous measurement at a second temperature being higher than the first temperature, wherein the measurement area is preferably heated above $38^\circ C$. In particular the sensor may be adapted for a heated transcutaneous measurement.

30 The object of the invention is also accomplished by a method for obtaining an indicator of tissue perfusion, comprising the following steps.

A first carbon dioxide level, in particular a tissue carbon dioxide level, of a patient is provided, preferably a transcutaneously measured tissue $PcCO_2$ value.

- 5 A second carbon dioxide level, in particular an arterial blood carbon dioxide level, of a patient is provided, preferably a transcutaneously measured arterial carbon dioxide value $tcPCO_2$.

10 Preferably the first and second carbon dioxide levels, such as the tissue carbon dioxide levels and the arterial blood carbon dioxide levels, are provided by independent measurements.

A measure for microcirculation is determined, preferably in septic patients, on the basis of the first and the second carbon
15 dioxide levels, such as the tissue carbon dioxide level and the arterial blood carbon dioxide level.

Preferably the measure for microcirculation is displayed in real-time.

20 The first and the second carbon dioxide levels may be provided by a data collection or may be measured, preferably by transcutaneous measurements. Other measurement principles may be used as explained above.

25 Preferably the first carbon dioxide level is measured at a first temperature and the second carbon dioxide level is measured with the measurement area being heated to a second temperature higher than the first temperature, preferably above 38° .

30 Preferably the second carbon dioxide level, in particular the arterial blood carbon dioxide level, is measured by transcutaneously measuring the arterial $PaCO_2$ with the measurement area being heated to a temperature above $38^\circ C$, preferably above $40^\circ C$,

such that arterialization of the skin is achieved, preferably heated by a heating element of a sensing unit and/or arranged in a sensor head.

5 Preferably the first carbon dioxide level, in particular the tissue carbon dioxide level, is measured by transcutaneously measuring the tissue $PcCO_2$. Preferably the measurement area is kept at the temperature of the patient, for example below 38°C and/or at 37.5°C. The measurement area is kept at the tempera-
10 ture which does not causes arterialization of the skin. When heat is applied metabolic activity changes and arterialization starts.

The measurements can be performed at the same time or alternat-
15 ing, preferably with a time lag that ensures the stable presence or absence of arterialization, for example with a time lag of at least 10 minutes.

The object of the invention is also accomplished by a computer
20 program product directly loadable into the internal memory of a digital comprising software code portions for performing the steps of a method for obtaining an indicator of tissue perfusion as described above, when said product is run on a computer.

25 The computer program may be loaded and/or run on a control unit of a device as described above.

The computer program may be loaded and/or run on a central com-
puter device or may be loaded and/or run on a measurement device
30 for measuring an arterial blood carbon dioxide level and/or a tissue carbon dioxide level of the patient.

The invention is further explained with reference to preferred embodiments and the following drawings which show:

Fig. 1: a schematic representation of a first example of a device;

Fig. 2: a schematic representation of a second example of a device;

Fig. 3: a schematic view on a sensor head of a third example for a device;

Fig. 4: a schematic cross-sectional view of the sensor head of figure 3;

Fig. 5: a schematic representation of a fourth example of a device;

Fig. 6: a schematic cross-sectional view of the sensor head of the fourth example of a device;

Fig. 7: a schematic representation of an example of microcirculatory conditions as measured by a device.

Figure 1 shows a schematic representation of a first example of a device 1 for obtaining an indicator of microcirculatory condition of a patient. The device 1 comprises a first sensor 13 measuring data indicative of tissue carbon dioxide levels and a second sensor 12, for transcutaneously measuring data indicative of arterial blood carbon dioxide levels.

The second sensor 12 is formed by a second sensing unit and the first sensor 13 is formed by a first sensing unit different from the second sensing unit.

The second sensor 12 and the first sensor 13 are arranged in a common housing 6 forming a sensor head 8.

The device 1 comprises a control unit 4 for determining a measure of microcirculation, in particular changes in tissue perfusion or microcirculatory condition, on the basis of values, measured by the first sensor 13 and the second sensor 12, in particular on the basis of the tissue carbon dioxide level and the heated transcutaneously measured carbon dioxide level.

The device 1 comprises an additional sensor 5 for measuring data indicative of a further parameter, such as the temperature, the oxygen level, the pH-value of the blood and/or another blood parameter, in particular for correcting the arterial blood carbon dioxide level and/or the tissue carbon dioxide level.

The sensor head 8 may be connected to a device base 9 by a cable 10. The control unit 4 may be arranged in the device base 9.

The control unit 4 is connected to an output device 7, such as a monitor or a display for displaying the measure of microcirculation. The output device 7 may also be arranged in the device base 9.

The sensor head 8 comprises a contact face 11 which is directable towards a measuring site. In this case, the measuring site is an area on the skin of a patient.

Figure 2 shows a schematic representation of a second example of a device 1' for obtaining an indicator of microcirculatory condition of a patient.

The device 1' comprises a sensor head 8 with a single sensing unit 14, comprising first and second sensors 13 and 12 respectively. Depending on the temperature, the sensing unit 14 is controlled for transcutaneously measuring data indicative of arterial blood carbon dioxide levels or indicative of tissue car-

bon dioxide levels. Skin temperature is controlled by a heating element 15 controlled by the control unit 4. Hence, the sensing unit 14 acts as a sensor for measuring data indicative of arterial blood carbon dioxide levels at a first temperature and as a sensor for measuring data indicative of tissue carbon dioxide levels at a second temperature.

The device 1 shown in FIGS. 3 and 4 comprises a surface 30 over which, in the embodiment shown, a membrane 50 is arranged and there between a thin layer of electrolyte 51. This membrane 50 is placed on the skin at a point of the human body which has a good blood flow, for example at a finger, at the forehead or at the earlobe (see figure 4).

The device 1 shown includes a sensor unit 19 adapted for transcutaneous measurement of the first and second tissue carbon dioxide level by electrochemical detection. The device 1 to this end preferably includes a micro-pH electrode 24 as well as an Ag/AgCl reference electrode 25 (see Fig 3). The carbon dioxide level can be measured potentiometrically in that the pH of the thin layer of the electrolyte solution 51 is measured which is in communication with the skin via the hydrophobic membrane 50 which has good gas permeability. A change in the carbon dioxide value at the skin surface effects a pH change of the electrolyte solution. The pH is measured in that the potential is measured between the miniature pH electrode 24 and a reference electrode 25. The micro-pH electrode 24 is conductively connected via the electrical inner deflector 16 to the control unit 4.

The device 1 comprises a heating element 26 and a temperature sensor 27.

The sensor unit 19 is adapted for a transcutaneous measurement at a first temperature, wherein the measurement area is kept below 38°C.

5 The sensor unit 19 is also adapted for a transcutaneous measurement at a second temperature being higher than the first temperature, wherein the measurement area is heated above 38°C by the heating element 26.

10 Thus the sensor unit 19 is a first sensor for measuring data indicative of first carbon dioxide levels, in particular tissue carbon dioxide levels, and a second sensor for measuring data indicative of second carbon dioxide levels, in particular arterial blood carbon dioxide levels.

15 Figure 5 shows a schematic representation of a fourth example of a device 1 for obtaining an indicator of microcirculatory condition of a patient.

20 A first sensing unit 13, a second sensing unit 12, an additional sensor 5, a housing of a processor or control unit 4 and an output device 7 may be arranged in a common housing 6.

25 Preferably the housing allows a combination, integration and suitable separation of components.

The first sensing unit 13 may be a first transcutaneous measurement device. The second sensing unit 12 may be a second transcutaneous measurement device and may comprise a heating element
30

The additional sensor 5 may detect temperature, transcutaneous O₂ and/or may comprise an input for external values.

The output device 7 may comprise a display for showing a digital or analogue output.

Figure 6 shows a schematic cross-sectional view of a sensor head 8 for obtaining an indicator of a microcirculatory condition of a patient in a fourth example of a device 1.

The sensor head 8 is placed in contact to the skin 103 of a patient.

A first sensing unit 13 for measuring data indicative of a tissue carbon dioxide level, an additional sensor 5, a second sensing unit 12 for measuring data indicative of an arterial carbon dioxide level and a heating element 15 are arranged in a common housing 6. The sensing unit 13 is adapted for a transcutaneous carbon dioxide measurement at a first temperature, wherein the measurement area is kept below 38°C. The sensing unit 12 is adapted for a transcutaneous carbon dioxide measurement at a second temperature being higher than the first temperature, wherein the measurement area is heated above 38°C. A processor or control unit 4 and an output device 7 (see figure 4), not shown in this figure, may also be arranged in the housing 6. The processor 4 is programmed to detect changes in skin perfusion and has an input for receiving a measured or estimated first carbon dioxide level value, in particular a tissue carbon dioxide level value from the first sensor 13, an input for receiving a measured or estimated second carbon dioxide level value from the second sensor 12, in particular an arterial blood carbon dioxide level value; and at least one output interface for submitting an indicator of a microcirculatory condition of a patient based on the received inputs.

The sensor head 8 is connected to an output connection 20, which may establish a connection to an external processor or controller and which may act as a power supply.

5 The skin 103 is permeated with arteries 101 and capillaries 102.

Figure 7 shows a schematic representation of an example of microcirculatory conditions as measured by a first sensor 13 and a second sensor 12 under condition of sepsis and under normal condition.

10

Blood supply in the skin arteries 101 remains unimpaired during sepsis.

15 However, blood supply in the capillaries 102 may be impaired in a septic condition. Consequently a significantly different amount of carbon dioxide diffuses from the skin surface, which may be detected by a transcutaneous measurement without heating the skin.

20 Surprisingly, heating of the skin leads to sufficient arterIALIZATION to mitigate influences that would affect skin diffusion, even in the presence of sepsis. Thus, carbon dioxide levels measured transcutaneously while heating the skin correlate with

25 arterial carbon dioxide levels.

A septic condition indicator can be outputted by the processor e.g. by outputting the difference between the first and the second carbon dioxide level, for example the difference between

30 tissue carbon dioxide level and the arterial carbon dioxide oxygen level, the ratio of the first and the second carbon dioxide level, for example the ratio of the tissue carbon dioxide level and the arterial blood carbon dioxide level and/or an index

based on the first and the second carbon dioxide level, for example the tissue carbon dioxide level and the arterial blood carbon dioxide level, preferably for a prediction of sepsis.

Claims

1. Device for obtaining an indicator of a microcirculatory condition of a patient, comprising

- at least one first sensor (13) for measuring data indicative of first carbon dioxide levels, in particular tissue carbon dioxide levels, the first sensor (13) comprising a measurement area to be contacted with the patient's tissue, and adapted for a transcutaneous carbon dioxide measurement at a first temperature, wherein the measurement area is kept below 38°C,

- at least one second sensor (12) for measuring data indicative of second carbon dioxide levels, in particular arterial blood carbon dioxide levels, the second sensor (12) comprising a measurement area to be contacted with the patient's tissue and adapted for a transcutaneous carbon dioxide measurement at a second temperature being higher than the first temperature, wherein the measurement area is heated above 38°C, and

- a control unit (4) for detecting changes in skin perfusion, the control unit (4) having at least one input for receiving a measured or estimated first carbon dioxide level value, in particular tissue carbon dioxide level value from the first sensor (13), at least one input for receiving a measured or estimated second carbon dioxide level value from the second sensor (12), in particular an arterial blood carbon dioxide level value; and at least one output interface for outputting an indicator of a microcirculatory condition of a patient based on the received inputs.

2. Device according to claim 1, wherein the first sensor (13) is a first sensing unit (13) and the

second sensor (12) is a second sensing unit (12) different from the first sensing unit (12).

3. Device according to any one of the preceding claims, wherein the device (1, 1') comprises at least one additional sensor (5) adapted for measuring data indicative of a further parameter, such as a temperature, the oxygen level or a pH-value of the blood and/or another blood parameter, in particular for correcting second carbon dioxide levels, in particular the arterial blood carbon dioxide levels, and/or the first carbon dioxide levels, in particular the tissue carbon dioxide levels.

4. Device according to one of the preceding claims, wherein the sensors (12, 13, 5) are adapted for continuous and/or intermittent and/or alternating measurement.

5. Device according to one of the preceding claims, wherein the first sensor (13) and the second sensor (12) are arranged in a common housing (6).

6. Device according to one of the preceding claims, wherein the first sensor (13) and the second sensor (12) are adapted to be placed on a part of the skin, in particular on an earlobe, at a fingertip, on a hand palm, on a foot and/or on the thorax.

7. Device according to one of the preceding claims, wherein the control unit (4) is adapted for inducing a measurement of the first carbon dioxide level at a first temperature and for inducing a measurement of the second carbon dioxide level, with the measurement area being heated to the second temperature, the second temperature being higher than the first temperature, in particular above 38°C,

wherein the control unit is adapted for controlling at least one heating element for keeping the measurement site of the skin at a certain temperature and wherein

the control unit comprises an output for controlling the heating element, the first sensor and/or the second sensor.

8. Device according to one of the preceding claims, wherein the control unit (4) is adapted for estimation of an arterial partial carbon dioxide pressure PaCO_2 based on a transcutaneous partial carbon dioxide pressure tcPCO_2 , obtained by a measurement by the second sensor (12), wherein the measurement area is heated to temperature above 38°C and/or a temperature that achieves arterialization.

9. Device according to one of the preceding claims, wherein the control unit (4) is adapted for estimation of tissue partial carbon dioxide pressure PcCO_2 based on a transcutaneous partial carbon dioxide pressure PcCO_2 , obtained by a measurement by the first sensor (13), wherein the measurement area is kept below 38°C .

10. Device according to one of the preceding claims, wherein the control unit is adapted for determining the indicator of a microcirculatory condition of a patient based on

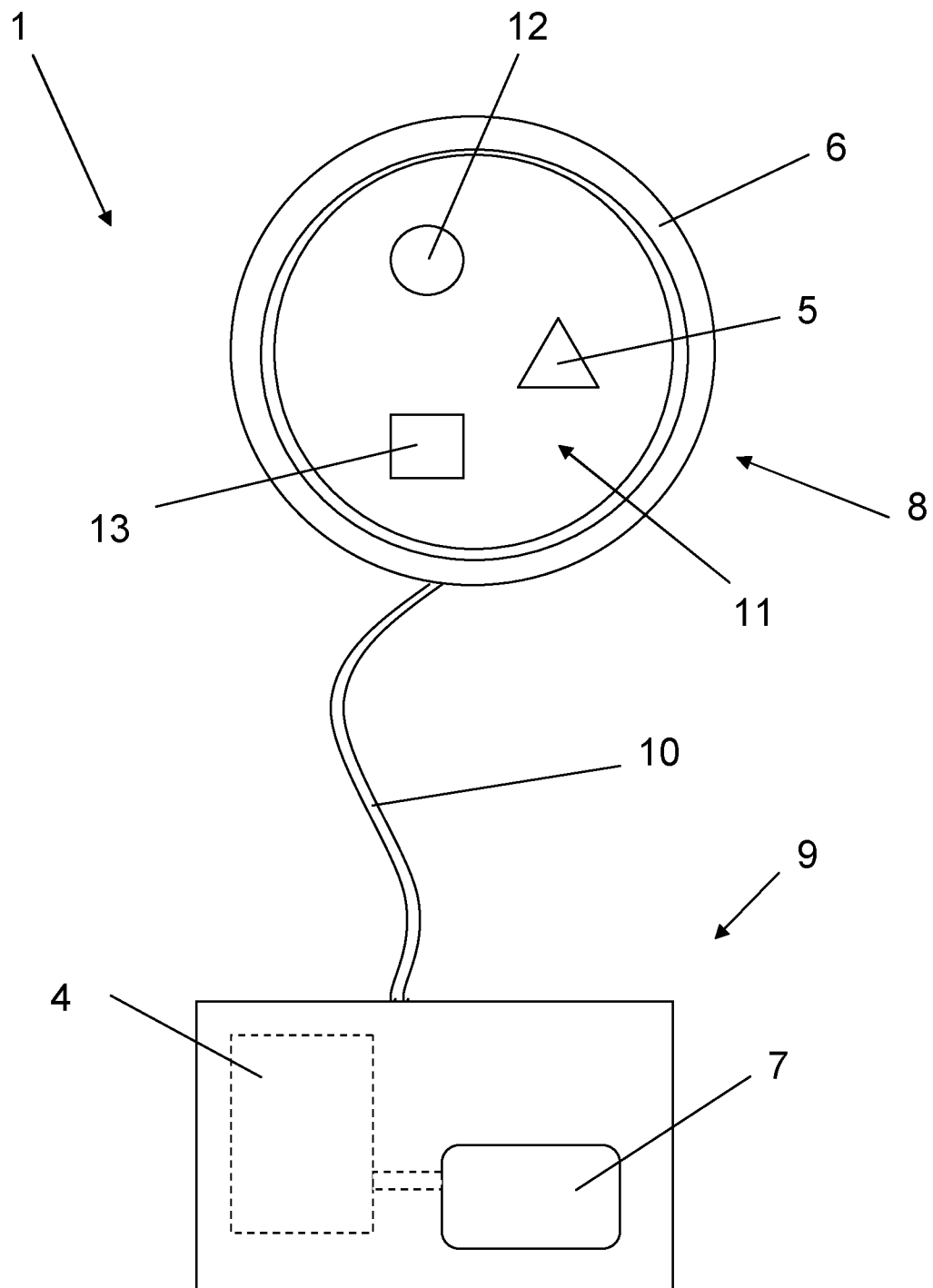
- the difference between the first and the second carbon dioxide level, in particular the difference between the tissue carbon dioxide level and the arterial blood carbon dioxide level,
- the ratio of the first and the second carbon dioxide level, in particular the ratio of the tissue carbon dioxide level and the arterial blood carbon dioxide level

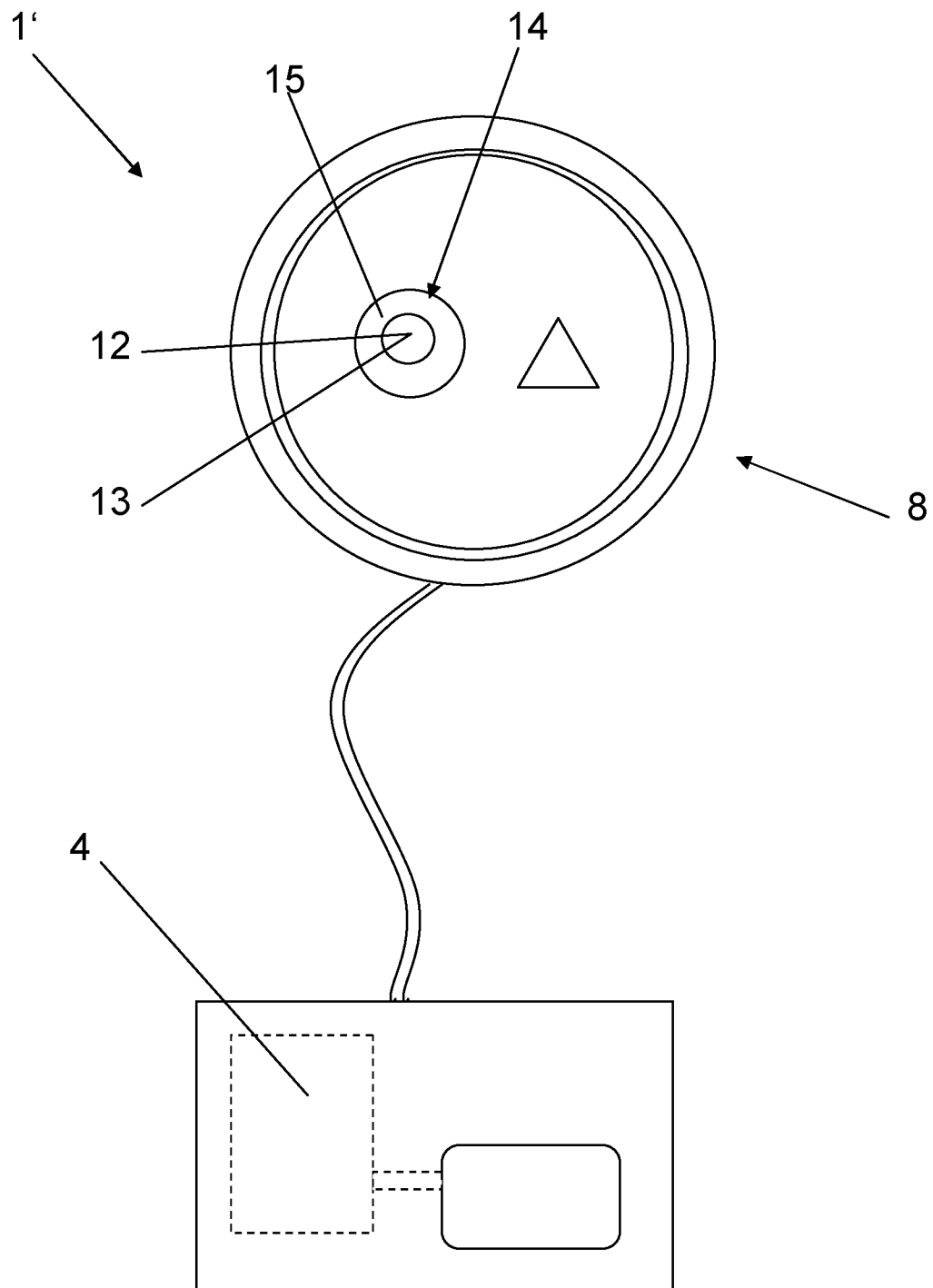
and/or

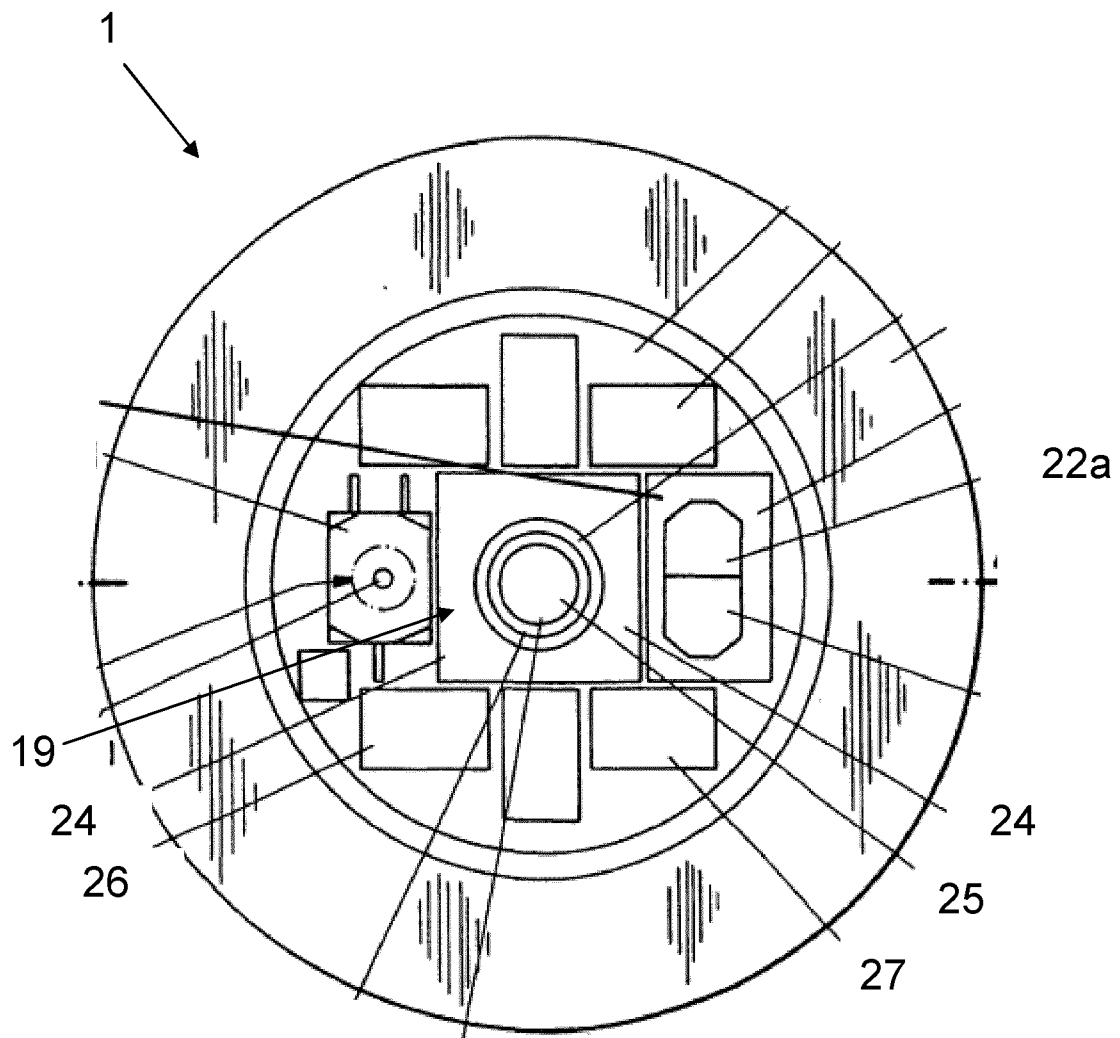
- an index based on the first and the second carbon dioxide level, for example the tissue carbon dioxide level and the arterial blood carbon dioxide level.

- 5 11. Device according to one of the preceding claims, wherein the output interface of the control unit (4) is connected or connectable to an output device, such as a monitor or a display.
- 10 12. Method for obtaining an indicator of tissue perfusion by a computer, comprising the steps of
- providing a first carbon dioxide level from a first sensor, in particular a tissue carbon dioxide level, preferably a transcutaneously measured tissue $PcCO_2$ value,
 - 15 - providing a second carbon dioxide level from a second sensor, in particular an arterial blood carbon dioxide level, preferably a transcutaneously measured arterial $PaCO_2$ value,
 - determining a measure for microcirculation, preferably in
 - 20 septic patients, on the basis of the first and the second carbon dioxide level, for example the tissue carbon dioxide level and the arterial blood carbon dioxide level.
13. Method according to claim 12, comprising the steps of
- 25 - measuring the first carbon dioxide level at a first temperature,
 - measuring the second carbon dioxide level with the measurement area been heated to a second temperature higher than the first temperature, preferably above $38^{\circ}C$.
- 30 14. Method according to claim 12 or 13, wherein further data are provided indicative of an oxygen level, a pH-level and/or a temperature, preferably by measuring data indicative of a pH-level and/or a temperature.

15. Computer program product directly loadable into the internal memory of a digital comprising software code portions for performing the steps of a method according to one of claims 12-15, when said product is run on a computer.

**Fig. 1**

**Fig. 2**

**Fig. 3**

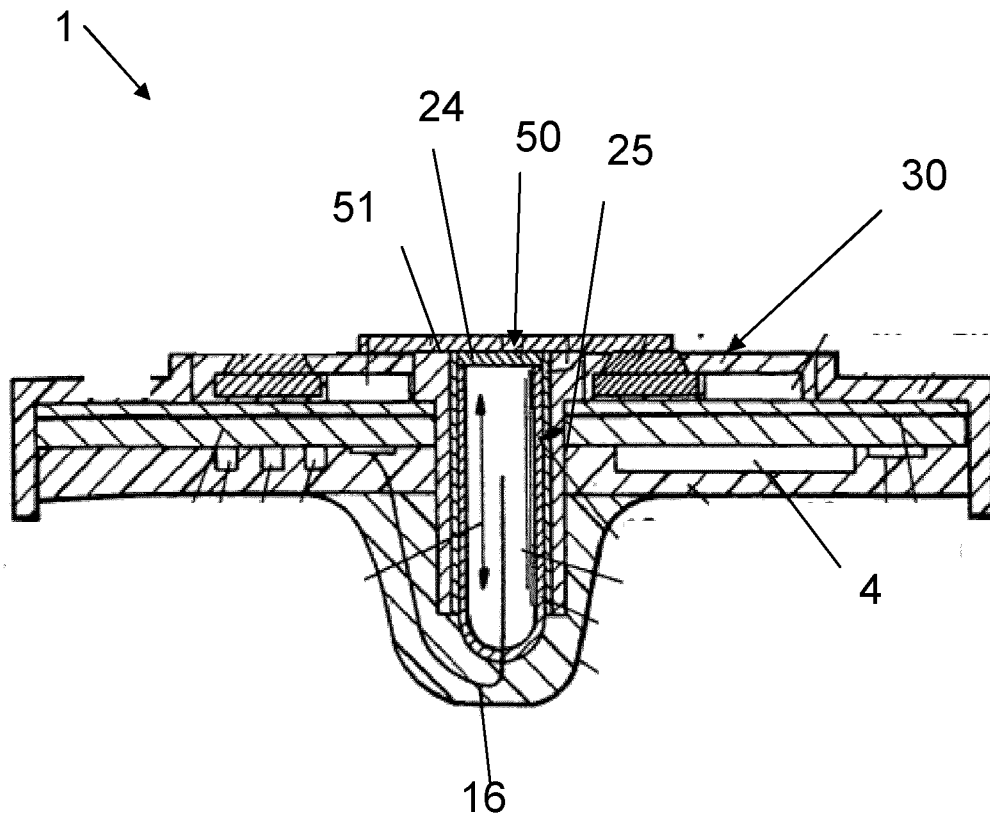
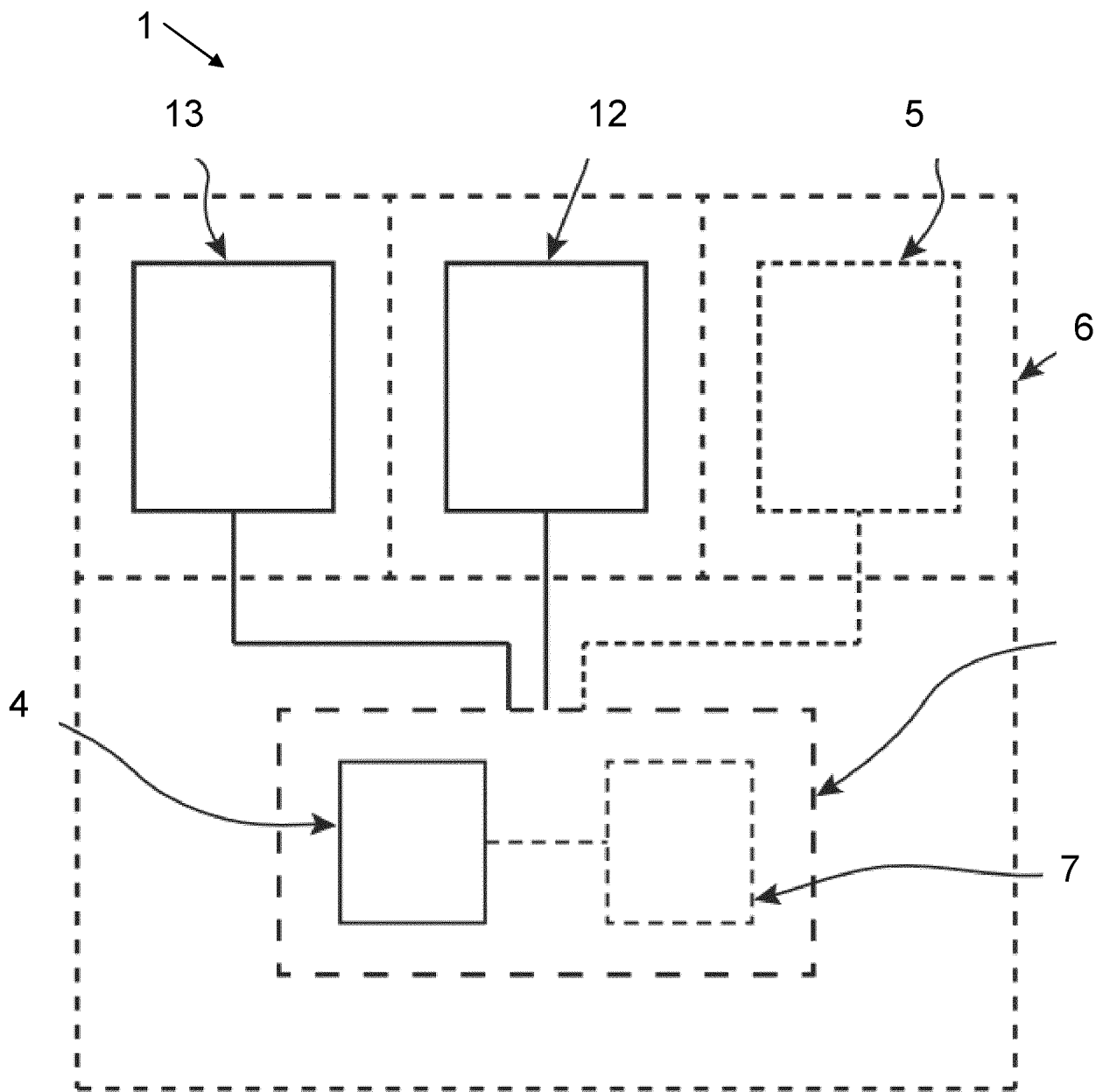


Fig. 4

**Fig. 5**

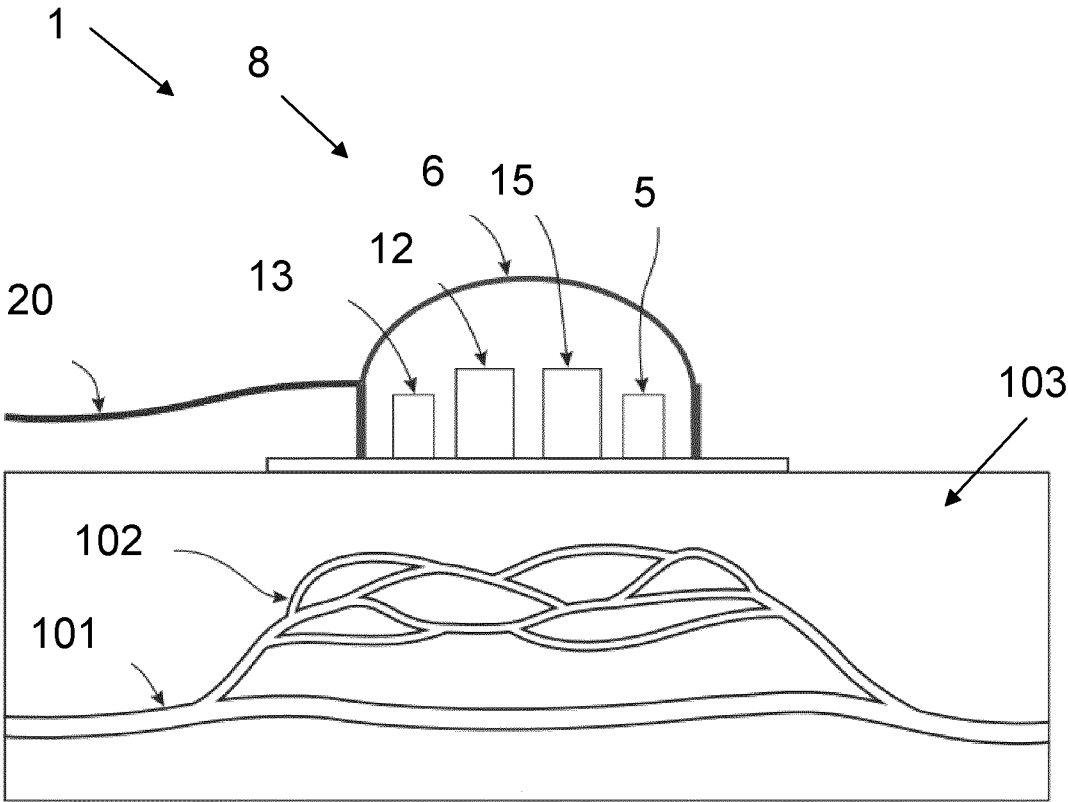


Fig. 6

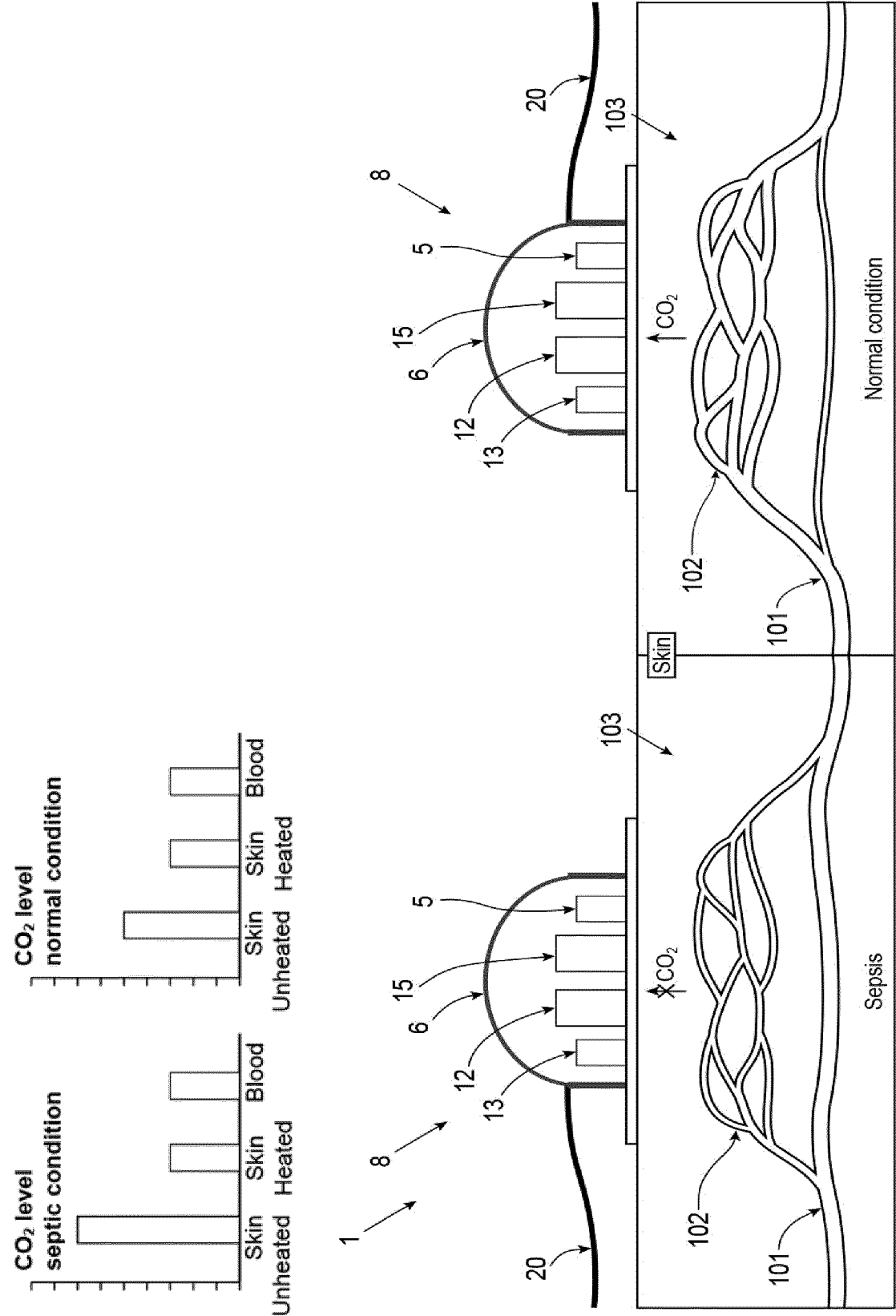


Fig. 7

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2021/066804

A. CLASSIFICATION OF SUBJECT MATTER INV. A61B5/145 A61B5/1477 A61B5/1491 ADD. A61B5/00		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) A61B		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) EPO-Internal, WPI Data, BIOSIS		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
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☒ Further documents are listed in the continuation of Box C.		
☒ See patent family annex.		
* Special categories of cited documents : "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier application or patent but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family		
Date of the actual completion of the international search		Date of mailing of the international search report
9 July 2021		19/07/2021
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016		Authorized officer
		Knoop, Jan

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