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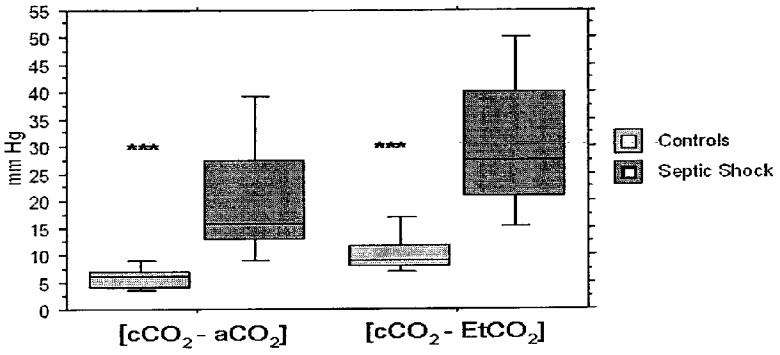

Figure 1

(57) Abstract: The present invention pertains to a non-invasive way of assessing tissue perfusion in a patient, especially for treatment follow-up and prognosis of septic shock. More specifically, tissue perfusion is assessed by measuring the cutaneous partial pressure of carbon dioxide of said patient, for example at ear lobe with a PCO_2 sensor which is not heated at a temperature superior to 37.5°C, and by calculating the difference between said cutaneous PCO_2 and either the arterial or the end-tidal partial pressure of CO_2. A device for performing a continuous non-invasive perfusion follow-up is also part of the invention.

WO 2011/024081 A1

A NON-INVASIVE METHOD FOR ASSESSING TISSUE PERFUSION IN A PATIENT

Several clinical situations, such as sepsis, hemorrhage and cardiac arrest lead to a decrease of tissue perfusion. Consequently, the carbon dioxide resulting from metabolism is not carried away as in healthy states, and the partial pressure of carbon dioxide increases.

Cardiovascular resuscitation in septic shock received recently more attention both for macro- and microcirculation parameters. If early goal optimization is recommended during the so called "golden hours" on the basis of macro-circulatory parameters (Dellinger et al., 2008), some patients continue to have compromised tissue perfusion in relation with microcirculatory disturbances. It has been clearly shown using different techniques that tissue microperfusion can be impaired in septic shock with low skin Laser Doppler blood flow (Neviere et al., 1996), reduction in sublingual small vessels perfusion using SDF (De Backer et al., 2002), or abnormal post-occlusion tissue hemoglobin saturation using NIRS (Creteur et al., 2007). During the last decade, gastric tonometry became popular to assess gastric tissue perfusion as an index of splanchnic perfusion. Some studies showed clearly the relation between high gastric PCO_2 and persistence of hypoperfusion in life threatening conditions, including septic shock (Gutierrez et al., 1992; Heino et al., 1998; Levy et al., 2003a). Because of the price, the relatively invasive technique and the debate on the conditions to perform measurements (with or without an H+ pump inhibitor), such a device is not widely used.

However, the concept of an increase in tissue CO_2 during stagnant perfusion remains relevant as shown by publications of Weil and colleagues (Fries et al., 2006; Weil, 2000; Weil and Sun, 2001). These authors clearly demonstrated the elevation in tissue CO_2 during experimental hemorrhagic (Jin et al., 1998; Ristagno et al., 2006) or septic shock (Fang et al., 2006). When systemic and regional blood flow decreases, a CO_2 accumulation can be detected by tonometry earlier than other hypoperfusion parameters such as lactate level (Marik and Bankov, 2003). This parameter seems also suitable to assess the reperfusion effectiveness during resuscitation. Because of these studies, simple sublingual devices have been proposed to monitor tissue CO_2 level. However, this device remains expensive and uncomfortable for the patient, especially if it is to be used for a continuous monitoring.

In the past, especially for pediatric patients for whom invasive technique is not adequate, intensivists have developed the use of transcutaneous CO_2 measurements to monitor the adequacy of ventilation. This technique imposes skin warming by the electrode to "arteriolize" capillary blood for PCO_2 measurements, so that the measured PCO_2 is representative of the arterial PCO_2 (Eberhard, 2007; Mindt et al., 1982). In practice, the sensor is heated at 42°C to 44°C, and up to 45°C (Kagawa et al., 2004) prior to its application on the skin.

Transcutaneous PCO_2 sensors have also been proposed for measuring metabolic acidosis, especially in sport or occupational medicine (Rooth et al., 1987). In this publication, the authors use the sensors at 37°C, so that the measured PCO_2 is the cutaneous rather than the transcutaneous PCO_2.

The inventors have now demonstrated that, contrarily to the currently accepted paradigm, it is possible to assess tissue perfusion, with a good reactivity, by measuring PCO_2 using a fully non-invasive technique at the skin level, and by subtracting to this measure the arterial PCO_2 or another measure representative thereof, such as the end-tidal PCO_2. Indeed, as shown in the experimental data below, the use of a cutaneous PCO_2 sensor, without heating it at a temperature superior to 37°C, gives reliable information about tissue perfusion in critically ill or injured patients. Moreover, this information can be used as a prognostic marker in certain conditions, especially in septic shock.

In the present text, the following definitions and notations will be used:

$aPCO_2$ is the arterial partial pressure of carbon dioxide.

$EtPCO_2$ means the end-tidal partial pressure of carbon dioxide.

Both arterial and end-tidal PCO_2 can be measured by any technique known by the skilled artisan.

$TcPCO_2$ is the transcutaneous partial pressure of carbon dioxide, *i.e.*, the partial CO_2 pressure measured with a sensor applied to the skin surface in conditions where the tissue underneath the sensor surface is arterialized, which means, in practice, that the sensor is heated at a temperature of 42°C to 44°C. Tanscutaneous partial pressure of carbon dioxide has been used for almost 40 years, especially in infants and premature neonates, as a surrogate measure of arterial PCO_2.

$cPCO_2$ is the cutaneous partial pressure of carbon dioxide, measured with a PCO_2 sensor applied to the skin surface in absence of arterialization of the tissue beneath the sensor surface. In practice, this means that the warming of the sensor is limited to normal central temperature (37°C or at most 37.5°C) or less (ambient or skin temperature).

A first aspect of the present invention is the use of $[cPCO_2 - aPCO_2]$ or $[cPCO_2 - EtPCO_2]$, as an indicator of tissue perfusion in a patient, wherein $[cPCO_2 - aPCO_2]$ is the difference between cutaneous and arterial partial pressures of carbon dioxide of said patient, and $[cPCO_2 - EtPCO_2]$ is the difference between cutaneous and end-tidal partial pressures of carbon dioxide of said patient. In particular, $[cPCO_2 - aPCO_2]$ and $[cPCO_2 - EtPCO_2]$ enable the *ex vivo* assessment of tissue microperfusion, *i.e.*, both macro- and microperfusion.

According to the present invention, $[cPCO_2 - aPCO_2]$ and $[cPCO_2 - EtPCO_2]$ during adequate ventilation also constitute markers which can be used by physicians for assessing impairment of blood circulation of a patient. Indeed, when $[cPCO_2 - aPCO_2]$ or $[cPCO_2 - EtPCO_2]$ are greater than predetermined thresholds, this indicates that the patient

undergoes perfusion failure. As described in the experimental part below, the inventors have determined that when using their measurement techniques, [$cPCO_2$ - $aPCO_2$] ≥ 9 mm Hg, or [$cPCO_2$ - $EtPCO_2$] ≥ 15 mm Hg,is indicative of perfusion failure. Of course, these thresholds could be modified in the future, especially if different techniques are used for measuring the carbon dioxide partial pressures (for example, if $cPCO_2$ is measured at a different locus or by a different type of sensor). Performance of the described method on a larger amount of patients will also enable to refine these thresholds for detecting perfusion failure, but it can be expected that the refined threshold for [$cPCO_2$ - $aPCO_2$] will stay over 7 mm Hg, and the refined threshold for [$cPCO_2$ - $EtPCO_2$] will stay over 12 mm Hg.

As mentioned above, PCO_2 sensors have been used for a long time for measuring $TcPCO_2$ as an indicator of $aPCO_2$, necessitating heating of the sensor at a temperature between 42°C to 45°C before applying it to the skin (Kagawa et al., 2004). To the contrary, according to the invention, the partial CO_2 pressure which is used is the cutaneous PCO_2. According to a specific embodiment of the invention, $cPCO_2$ is measured with a transcutaneous PCO_2 sensor heated at a temperature ≤ 37°C, or applied to the skin without previous heating. Preferred locations for obtaining $cPCO_2$ according to the present invention are ear lobes and the scalp.

Another important aspect of the present invention is hence a method for assessing perfusion failure of a patient, comprising:

(i) placing a carbon dioxide sensor on the ear lobe or on the scalp of said patient, without previous heating of said sensor at a temperature significantly superior to 37°C (normal body temperature), *i.e.*, without heating at all or with a heating at a temperature ≤ 37.5°C, preferably at ≤ 37°C, for example between 25 and 37°C;

(ii) measuring a partial pressure of carbon dioxide at the skin surface ($cPCO_2$);

(iii) measuring the arterial partial pressure of carbon dioxide ($aPCO_2$);

wherein [$cPCO_2$ - $aPCO_2$] ≥ 9 mm Hg is indicative of perfusion failure in the patient.

Alternatively, the above method can be performed by measuring the end-tidal pressure of carbon dioxide ($EtPCO_2$) instead of the arterial partial pressure; in this case, [$cPCO_2$ - $EtPCO_2$] ≥ 15 mm Hg is indicative of perfusion failure in the patient. In this embodiment, it is preferable to perform, in addition, a control of the arterial PCO_2, since the difference between $aPCO_2$ and $EtPCO_2$ depends on the patient's lung function, and hence may vary from one patient to another.

According to another embodiment, the invention pertains to the use of [$cPCO_2$ - $EtPCO_2$], for performing a continuous and non-invasive hemodynamic monitoring of a patient in a life-threatening condition. This difference is indeed a more sensitive marker

than any other parameter described before, especially since in low pulmonary flow state, end-tidal PCO_2 decreases and tissue PCO_2 increases.

The invention hence also relates to a method for performing a continuous and non-invasive hemodynamic monitoring of a patient, comprising:

(i) placing a carbon dioxide sensor on the ear lobe or on the scalp of said patient, without previous heating of said sensor at a temperature superior to 37.5°C (*i.e.*, without heating at all or with a heating at a temperature $\leq$ 37.5°C, preferably at $\leq$ 37°C, for example between 25 and 37°C);

(ii) measuring a partial pressure of carbon dioxide at the skin surface ($cPCO_2$);

(iii) measuring the end-tidal partial pressure of carbon dioxide ($EtPCO_2$);

(iv) calculating [$cPCO_2$ - $EtPCO_2$],

wherein an increase of [$cPCO_2$ - $EtPCO_2$] indicates a deterioration of the hemodynamic state of the patient, and a decrease of [$cPCO_2$ - $EtPCO_2$] indicates an amelioration of the hemodynamic state of the patient.

When performing the above method, steps (ii) to (iv) can be performed continuously or punctually, with a frequency ranging from once a minute of once a day. As above-mentioned, the arterial partial pressure of carbon dioxide is also advantageously measured (to interprete $EtPCO_2$), for example once a day.

According to a particular aspect of the invention, [$cPCO_2$ - $aPCO_2$] or [$cPCO_2$ - $EtPCO_2$] is used for outcome prediction of a patient in intensive care unit. For example, for a patient in septic shock, a decrease of [$cPCO_2$ - $aPCO_2$] or [$cPCO_2$ - $EtPCO_2$] during the 24 hours following the onset of septic shock is indicative of a good prognosis, whereas the absence of decrease (steady state or increase) is indicative of a bad prognosis. More specifically, the inventors have demonstrated that in case of septic shock, [$cPCO_2$ - $aPCO_2$] and [$cPCO_2$ - $EtPCO_2$] must have decreased under certain thresholds, within the 24 hours following the onset of the treatment of septic shock, to be indicative of a good prognosis. Indeed, if [$cPCO_2$ - $aPCO_2$] $\geq$ 16 mm Hg, or if [$cPCO_2$ - $EtPCO_2$] $\geq$ 25 mm Hg 24 hours after the beginning of septic shock treatment, this is indicative of a bad prognosis (the patient is at high risk of death, its chances to recover from the shock are very poor).

Of course, the present invention also pertains to the *ex vivo* steps of the above methods, *i.e.*, the calculation of [$cPCO_2$ - $aPCO_2$] and/or [$cPCO_2$ - $EtPCO_2$], followed by the interpretation of the obtained result(s) as described above.

Another aspect of the present invention is a device for performing a method as described above, comprising:

- a first carbon dioxide sensor for detecting a partial pressure of carbon dioxide (PCO_2), the sensor being adapted for being attached on the ear

lobe and/or the scalp and measuring the cutaneous PCO_2 ($cPCO_2$) of a patient;

- a second carbon dioxide sensor for detecting a partial pressure of carbon dioxide (PCO_2), the sensor being adapted for measuring the end-tidal PCO_2 ($EtPCO_2$) of an intubated patient; and
- a computer operably connected to both sensors, wherein said computer calculates the difference between the partial pressures of carbon dioxide measured by said sensors.

The computer comprises at least calculator means, but it can also advantageously comprise a memory for stocking all the data of each patient, so that the history of the hemodynamic monitoring can be obtained for each patient.

According to a preferred embodiment, the device further comprises a third carbon dioxide sensor, said third sensor being adapted for measuring the arterial PCO_2 ($aPCO_2$). In this case, the computer calculates [$cPCO_2$ - $aPCO_2$] and [$EtPCO_2$ - $aPCO_2$]. Alternatively, the arterial PCO_2 is measured by means independent from the device, and the obtained value is entered in the computer *via* an interface. Another alternative is to use the first sensor to punctually measure transcutaneous PCO_2 (and hence, $aPCO_2$), by transiently warming said sensor.

The device according to the present invention can also comprise indicating means operably connected to the computer, wherein the indicating means indicate a degree of perfusion of the patient associated with the detected partial pressures of carbon dioxide. Optionally, the device also comprises a circuit for generating an alarm indicating a change of [$cPCO_2$ - $EtPCO_2$] with time. The computer can be programmed so that the signal sounds when [$cPCO_2$ - $EtPCO_2$] becomes higher than a predetermined value, for example 15 mm Hg to indicate perfusion failure. For a patient who already has a perfusion failure but for whom [$cPCO_2$ - $EtPCO_2$] is under 25 mm Hg, this threshold can be increased to 25 mm Hg, so that the signal rings if the patient's state worsens.

Other characteristics of the invention will also become apparent in the course of the description which follows of the experimental data obtained by the inventors and which provide it with the required experimental support, without limiting its scope.

LEGENDS TO THE FIGURES

Figure 1: Comparison of baseline value of [cPCO2 - aPCO2] and [cPCO2 - EtPCO2] between ICU-controls patients and septic shock patients. *, **, ***: $p<0.05$, 0.01, 0.001.

Figure 2: ROC curves comparing the ability of [cPCO2 - aPCO2] (solid line) and [cPCO2 - EtPCO2] (dash line) to distinguish shock and control patients at baseline. ROC curve area: 0.95 (0.85-0.99) and 0.96 (0.86-0.99) for [cPCO2 - aPCO2] and [cPCO2 -

EtPCO2], respectively. The best cut-off values were 9 mm Hg for [cPCO2 - aPCO2] and 15 mm Hg for [cPCO2 - EtPCO2].

Figure 3: Evolution from H0 to H36 and comparison between survivors and non-survivors of ScvO2 (%), Cardiac output (l/min), MAP (mmHg), CVP (mmHg), [cPCO2 - aPCO2] (mmHg), and [cPCO2 - EtPCO2] (mmHg). Expressed as mean ± SD.

Figure 4: ROC curves comparing the ability of [cPCO2 - aPCO2] (solid line) and [cPCO2 - EtPCO2] (dash line) to distinguish survivors from non survivors at H24. ROC curve areas for [cPCO2 - aPCO2] and [cPCO2 - EtPCO2] were 0.85 (0.66-0.95) and 0.87 (0.69-0.96), respectively. A threshold of 16 mmHg for [cPCO2 - aPCO2] and 25 mmHg for [cPCO2 - EtPCO2] (dash line) discriminated survivors from non-survivors with a sensibility of 83% and a specificity of 90%.

Figure 5: Relation between changes in [cPCO2 - aPCO2] and [cPCO2 - EtPCO2] and changes in tissue microperfusion (delta TPU) assessed by laser Doppler during 16 fluid challenges.

EXAMPLES

The aims of the present study were to: 1- propose the use a transcutaneous measurement of PCO_2 in normothermic condition (37°C) as a cutaneous PCO_2 measurement: ($cPCO_2$); 2- validate such measurement as an indicator of skin hypoperfusion in septic shock; 3- evaluate the interest of the gradient between arterial PCO_2 and cutaneous PCO_2 [$cPCO_2$ - $aPCO_2$] as a marker of hypoperfusion and therapeutic improvement; 4- propose a continuous non-invasive gradient between end tidal PCO_2 and cutaneous PCO_2 [$cPCO_2$ - $EtPCO_2$] as an alternative to evaluate the macro and microcirculation impact on cutaneous perfusion in septic shock-induced circulatory failure.

Material and Methods

Study population: Thirty septic shock patients were studied within 24 hours after the onset of septic shock. Fifteen hemodynamically stable ICU patients without infection were studied and considered as control.

Study Protocol: For septic patients and "control" patients, following parameters were collected: central temperature, systemic hemodynamic and respiratory parameters, cutaneous PCO_2 ($cPCO_2$) and received treatment. Timing for data collection in septic patients was: just before inclusion (H0) and every 6 hours from H0 to H36 or until death. At each time, arterial and central venous blood samples were drawn for arterial and central venous blood gases analysis. Systemic hemodynamic data, blood samples and $cPCO_2$ were also collected just before and 10 min after performing a fluid challenge: a volume expansion of 500 ml saline or 250 ml of gelatin infused in 15 minutes.

Cutaneous PCO_2 measurement: Cutaneous PCO_2 was measured at ear lobe with TOSCA 500 monitor, (TOSCA®, Radiometer Copenhagen, Denmark)(Eberhard et al., 2002). The sensor was calibrated *in vitro*, and then fixed on the provided clip to be put at ear

lobe after application of one drop of contact gel (Eberhard et al., 2002). After a few minutes for $cPCO_2$ value equilibration, measurements could be recorded. In the present study, the sensor was heated at 37°C instead of 42°C and the automatic correction (4 mm Hg) (Hazinski and Severinghaus, 1982) was not used.

Carbon dioxide gradients: [$cPCO_2$ - $aPCO_2$] and [$cPCO_2$ - $EtPCO_2$] gradients were calculated just before inclusion (H0) and every 6 hours from H0 to H36 or until death.

Microcirculation blood flow assessment: to separate eventual microcirculatory impairment from macrocirculation, the skin microcirculatory blood flow (mBF_{skin}) was measured in 16 patients on the other ear lobe, at the same location as $cPCO_2$, using Laser Doppler (Transonic system HT107/HT207). Laser Doppler measurement was also performed during the fluid challenge as described above (Levy et al., 2003b).

Results

Comparison between septic shock and control patients

At baseline, [$cPCO_2$ - $aPCO_2$] and [$cPCO_2$ - $EtPCO_2$] were significantly higher in septic shock than in control patients: 20.3±11.1 versus 5.9±2.1mm Hg and 30±12 versus 10±4mmHg, $p<0.0001$, respectively (Fig. 1). Area under ROC curve was 0.95 (0.85-0.99) for [$cPCO_2$ - $aPCO_2$] and 0.96 (0.86-0.99) for [$cPCO_2$ - $EtPCO_2$] ,. A threshold of 9 mmHg for [$cPCO_2$ - $aPCO_2$] discriminated shock patients from control patients with a sensibility of 90% and a specificity of 93%. A threshold of 15 mmHg for [$cPCO_2$ - $EtPCO_2$] discriminated shock patients from control patients with a sensibility of 89% and a specificity of 87% (Fig. 2).

[$cPCO_2$ - $aPCO_2$] and [$cPCO_2$ - $EtPCO_2$] evolution in septic shock patients

Among the 30 septic shock patients included, 23 (77%) survived and 7 died (23%). At baseline, there was no statistically significant difference for any hemodynamic parameters, gravity score and treatment received between survivors and non-survivors. During the next 36 hours of evolution, [$cPCO_2$ - $aPCO_2$] and [$cPCO_2$ - $EtPCO_2$] decreased significantly in survivors (20.2±11.1 to 10.2±4.3 mmHg and 31.3±12.8 to 20.3±10.3 mmHg, $p<0.01$, respectively). During the same time interval, the evolution of macro-hemodynamic parameters, such as mean arterial pressure (MAP), central venous pressure (CVP), cardiac output (CO) and central venous saturation (ScvO2), was not different between survivors and non-survivors (Fig. 3).

[$cPCO_2$ - $aPCO_2$] and [$cPCO_2$ - $EtPCO_2$] at H24 and relation with outcome

At H24, [$cPCO_2$ - $aPCO_2$] and [$cPCO_2$ - $EtPCO_2$] were significantly higher in non-survivors than in survivors: 27.3±13.5 versus 11.4±4.5mm Hg and 34±10 versus 20±10mmHg, $p<0.01$ respectively (Fig. 3). Areas under ROC curves for [$cPCO_2$ - $aPCO_2$] and [$cPCO_2$ - $EtPCO_2$] were 0.85 (0.66-0.95) and 0.87 (0.69-0.96), respectively. A threshold

of 16 mmHg for [$cPCO_2$ - $aPCO_2$] and 25 mmHg for [$cPCO_2$ - $EtPCO_2$] discriminated survivors from non-survivors with a sensibility of 83% and a specificity of 90% (Fig. 4).

[$cPCO_2$ - $aPCO_2$] and [$cPCO_2$ - $EtPCO_2$] acute variation during fluid challenges

In the 30 septic shock patients, 66 fluid challenges were performed. During fluid challenges, [$cPCO_2$ - $aPCO_2$] and [$cPCO_2$ - $EtPCO_2$] decreased significantly: from 14.5±7.2 to 12.7±7.2 mm Hg and from 23.4±8.7 to 21.7±8.5 mm Hg, $p<0.001$, respectively.

Relationship to microcirculatory blood flow(mBF_{skin})

In the 16 patients for whom mBF_{skin} on the controlateral ear lobe was measured (tissular perfusion unit TPU (Schabauer and Rooke, 1994)), the fluid challenge increased significantly mBF_{skin} :from 23±11 to 29±16 (26%), $p<0.01$. This increase in TPU strongly and inversely correlated with the decrease in either [$cPCO_2$ - $aPCO_2$] or [$cPCO_2$ - $EtPCO_2$]: $r^2=0.74$, $p<0.001$ and $r^2=0.67$, $p<0.001$, respectively (Fig. 5).

Discussion

This study shows that: (1) a cut off-value of 9 mm Hg for the gradient [$cPCO_2$ - $aPCO_2$] measured at ear lobe at 37°C discriminates shocked and non-shocked patients with a sensibility of 90% and a specificity of 93%.(2) The evolution of such a gradient [$cPCO_2$ - $aPCO_2$] related to the prognosis of septic shock patients better than macro-circulation parameters. (3) [$cPCO_2$ - $aPCO_2$] during fluid challenge decreased in correlation with increase of mBF_{skin}. (Laser Doppler). (4) These results were also observed using a strictly non invasive and continuous gradient [$cPCO_2$ - $EtPCO_2$] in mechanically ventilated patients.

First, warming the sensor to normal body temperature allowed to: 1) normalize the tonometry to physiologically compare the patients together; 2) largely limit the impact of arterial PCO_2 on cutaneous PCO_2, since the "arterialisation of the blood" was less than during warming between 42 to 44°C; 3) avoid the substraction of the metabolic constant (Hazinski and Severinghaus, 1982). In these conditions, cutaneous PCO_2 is significantly higher in shock patients compared to control patients (Fig. 1). This might result from an increase in tissue metabolism leading to higher CO_2 production or to a severe reduction in local blood flow washing the produced CO_2, or both. The difference with arterial PCO_2, or with the surrogate $EtPCO_2$, limits the impact of arterial PCO_2 and lung function, a reason to support the use of the gradient rather than cutaneous PCO_2 alone.

Second, the evolution of $cPCO_2$ gradients during 36 hours of intensive treatment differentiates survivors and non-survivors better than macro-circulation parameters (Fig. 3 and 4). These results are new since the use of transcutaneous PCO_2 measured at 42-44°C could not discriminate survivors and non-survivors in two recent studies (Yu et al., 2007; Yu et al., 2006). The use of these gradients are then relevant during shock state to predict outcome (Levy et al., 2003a; Weil, 2000). Cutaneous PCO_2 at normal body

temperature better fits with tissue perfusion than macro-hemodynamic parameters nor oxygenation parameters.

Third, the cPCO2 gradients ([$cPCO_2$ - $aPCO_2$] and [$cPCO_2$ - $EtPCO_2$]) can also be used as a monitor for treatment response, especially for blood volume as suggested by the effect of fluid challenge. Importantly, the reduction in PCO_2 gradients correlated well with the increase in microcirculatory skin blood flow during fluid challenge (Fig. 5).

Finally, even when arterial PCO_2 is not measured, the strict non-invasive gradient [$cPCO_2$ - $EtPCO_2$] can be used continuously to monitor the tissue perfusion (Fig. 1 to 5).

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CLAIMS

1. Use of [$cPCO_2$ - $EtPCO_2$] or [$cPCO_2$ - $aPCO_2$], for *ex vivo* assessing tissue perfusion in a patient, wherein $cPCO_2$ is the cutaneous partial pressure of carbon dioxide of said patient, $EtPCO_2$ is the end-tidal partial pressure of carbon dioxide, and $aPCO_2$ is the arterial partial pressure of carbon dioxide of the same patient.

2. The use of claim 1, for assessing impairment of blood circulation of a patient, wherein [cPCO2 - $EtPCO_2$] $\geq$ 15 mm Hg, or [$cPCO_2$ - $aPCO_2$] $\geq$ 9 mm Hg is indicative of perfusion failure.

3. The use according to any of claim 1 or claim 2, wherein $cPCO_2$ has been measured with a transcutaneous PCO_2 sensor heated at a temperature $\leq$ 37°C.

4. The use according to any of claims 1 to 3, wherein $cPCO_2$ has been measured at ear lobe or on the scalp.

5. The use of [$cPCO_2$ - $EtPCO_2$] according to any of claims 1 to 4, for performing a continuous and non-invasive hemodynamic monitoring of a patient in a life-threatening condition.

6. The use according to any of claims 1 to 5, for outcome prediction of a patient in intensive care unit.

7. The use of claim 6, for outcome prediction of a patient in septic shock, wherein a decrease of [$cPCO_2$ - $EtPCO_2$] or [$cPCO_2$ - $aPCO_2$] during the 24 hours following the onset of septic shock is indicative of a good prognosis, whereas the absence of decrease is indicative of a bad prognosis.

8. The use of claim 7, wherein [cPCO2 - $EtPCO_2$] $\geq$ 25 mm Hg, or [$cPCO_2$ - $aPCO_2$] $\geq$ 16 mm Hg 24 hours after the onset of septic shock is indicative of a bad prognosis.

9. A method for *ex vivo* assessing perfusion failure of a patient, comprising:

(i) calculating [$cPCO_2$ - $aPCO_2$] or [$cPCO_2$ - $EtPCO_2$], wherein $cPCO_2$ is the cutaneous partial pressure of carbon dioxide of said patient, measured with a carbon dioxide sensor placed on the ear lobe or on the scalp of said patient, without previous heating of said sensor at a temperature superior to 37.5°C, $EtPCO_2$ is the end-tidal partial pressure of carbon dioxide, and $aPCO_2$ is the arterial partial pressure of carbon dioxide of the same patient;

(ii) comparing the obtained result with a predetermined threshold;

wherein if the result obtained in step (i) is superior to said predetermined threshold, it is indicative of perfusion failure in the patient.

10. The method of claim 9, wherein said predetermined threshold is 9 mmHg for [$cPCO_2$ - $aPCO_2$] and said predetermined threshold is 15 mmHg for [$cPCO_2$ - $EtPCO_2$].

11. A method for *ex vivo* performing a continuous and non-invasive hemodynamic monitoring of a patient, comprising:

(i) calculating the difference between $cPCO_2$ and $EtPCO_2$, wherein $cPCO_2$ is the partial pressure of carbon dioxide at the skin surface, measured by a carbon dioxide sensor placed on the ear lobe or on the scalp of said patient, without previous heating of said sensor at a temperature superior to 37.5°C, and $EtPCO_2$ is the end-tidal partial pressure of carbon dioxide;

(ii) observing the evolution of [$cPCO_2$ - $EtPCO_2$],

wherein an increase of [$cPCO_2$ - $EtPCO_2$] indicates a deterioration of the hemodynamic state of the patient, and a decrease of [$cPCO_2$ - $EtPCO_2$] indicates an amelioration of the hemodynamic state of the patient.

12. A method for *ex vivo* predicting the outcome of a patient in septic shock, comprising:

(i) calculating [$cPCO_2$ - $EtPCO_2$] or [$cPCO_2$ - $aPCO_2$], wherein $cPCO_2$ is the cutaneous partial pressure of carbon dioxide of said patient, measured with a carbon dioxide sensor placed on the ear lobe or on the scalp of said patient, without previous heating of said sensor at a temperature superior to 37.5°C, $EtPCO_2$ is the end-tidal partial pressure of carbon dioxide, and $aPCO_2$ is the arterial partial pressure of carbon dioxide of the same patient;

(ii) repeating step (i) at least one time ;

(iii) comparing the results obtained in the preceding steps;

wherein a decrease of [$cPCO_2$ - $EtPCO_2$] and/or [$cPCO_2$ - $aPCO_2$] during the 24 hours following the beginning of the treatment of septic shock is indicative of a good prognosis, and the absence of decrease is indicative of a bad prognosis.

13. The method of claim 12, wherein [cPCO2 - $EtPCO_2$] $\geq$ 25 mm Hg, or [$cPCO_2$ - $aPCO_2$] $\geq$ 16 mm Hg 24 hours after the beginning of the treatment of septic shock is indicative of a high risk of death.

14. A device for performing a method according to any of claims 9 to 13, comprising:

a first carbon dioxide sensor for detecting a partial pressure of carbon dioxide (PCO_2), the sensor being adapted for being attached to the ear lobe and/or the scalp and measuring the cutaneous PCO_2 ($cPCO_2$) of a patient;

a second carbon dioxide sensor for detecting a partial pressure of carbon dioxide (PCO_2), the sensor being adapted for measuring the end-tidal PCO_2 ($EtPCO_2$) of an intubated patient; and

a computer operably connected to both sensors, wherein said computer calculates the difference between the partial pressures of carbon dioxide measured by said sensors.

15. The device of claim 14, which further comprises a third carbon dioxide sensor, said third sensor being adapted for measuring the arterial PCO_2 ($aPCO_2$).

16. The device of claims 14 and 15, further comprising indicating means operably connected to the computer, wherein the indicating means indicates a degree of perfusion of the patient associated with the detected partial pressures of carbon dioxide.

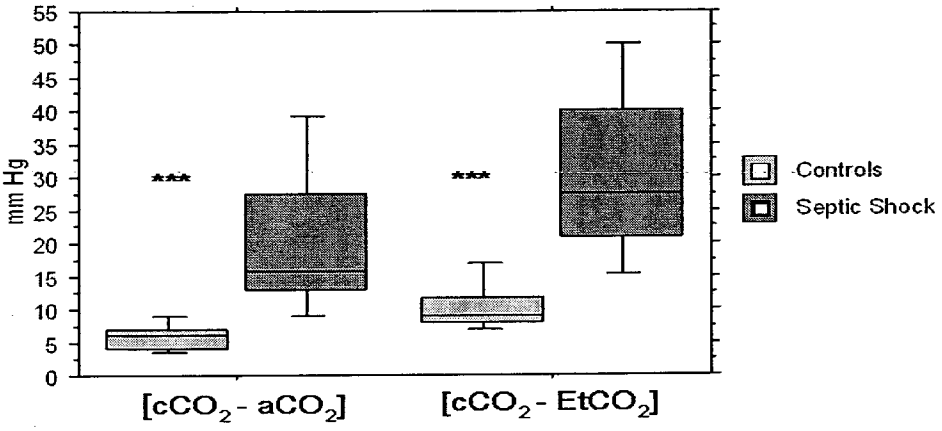

Figure 1

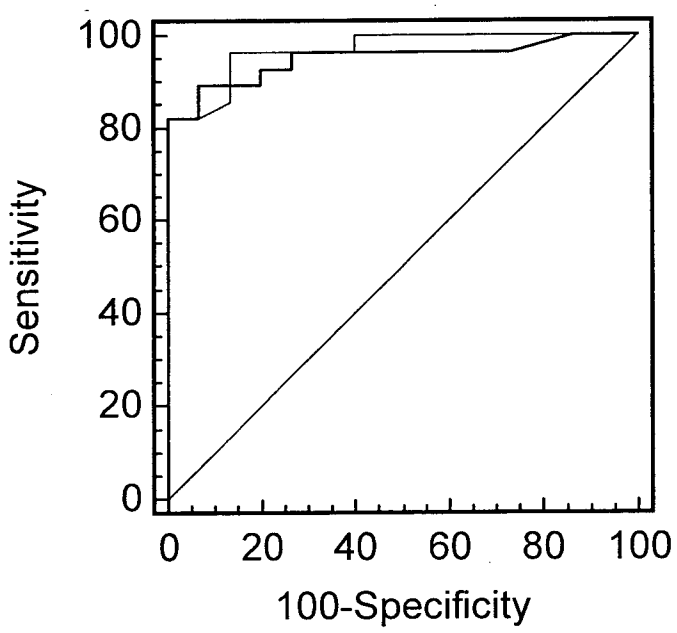

Figure 2

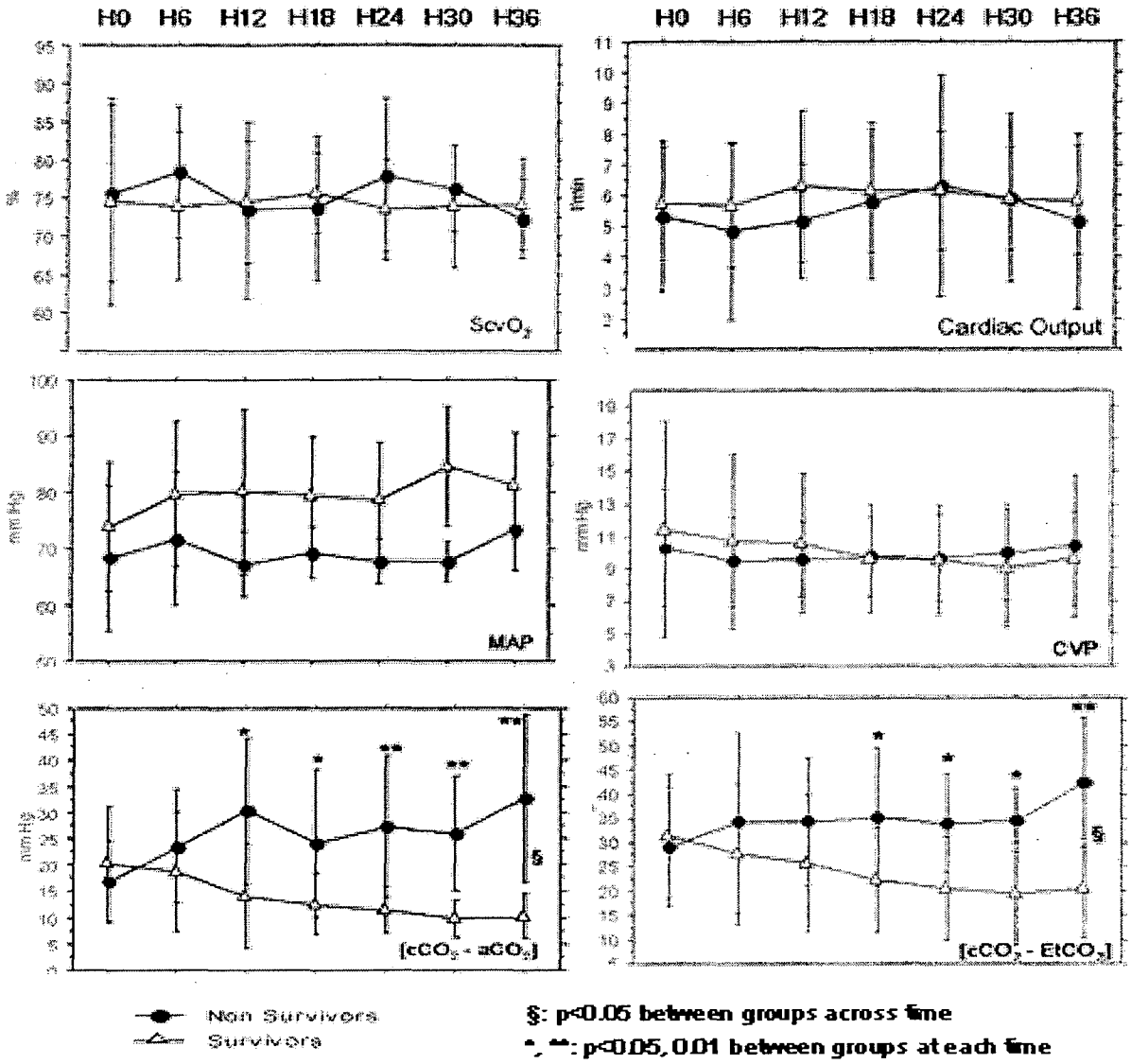
H0 H6 H12 H18 H24 H30 H36
ScvO2
Cardiac Output
MAP
CVP
[cCO2 - aCO2]
[cCO2 - EtCO2]
Non Survivors
Survivors
§: p<0.05 between groups across time
*, **: p<0.05, 0.01 between groups at each time

Figure 3

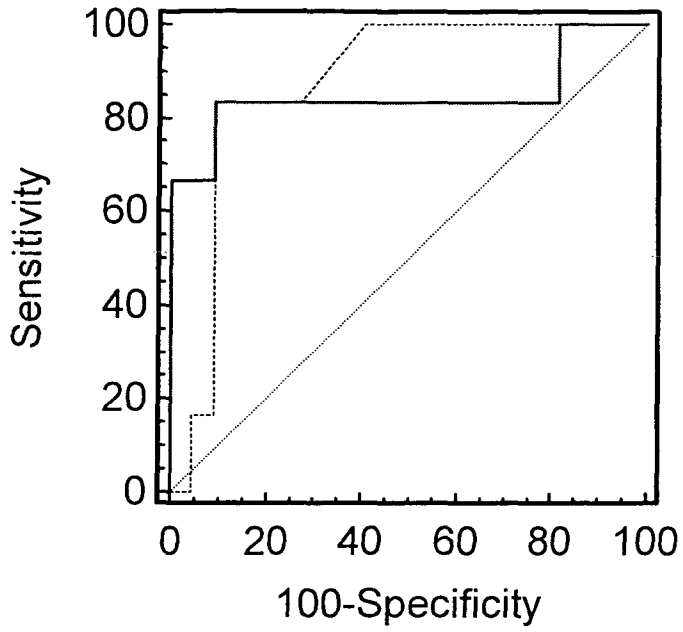

Figure 4

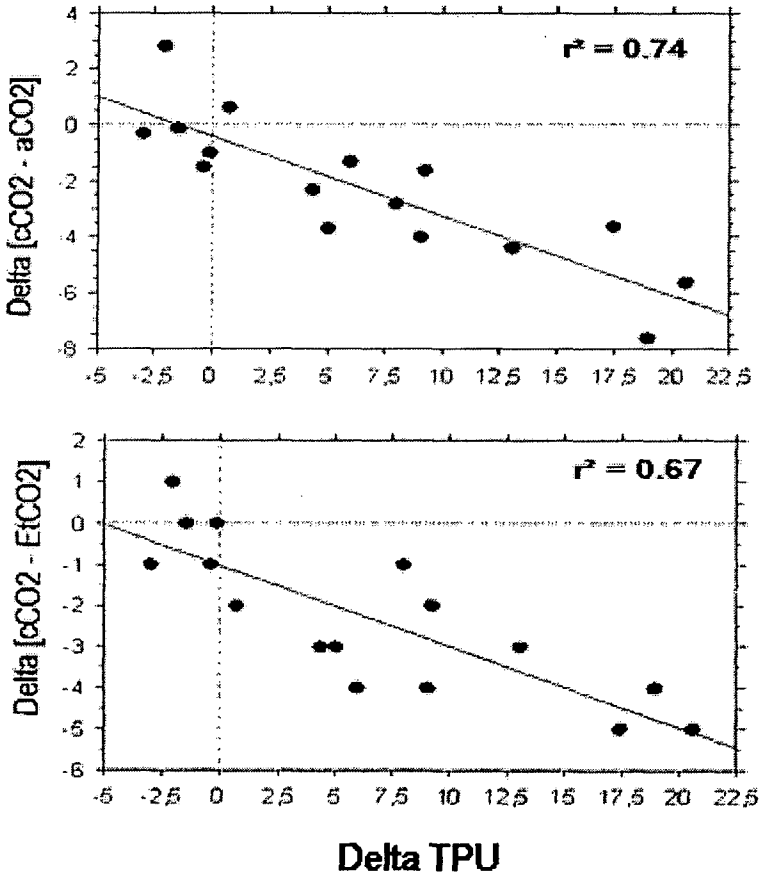

Figure 5

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2010/002407

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61B5/00 A61B5/026 A61B5/083
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61B

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	ROOTH, G. , EWALD, U. AND CALIGERA, F.: "Transcutaneous PO2 and PCO2 monitoring at 37 degrees Celsius cutaneaous PO2 and PCO2", ADV. EXP. MED. BIOL., vol. 220, 1987, pages 23-32, XP009131627, cited in the application the whole document	1-16
A	YAKOV SIVAN ET AL.: "Estimation of Arterial Carbon Dioxide by End-Tidal and Transcutaneous PCO2 Measurements in Ventilated Children", PEDIATRIC PULMONOLOGY, vol. 12, no. 3, March 1992 (1992-03), pages 153-157, XP002581196, the whole document	1-16

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[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

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"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
5 January 2011	18/01/2011
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 Manschot, Jan

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INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2010/002407

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	MAURO MANISCALCO ET AL: "Evaluation of a transcutaneous carbon dioxide monitor in severe obesity", INTENSIVE CARE MEDICINE, SPRINGER, BERLIN, DE, vol. 34, no. 7, 26 March 2008 (2008-03-26) , pages 1340-1344, XP019619062, ISSN: 1432-1238 the whole document	1-16

Form PCT/ISA/210 (continuation of second sheet) (April 2005)

专利名称(译)	用于评估患者组织灌注的非侵入性方法		
公开(公告)号	EP2470066A1	公开(公告)日	2012-07-04
申请号	EP2010768281	申请日	2010-08-27
申请(专利权)人(译)	援助PUBLIQUE - HÔPITAUXDE PARIS		
当前申请(专利权)人(译)	援助PUBLIQUE - HÔPITAUXDE PARIS		
[标]发明人	VALLEE FABRICE MATEO JOAQUIM PAYEN DE LA GARANDERIE DIDIER		
发明人	VALLEE, FABRICE MATEO, JOAQUIM PAYEN DE LA GARANDERIE, DIDIER		
IPC分类号	A61B5/00 A61B5/026 A61B5/083		
CPC分类号	A61B5/026 A61B5/0836 A61B5/1477 A61B5/412		
优先权	PCT/IB2009/006903 2009-08-28 WO		
其他公开文献	EP2470066B1		
外部链接	Espacenet		

摘要(译)

本发明涉及评估患者组织灌注的非侵入性方式，特别是用于治疗随访和脓毒性休克的预后。更具体地，通过测量所述患者的二氧化碳的皮肤分压来评估组织灌注，例如在具有PCO2传感器的耳垂处，其不在高于37.5℃的温度下加热，并且通过计算所述皮肤之间的差异。 PCO2和CO2的动脉或潮气末分压。用于执行连续非侵入性灌注随访的装置也是本发明的一部分。