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[Continued on next page]

(54) Title: METHOD OF DETECTING ARDS AND SYSTEMS FOR DETECTING ARDS

(57) Abstract: The invention is directed to a system and method for providing an ARDS indication of a patient comprising a sampling device for obtaining a gas sample of the exhaled breath of a patient, a measuring unit for measuring a content of n-octane in the exhaled breath of a patient, a controller which is able to distinguish if the patient has or may develop ARDS based on the content of n-octanein the exhaled breath of a patient resulting in a ARDS indication of the patient and provided with a protocol for providing output regarding the ARDS indication of the patient, and a user interface for indicating the ARDS indication to a user.

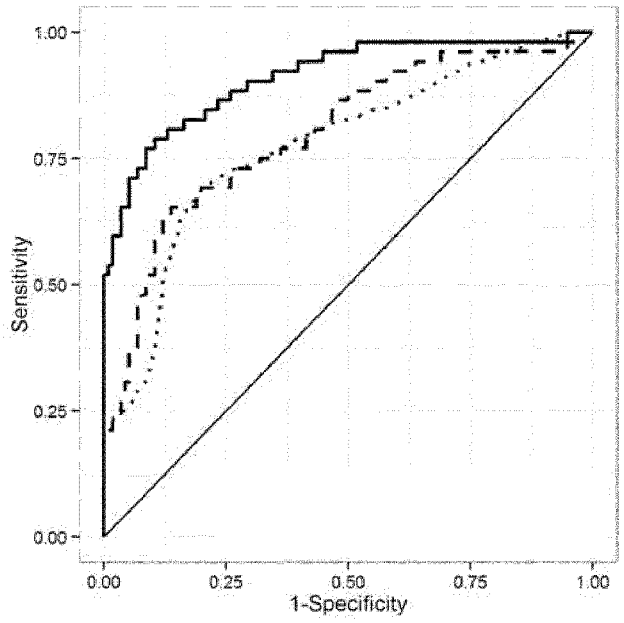

Fig. 3

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SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

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

Method of detecting ARDS and systems for detecting ARDS

The present invention is directed to a method to determine if a patient has or is developing ARDS. The invention is also directed to a system for detecting acute respiratory distress syndrome, also referred to as ARDS.

The lungs of intubated and mechanically ventilated patients are prone to infection and injury, at least in part because of the artificial airway, use of non–physiologic positive airway pressures and tidal volume/pressure–associated over distension of lung tissue. Prevalent complications include ventilator–acquired pneumonia (VAP) and ventilator–associated lung injury (VALI). Preexistent pulmonary damage, due to pneumonia and/or acute respiratory distress syndrome (ARDS) can be aggravated by mechanical ventilation resulting in increased mortality and morbidity. The clinical manifestation of infection and/or injury, including pulmonary infiltrations on chest X–ray, is preceded by molecular and cellular changes within the lung. Adequate and timely detections of the primary pathophysiological molecular and cellular mechanisms potentially could lead to prompt treatment initiation and targeted therapeutic interventions. Therefore, early and accurate biological markers of pulmonary injury and especially for ARDS are very much needed to either predict ARDS development in a patient or when ARDS has developed to enhance early diagnosis.

A valid and reliable definition for ARDS is furthermore considered important for clinical management and to facilitate enrolment of consistent patient phenotypes into clinical trials. The presently used Berlin criteria are empirically selected clinical, radiological and physiological variables. This definition is highly suitable for epidemiological studies but show a moderate correlation with post–mortem pathological findings. ARDS can still be mistaken for pneumonia or cardiogenic pulmonary edema (CPE), and vice versa.

In Crader et al., J Pulmonar Respirat Med 2012, 2:1 a number of potential biomarkers are described to predict ARDS for a patient. This overview paper states that a number of approaches for assessing biomarkers in breath and breath condensates have been proposed but none used so far. The paper also mentions that the potential for using breath biomarkers is substantial because it could provide a non-invasive way of directly and repeatedly analyzing the conditions which may contribute to ARDS development.

Currently chest X-rays allow diagnosis of ARDS in advanced stages. A disadvantage is that it exposes patients to radiation doses. Airway suction or lavage provides early detection. A disadvantage of these methods is that they are invasive and harmful to the patient. All of the above methods are furthermore not suitable for frequent checks if a patient has or may develop ARDS.

The invention is directed to method and systems which could provide adequate and timely detections of ARDS which could lead to prompt treatment initiation and targeted therapeutic interventions.

This is achieved by the following method. A method comprising sampling part of the exhaled breath of a patient to obtain a gas sample, measuring the content of n-octane in the gas sample and determining if the patient has ARDS or may develop ARDS using the measured content of n-octane in the gas sample.

Applicants found that higher contents of n-octane in exhaled breath is indicative for ARDS compared to the content of n-octane in the exhaled breath of patients not having ARDS. Thus n-octane is a suited breath biomarker for assessing if a patient has developed ARDS. This method thus enhances timely detection of ARDS. The method is further found to be not influenced by severity of the ARDS illness, ventilator settings or comorbidities.

The invention is also directed to

a system for providing an ARDS indication of a patient comprising a sampling device for obtaining a gas sample of the exhaled breath of a patient,

a measuring unit for measuring a content of n-octane in the exhaled breath of a patient,

a controller which is able to distinguish if the patient has or may develop ARDS based on the content of n-octane in the exhaled breath of a patient resulting in a ARDS indication of the patient and provided with a protocol for providing output regarding the ARDS indication of the patient, and

a user interface for indicating the ARDS indication to a user.

Preferably, the method is used for mechanically ventilated patients, invasively, for example via intubation, or non-invasively, for example using a mask. The method may be performed at home, in service flats, nursing homes and in hospitals. The method is especially suited for patients treated in an intensive care unit of a hospital.

The determining if the patient may develop ARDS and more especially if the patient has ARDS by using the measured content of n-octane in the gas sample may be

performed by determining if the measured content is above a predetermined threshold value which has been found to be predictive for ARDS. It may also be envisaged that the sensitivity of the prediction for some values of the n-octane content is not sufficient for practical use and that additional validation is required. Possible additional measurements and data for such validation will be discussed below. When the n-octane content is measured continuously or semi-continuously, for example when performing the method on-line, it may also be possible to use the rate of increase in n-octane content in the patients exhaled breath as the measurement determining if the patient has ARDS or may develop ARDS. The determination if a patient has ARDS or may develop ARDS may be communicated to a user by means of a user interface as will be further described below.

Applicants further found that lower acetaldehyde and/or 3-methylheptane contents are also indicative for ARDS when compared to the content of acetaldehyde and/or 3-methylheptane in exhaled breath of patients not having ARDS. Preferably the measured content of either one or both of these compounds is used to determine if the patient has ARDS or may develop ARDS. More preferably the measured content of either one or both of these compounds is used to validate the relevancy of the measured content of n-octane when determining if the patient has ARDS or may develop ARDS. Applicants found that when a content of n-octane is measured which lies in a region which is less significant for determining ARDS such additional data will improve the sensitivity of the method. In addition or alternatively the sensitivity of the method may also be improved using other patient parameters. With other patient parameters is meant any information regarding the patient not being the above described content of n-octane, acetaldehyde and/or 3-methylheptane in the exhaled breath of the patient. Such other patient parameters may be for example the ventilator settings and/or parameters, the patient monitoring data, such as for example heart rate, oxygenation, body temperature, and patient history data, such as for example pneumonia, heart failure, sepsis, and pancreatitis. An example of such other patient parameters comprises the lung injury prediction score (LIPS) of the patient. Applicants found that the LIPS can be used to validate the relevancy of the measured content of n-octane when determining if the patient has ARDS or may develop ARDS. The lung injury prediction score (LIPS) is well known and described by Gaijc O., et al in Am J Respir Crit Care Med 2011 Feb 15; 183(4):462-70.

The method comprises sampling part of the exhaled breath of a patient to obtain a gas sample and subsequent measurement of the gas sample as to its n-octane and optionally also to its acetaldehyde and/or 3-methylheptane content. Breath may be sampled

and measured off-line or online. The sampling device of a system for use in such an off-line method suitably comprises a sorbent tube and/or an air bag. An example of an off-line performed method is the following, wherein a patient breathes into an air bag, for example a Tedlar bag, for a certain amount of time. This results in that the bag is filled with the exhaled breath of the patient. The contents of the air bag may be measured directly. Alternatively a pump and a mass flow controller may be connected to the bag and the collected air is pushed or pulled with a fixed flow for a fixed amount of time through a sorbent tube. Mechanically ventilated patients, which are unable to breathe in a bag, may be sampled off-line by means of a small pump at the bed side which pulls breath samples directly through a sorbent tube. The thus obtained sorbent tube will contain a representative amount of the compounds present in the exhaled breath of the patient.

Subsequently the content of n-octane and optionally acetaldehyde and/or 3-methylheptane as present in the sampling device may be measured by means of analytical techniques. Preferably such a technique is a spectroscopy technique for example Time Of Flight Mass Spectrometry (TOF-MS), infra-red spectroscopy and Ion Mobility Spectrometry (IMS) and preferably Gas Chromatography Mass-Spectrometry (GC-MS). These techniques provide knowledge on individual molecular compounds and can provide precise measures on the n-octane content and the optional acetaldehyde and/or 3-methylheptane content in a breath sample. Sampling part of the exhaled breath may thus be performed using a sorbent tube and measuring the content is performed by means of gas–chromatography and mass–spectrometry (GC–MS). Such a method however requires rather laborious procedures, relatively large devices and trained operators.

For the above reason the method is preferably performed on-line. In such an on-line method the breath of a patient is passively or actively transported to a sensor or array of sensors. For monitoring this approach has a preference due to the ease and speed of processing. Using this method the breath analyzer can be embedded in the device that samples breath from the ventilator hoses, for example by using a pump. The on-line measurement of the content of n-octane and the optional acetaldehyde and/or 3-methylheptane in the breath samples may be performed by for example so-called Electronic Noses (eNoses) or miniaturized spectroscopy units as for example miniaturized GC (microGC) and/or Mass Spectrometry, Ion Mobility Spectroscopy (IMS)) and/or FAIMS (High-Field Waveform IMS) . Preferably such a breath analyzer is adapted to measure n-octane and optionally acetaldehyde and/or 3-methylheptane specifically.

An eNose consists of an array of non-specific gas chemical sensors combined with a chemometric processing tool. Different techniques exist for the precise type of chemical sensor and chemometric processing method. The choice of sensor and processing method will be based upon n-octane and optionally also acetaldehyde and/or 3-methylheptane. A possible measuring method may be based on molecular imprinting or optical techniques using infrared lighting. A skilled person will know that by adjusting the threshold while balancing sensitivity and specificity, an optimal setting can be found for such a device.

A more preferred on-line method is wherein a breath analyzer is embedded in the ventilator system or embedded in the patient monitor. This prevents the need for an additional device at the patient's bedside, and allows continuous monitoring of breath. Additionally, the lungs of ARDS patients are vulnerable to changes in pressure. Coupling or decoupling an additional device to the ventilator tubes may negatively influence the continuous pressure in the mechanical ventilator system, and may therefore damage the lungs. For embedding the breath analysis into the ventilator system eNose type of techniques can be used, or a dedicated n-octane, acetaldehyde and/or 3-methylheptane sensor as for example the miniaturized spectroscopy units described above.

The invention is also directed to n-octane for use in in-vivo diagnosis of ARDS and to acetaldehyde and/or 3-methylheptane for use in in-vivo diagnosis of ARDS.

The invention is also directed to a system described above. Such a system for providing an ARDS indication of a patient comprises a sampling device for obtaining a gas sample of the exhaled breath of a patient. The system further comprises a measuring unit for measuring a content of n-octane and optionally acetaldehyde and/or 3-methylheptane in the exhaled breath of a patient. The system also comprises a controller which is able to distinguish if the patient has or may develop ARDS based on the content of n-octane, acetaldehyde and/or 3-methylheptane in the exhaled breath of a patient resulting in a ARDS indication of the patient and provided with a protocol for providing output regarding the ARDS indication of the patient. The controller may suitably use the logic for determination if a patient has ARDS or may develop ARDS as described above for the method according to the invention. The system also comprises a user interface for indicating the ARDS indication to a user. Such a user interface may be present at the point of care, may be part of the monitor of a mechanical ventilator unit or may even be mobile interface which can be used in combination with more than one system according to the invention.

Preferably the measuring unit is a unit for measuring a content of n-octane and the controller is preferably able to distinguish if the patient has or may develop ARDS based on the content of n-octane in the exhaled breath of a patient and more especially according to the method described above.

The sampling device may be suited for off-line measurement of the content of the specific compounds in the exhaled breath. Suitably the sampling device comprises a sorbent tube and or an air bag and the measuring unit is a spectroscopy measuring unit as described for the above method.

More preferably the sampling device and measuring unit enable an on-line measurement of the exhaled breath. As explained above such a sampling device suitably is a device which samples breath from a ventilator hose which is part of a system to mechanically ventilate a patient. The measuring unit of such an on-line system is suitably the afore mentioned Electronic Nose, miniaturized spectroscopy units as for example miniaturized forms of GC (microGC) and/or Mass Spectrometry, Ion Mobility Spectroscopy (IMS) and/or FAIMS (High-Field Waveform IMS), wherein such measuring unit is specifically adapted to measure n-octane and optionally acetaldehyde and/or 3-methylheptane.

Preferably the method and system should not interfere with the ventilator in terms of pressures and flows, especially in the context of regulatory issues. Therefore, a side stream approach is preferred as for example illustrated in Figure 1. Figure 1 shows a schematic set up for an off-line system wherein air from a mechanically ventilated patient 4 is sampled using a so-called side stream approach. The exterior part of an intubation tube 5 is shown which is connected to a ventilator unit 7 via conduit 6 and a heat and humidity exchanger (HME) 3. Ventilator unit 7 may comprise of a flow sensor, a controller and a gas flow generator. The air is collected via side stream conduit 8 using pump and flow controller 1. Pump and flow controller 1 enable a controlled flow of exhaled breath to pass sorbent tube 2 using a small mechanical pump. An on-line system may be as in Figure 1 wherein a sorbent tube is not incorporated. In such a system the pump and flow controller 1 also comprises of a measurement unit for measuring the content of n-octane and optionally acetaldehyde and/or 3-methylheptane. Suitably such a side stream approach is integrated in the ventilator device, avoiding extra devices at the bedside, and avoiding abrupt pressure changes in the ventilator systems, which may harm the vulnerable lungs.

Examples

In a clinical trial with 54 mechanically ventilated intensive care unit patients (24 ARDS, 30 non-ARDS) have been subjected to an exhaled breath analysis using a system as in Figure 1. The content of n-octane in the sorbent tubes were analyzed by means of gas–chromatography and mass–spectrometry (GC–MS). In Figure 2 the results are presented. In this Figure a significant difference in abundance of n-octane for patients having ARDS is observed in comparison with the abundance of n-octane in the exhaled breath of patients not having ARDS. The abundancy of n-octane is expressed in counts of the GC-MS fragment at m/z = 114, as measured by the mass-spectrometer as part of the GC-MS which uses electron ionization to produce fragments of different mass over charge (m/z). Building a classifier model, and internally validating this, has shown that by using breath analysis and monitoring n-octane abundance we can distinguish patients with ARDS from patients without ARDS. This is illustrated by Figure 3. Figure 3 shows a so-called receiver operating characteristic (ROC) curve. Figure 3 shows three curves:

A dashed line which represents the performance of a classifier based on n-octane (C8) on distinguishing ARDS patients (AUC: 0.80 (95%-CI: 0.71-0.88).

A dotted line represents the performance of a classifier based on LIPS on distinguishing ARDS patients (AUC: 0.78 (95%-CI: 0.70-0.87).

A solid line represents the performance of a classifier based on n-octane (C8) and validated by LIPS on distinguishing ARDS patients (AUC: 0.91 (95%-CI: 0.85-0.97).

The results in Figure 3 show that n-octane is a good biomarker for ARDS and that the sensitivity at a given specificity can be even further enhanced by validating the measured n-octane content with the LIPS of the patient.

In their experiments applicants further identified acetaldehyde and 3-methylheptane as suitable biomarker for ARDS. They further found no differences in exhaled isoprene concentrations between patients with and without ARDS were observed. Isoprene was reported as a biomarker by Schubert et al. Application of a new method for analysis of exhaled gas in critically ill patients. Intensive Care Med 1998;24:415-421. The difference in results is believed to result from the fact that the patients in this study were included within 24 hours after ICU–admission, thereby early in the development of ARDS, whereas the patients in the study of Schubert *et al.* were included later during the course of disease. Thus the method and system according to the present invention is more effective in detecting the early development of ARDS.

CLAIMS:

1. A system for providing an Acute Respiratory Distress Syndrome (ARDS) indication of a patient comprising a sampling device for obtaining a gas sample of the exhaled breath of a patient,

a measuring unit for measuring a content of n-octane in the exhaled breath of a patient,

a controller which is able to distinguish if the patient has or may develop ARDS based on the content of n-octane in the exhaled breath of a patient resulting in a ARDS indication of the patient and provided with a protocol for providing output regarding the ARDS indication of the patient, and

a user interface for indicating the ARDS indication to a user.

2. System according to claim 1, wherein the system comprises a measuring unit for measuring a content of acetaldehyde and/or 3-methylheptane and a controller which is able to distinguish if the patient has or may develop ARDS based on the content of n-octane and the content of acetaldehyde and/or 3-methylheptane in the exhaled breath of a patient.

3. System according to any one of claims 1-2, wherein the sampling device comprises a sorbent tube and/or an air bag.

4. System according to any one of claims 1-3, wherein the sampling device and measuring unit enable an on-line measurement of the exhaled breath.

5. System according to any one of claims 1-4, wherein the sampling device is a device which samples exhaled air from a ventilator hose which is part of a system to mechanically ventilate a patient.

6. System according to any one of claims 1-5, wherein the controller in addition makes use of other patient parameters.

7. System according to claim 6, wherein the other patient parameters comprises the lung injury prediction score (LIPS) of the patient.

8. A method comprising sampling part of the exhaled breath of a patient to obtain a gas sample, measuring the content of n-octane in the gas sample and determining if the content of n-octane in the gas sample is above a predetermined threshold value.

9. A method according to claim 8, wherein the threshold value has been determined to be predictive for Acute Respiratory Distress Syndrome (ARDS).

10. Method according to claim 8 or 9, wherein the threshold value has been determined by balancing sensitivity and specificity of a chemical sensor used for the sampling to obtain the gas sample and the measuring the content of n-octane in the gas sample.

11. A method comprising sampling part of the exhaled breath of a patient to obtain a gas sample, measuring the content of n-octane in the gas sample and determining if the patient has Acute Respiratory Distress Syndrome (ARDS) or may develop ARDS using the measured content of n-octane in the gas sample.

12. Method according to any one of the claims 8-11, wherein the content of acetaldehyde and/or 3-methylheptane is measured and wherein determining if the patient has ARDS or may develop ARDS is performed by using the measured content of n-octane and the measured content of acetaldehyde and/or 3-methylheptane in the gas sample.

13. Method according to any one of claims 8-12, wherein sampling part of the exhaled breath is performed using a sorbent tube and/or an air bag.

14. Method according to any one of claims 8-12, wherein the sampling and measurement of the content is performed on-line.

15. Method according to any one of claims 8-14, wherein the patient is a mechanically ventilated patient.

16. Method according to any one of claims 8-15, wherein other patient parameters are used to validate the relevancy of the measured content of n-octane when determining if the patient has ARDS or may develop ARDS.

17. Method according to claim 16, wherein the other patient parameters comprises the lung injury prediction score (LIPS) of the patient.

18. n-octane for use in diagnosis of Acute Respiratory Distress Syndrome (ARDS).

19. n-octane for use in diagnosis of ARDS according to claim 19, wherein the diagnosis is an in vivo diagnosis.

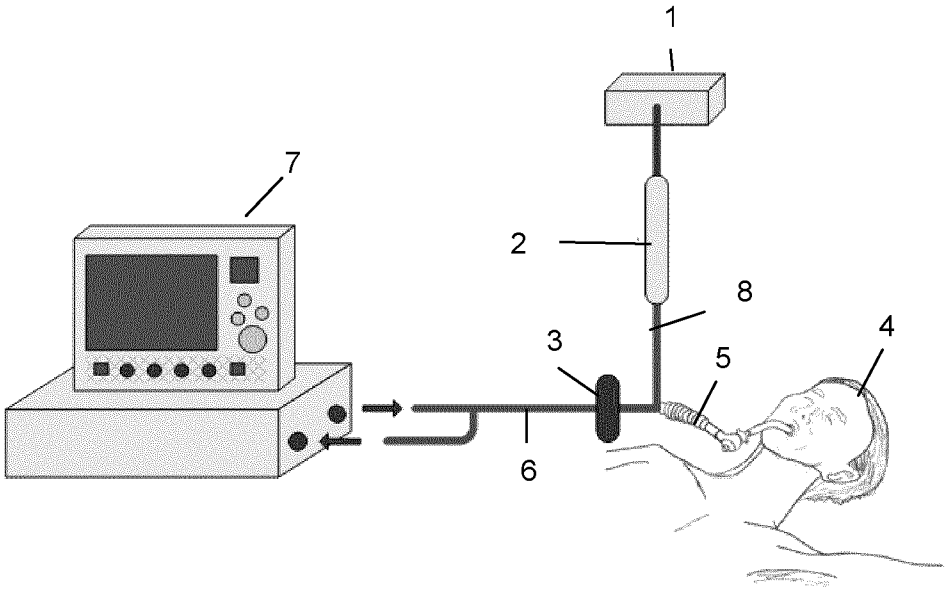
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Fig. 1.

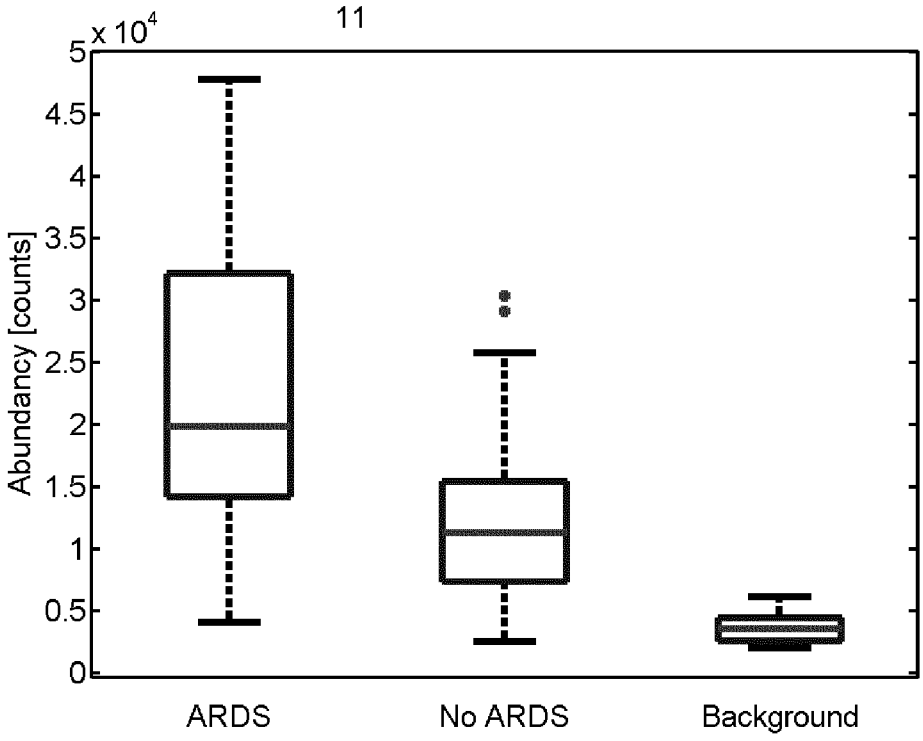
x 10^4
11
5
4.5
4
3.5
3
2.5
2
1.5
1
0.5
0
Abundancy [counts]
ARDS
No ARDS
Background

Fig. 2

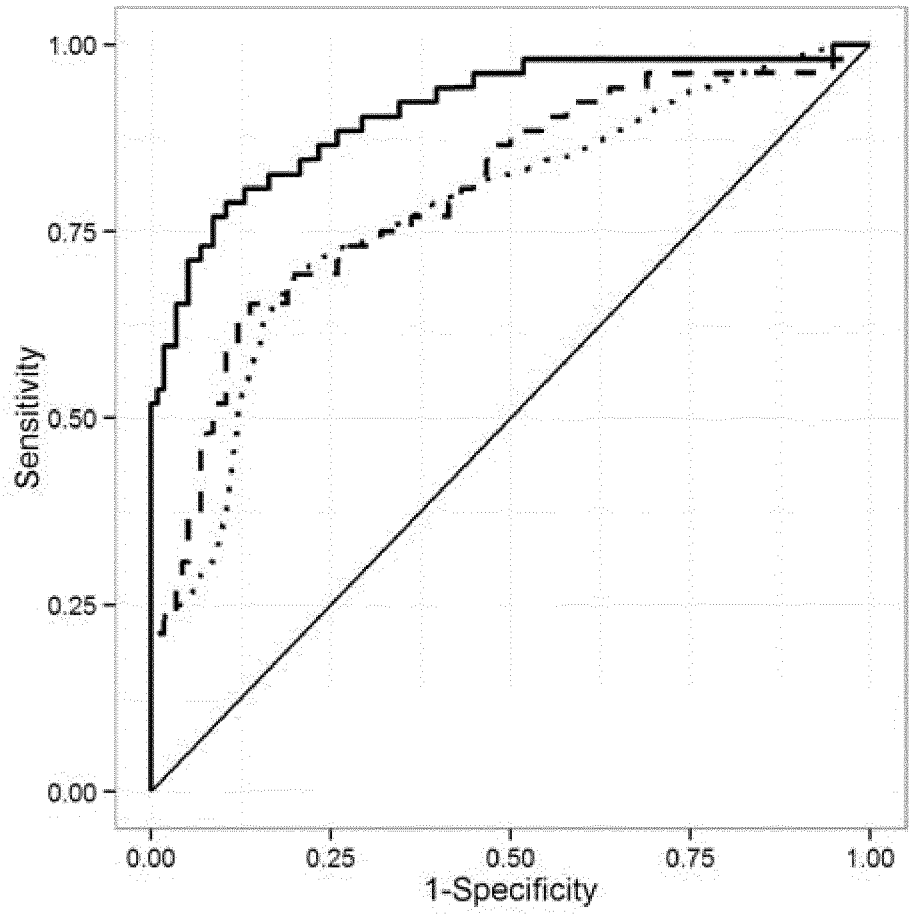
1.00
0.75
0.50
0.25
0.00
Sensitivity
0.00
0.25
0.50
0.75
1.00
1-Specificity

Fig. 3

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2015/052806

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61B5/08
ADD. G01N33/497 A61M16/00

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 G01N A61M

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	LIEUWE D.J. BOS ET AL: "A simple breath sampling method in intubated and mechanically ventilated critically ill patients", RESPIRATORY PHYSIOLOGY & NEUROBIOLOGY, vol. 191, 1 January 2014 (2014-01-01), pages 67-74, XP055106886, ISSN: 1569-9048, DOI: 10.1016/j.resp.2013.11.001	8
A	abstract page 67 - page 71 tables 1,3 figure 1	1-7

-/--

[X] 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
2 April 2015	13/04/2015

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Marteau, Frédéric

1

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

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	KIM DG VAN DE KANT ET AL: "Clinical use of exhaled volatile organic compounds in pulmonary diseases: a systematic review", RESPIRATORY RESEARCH, BIOMED CENTRAL LTD., LONDON, GB, vol. 13, no. 1, 21 December 2012 (2012-12-21), page 117, XP021134470, ISSN: 1465-9921, DOI: 10.1186/1465-9921-13-117 abstract tables 1-2 -----	1-8
A	BOS L D J ET AL: "Metabolomics in Critically ill Patients: Focus on Exhaled Air", ANNUAL UPDATE IN INTENSIVE CARE AND EMERGENCY MEDICINE 2012, SPRINGER, DE, vol. 2012, 1 January 2012 (2012-01-01), pages 53-62, XP008168116, ISBN: 978-3-642-25715-5 page 55 - page 60 -----	1-8

1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2015/052806

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 9-19
because they relate to subject matter not required to be searched by this Authority, namely:

see FURTHER INFORMATION sheet PCT/ISA/210

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

[ ] The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.1

Claims Nos.: 9-19

The subject-matter of claims 9-19 comprises the four steps acknowledged to form a diagnostic method practised on the human or animal body. In claim 9 -which is dependent on claim 8-, the step of 'measuring the content of n-octane in the gas sample' constitutes the examination phase , whereas the step of 'determining if the content of n-octane in the gas sample is above a predetermined threshold value' comprises both the comparison and finding of any significant deviation with standard value. Finally, 'wherein the threshold has been determined to be predictive for Acute Respiratory Distress Syndrome (ARDS)' is considered to give to the step of 'determining if the content of n-octane in the gas sample is above a predetermined threshold value' the characteristic of a decision phase . In claim 11, the step of 'measuring the content of n-octane in the gas sample' constitutes the examination phase , whereas the steps of comparison and finding of any significant deviation with standard value are implicitly claimed. Indeed, in light in the description, these steps are mandatory in order to perform the last step of 'determining if the patient has ARDS or may develop ARDS using the measure content of n-octant in the gas sample' which is considered to constitute the decision phase . The subject-matter of claims 18-19 explicitly relates to a method of diagnostic on human or animal body. For the sake of completeness, in the light of the description, the claimed methods 9-19 encompass the case of the method being performed on the human body as the applicant describes it in the present invention as a on-line measurement of the n-octane (see figure 1, page 6, lines 11-31) on a ventilated patient (see page 2 lines 29-32). Therefore, this Authority is not required to search the present application with respect to the aforementioned claims (Article 17(2)(b) PCT and Rule 39.1(iv) PCT). Consequently, no International Search Report and no Written Opinion (Rule 67.1 PCT in combination with Rule 43bis.1(b) PCT) have been established with respect to them.