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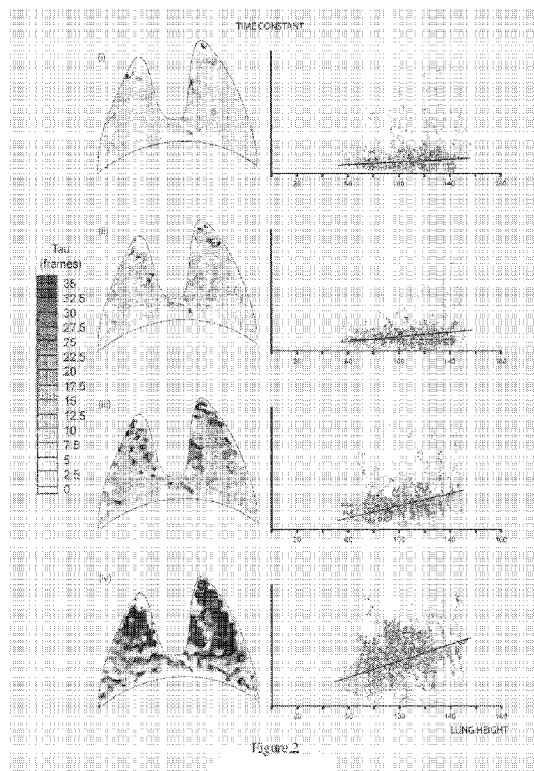
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(54) Title: METHOD AND SYSTEM FOR CLINICAL MEASUREMENT OF LUNG HEALTH

(57) Abstract: A method for investigating a subject lung, the method comprising the steps of (i) applying resistance to respiration of the lung, (ii) carrying out a functional measurement of the lung and (iii) correlating the resistance applied with the functional measurement to obtain information regarding lung function.





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METHOD AND SYSTEM FOR CLINICAL MEASUREMENT OF LUNG HEALTH

FIELD OF INVENTION

[0001] The present invention relates to the field of clinical measurement of the lung for diagnostic or research applications.

[0002] In one form, the invention relates to dynamic lung health measurement in a human or animal.

[0003] In one particular aspect the present invention is suitable for use in lung function testing for assessing lung function and lung condition.

[0004] It will be convenient to hereinafter describe the invention in relation to human medical applications; however it should be appreciated that the present invention is not so limited and could additionally be used in relation to veterinary applications.

BACKGROUND ART

[0005] It is to be appreciated that any discussion of documents, devices, acts or knowledge in this specification is included to explain the context of the present invention. Further, the discussion throughout this specification comes about due to the realisation of the inventor and/or the identification of certain related art problems by the inventor. Moreover, any discussion of material such as documents, devices, acts or knowledge in this specification is included to explain the context of the invention in terms of the inventor's knowledge and experience and, accordingly, any such discussion should not be taken as an admission that any of the material forms part of the prior art base or the common general knowledge in the relevant art in Australia, or elsewhere, on or before the priority date of the disclosure and claims herein.

[0006] Lung diseases adversely affect airflow during breathing and alter normal lung motion. Specifically, lung diseases change the elasto-mechanical and aero-resistive properties of the lung which in turn alters the airflow in and out of the lung. For example, interstitial fibrosis increases distal airway stiffness, asthma increases airway resistance

and emphysema reduces lung tissue recoil thereby increasing its compliance. Although these diseases differ markedly in both cause and consequence, the mechanical properties of diseased regions are invariably impaired and this must also alter motion of these regions.

[0007] Little is known about the dynamics of lung motion during respiration, particularly how different regions of the lung move in relation to other regions during both inspiration and expiration. It is not known whether the lung expands and deflates uniformly, or whether specific regions lead or trail other regions due to differences in local compliances or proximity to the diaphragm. Similarly, it is generally unknown how diseases affect regional lung motion and whether motion in healthy regions is altered to compensate for diseased regions. Although this information is best provided by imaging the lung in situ, it has not hitherto been possible to image the lung with sufficient spatial and temporal resolution.

[0008] Previous techniques to measure lung motion have relied on techniques such as the surgical placement of markers, inhalation of contrast agents or removal of the chest wall for imaging.

[0009] A commonly used clinical measure of lung health is spirometry, which assesses global pulmonary function by measuring the amount (volume) and/or speed (flow) of air that can be inhaled and exhaled. Spirometry is an important tool used for generating pneumo-tachographs and calculating the expiratory time-constant which is the product of lung compliance (elasticity) and resistance. Both are helpful in assessing conditions such as asthma, pulmonary fibrosis, cystic fibrosis and chronic obstructive pulmonary disease.

[0010] Forced Oscillation Technique (FOT) is a very popular and successful global lung function test. FOT works by applying an oscillation to the airway opening and then simultaneously measuring the pressure and flow at the airway opening. FOT determines the impedance of the lungs with very limited regional information. This technique is popular for determining the state and function of lung tissue non-invasively by measuring the lungs' reaction to a series of input oscillations. Oscillations are generally in the order of 4-48Hz and as a result any technique to measure the lung response across such a

broad range will obviously require very high temporal resolution. For example, US patent 5,318,038 (Jackson et al) describes an infant respiratory impedance measuring apparatus and method that use FOT.

[0011] One of the drawbacks of this technology is that it cannot measure compliance or resistance locally within the lungs in a true regional fashion and as a result it is unable to detect subtle physiological changes throughout the lungs. Due to the global nature of the measurements involved in these lung function tests and the potential of destructive interference between different signals in lung regions there is the likelihood that these approaches will result in lost information.

[0012] Standard imaging techniques such as X-ray Computer Tomography (CT) and Magnetic Resonance Imaging (MRI) imaging during breath-holds provide little or no information on lung motion and cannot detect disease that cause subtle changes in lung structure or function. These approaches are particularly limited by the need to image the lung while it is stationary to minimise blurring. In particular, MRI and CT have poor temporal resolution preventing them from being used to image the lungs during a dynamic lung test. Furthermore, due to long acquisition times, both MRI and CT are often used to compare the state of the lung at two different time intervals, usually minutes apart. Interpolation is required to deduce lung motion between two steady state conditions within a breath and such methods assume that the motion follows a linear or defined path. This has obvious drawbacks and limits the ability of the techniques to be used for dynamic lung function testing.

[0013] Clinical gated 4D-CT has also been used for measurement of lung function, including expansion using traditional absorption based imaging at the expense of significant levels of radiation dose. Typically, the phase matching is performed to an accuracy of 7.1% of the breath cycle or 400ms. This results in poor temporal resolution for investigation for the dynamic patterns of motion and expansion within the lung, particularly for small animal studies.

[0014] US patent applications 2011/0034818 (Gat), 2010/0298740 (Gelman), 2008/0281219 (Glickman) and 2008/0221467 (Papayan) describe inventions relating to vibration response imaging (VRI), which measures air flow in the lungs using pressure

sensors placed on the subject thorax. VRI is an external measurement of interference from the chest wall and pleural cavity. It is a very general measurement of pressure change and is subject to many forms of interference (eg from the chest wall, ribs, pleural space and heart). However it has extremely poor spatial resolution and cannot provide information regarding lung tissue motion.

[0015] Vibration Response Imaging (VRI) is a technology developed for investigating regional lung function and for diagnosis of conditions. US patent application 2007/0244401 relates to a method and system for assessing an interventional pulmonology procedure including VRI imaging. Images indicative of airflow in at least a portion of the respiratory tract are generated from signals indicative of pressure waves at transducers applied to the skin of a subject. Specifically, the signals are measured before and after the interventional pulmonology procedure and used to generate images for comparison. This technique however, suffers from very poor spatial resolution and is based on measurements taken through the chest wall resulting in poor dynamic range of measurements.

[0016] Electrical Impedance Tomography (EIT) is a technique of measuring the impedance through the chest of an electrical signal. EIT provides information through a horizontal slice of the lung, is easily affected by the electrical signals of the heart and has very poor spatial resolution. Typically temporal resolutions of only up to 44Hz have been used.

[0017] A number of devices have also been developed in an attempt to provide more informative data relating to lung function. US patent application 2011/0054341 (Jeong et al) teaches the use of a spirometer apparatus worn in association with a band around the patient's chest. The band includes a variable resistor with a conductive yarn, the length (and concomitantly the resistance) of which changes according to the change in circumference of the patient's chest during breathing. However, this apparatus is only capable of measuring resistance globally across the whole lung and provides no regional information. This method is also affected by changes in lung structure, such as the deformation of the lung due to the action of the diaphragm.

[0018] US patent 5,720,709 (Schnall) teaches the use of an apparatus for measuring airway resistance by short-time occlusion of inhalation. A pneumo-tachograph is mounted in a narrow airway and connected to recording instrumentation. An elastic balloon is positioned in the inlet channel and manually inflated and deflated with liquid using a syringe. This alternately hinders or allows air to flow through the airway. However the information recorded is limited to the airway measured and because it is manually controlled, issues arise in relation to the accuracy, reliability, repeatability and meaning of the measurements.

[0019] Despite advances in lung imaging, altered patterns of lung motion at specific locations have not hitherto been utilised for disease detection. Accordingly, there is a need for improved technologies for assessing lung function and diagnosing lung conditions.

SUMMARY OF INVENTION

[0020] An object of the present invention is to provide improved technology for assessing lung function and diagnosing lung conditions.

[0021] Another object of the present invention is to provide an improved method for dynamic lung function testing.

[0022] Another object of the present invention is to provide improved technology for assessing lung function and lung condition in a localised manner.

[0023] Another object of the present invention is to provide a method and apparatus for measuring regional respiratory impedance using a flow restriction, or resistance to respiration.

[0024] A further object of the present invention is to alleviate at least one disadvantage associated with the related art.

[0025] It is an object of the embodiments described herein to overcome or alleviate at least one of the above noted drawbacks of related art systems or to at least provide a useful alternative to related art systems.

[0026] In a first aspect of embodiments described herein there is provided a method for investigating a subject lung, the method comprising the steps of (i) applying resistance to respiration of the lung, (ii) carrying out a functional measurement of the lung and (iii) correlating the resistance applied with the functional measurement to obtain information regarding lung function.

[0027] The functional measurement may, for example, be carried out multiple times in response to changes in resistance. Specifically, at least steps (i) and (ii) may be repeated with the application of different resistance. At least one of the repetitions is preferably zero external resistance. Typically the outcome of the method is a record of volume flow versus resistance, thus providing a measure of lung compliance.

[0028] The method may include a step of varying another parameter that affects respiration. For example, the inhaled air may include an agonist or antagonist, such as beta-2-adrenergic receptor agonists, methylxanthines or leukotriene antagonists which are used to treat asthma and other pulmonary disease states. The method of the present invention may be carried out each time the subject lung is exposed to a different dosage.

[0029] In a second aspect of embodiments described herein there is provided a method for investigating a subject lung, the method comprising the steps of (i) applying resistance to respiration of the lung, (ii) carrying out a functional measurement of the lung comprising imaging and, (iii) correlating the resistance applied with the functional measurement to obtain information regarding lung function.

[0030] Steps (i), (ii) and (iii) may be carried out simultaneously, or in sequence. For example, step (ii) may be carried out simultaneously or subsequently to step (i), and step (iv) may be carried out simultaneously or subsequently to step (ii).

[0031] In a third aspect of embodiments described herein there is provided a method for investigation of a subject lung, the method comprising the steps of;

- (i) applying resistance to respiration of the subject lung,
- (ii) carrying out a functional measurement of the subject lung comprising imaging,

and

- (iii) correlating the functional measurement with the imaging to obtain information regarding lung function.

[0032] **Functional Measurement:** The present invention includes any convenient functional measurement at one or more locations. In a particularly preferred embodiment the functional measurement is performed with a change in expiratory resistance. In another embodiment the functional measurement is performed with a change in changing resistance to inhalation. By adding an external resistance to respiration, typically at the airway opening, the variation of lung mechanics can be assessed. For example, the subject may be made to expire through one or more resistors. The resistors can be located at the subject's mouth to control and change expiratory resistance of the subject. The resistor could also be placed in a specific airway of the subject to restrict only a specific airway or region of the lung. The resistor could be located in place by any convenient method such as via a catheter balloon.

[0033] A commonly used functional measurement of lung health is the expiratory time constant, which is known to be equal to the product of lung compliance (elasticity) and resistance. It is typically clinically measured by spirometry. External resistance increases the time constant for both inspiration and expiration.

[0034] In a preferred embodiment of the present invention, resistance is applied to the subject lung during inspiration and expiration. In another preferred embodiment, resistance is applied to inspiration only. In another preferred embodiment resistance is applied to expiration only.

[0035] In another preferred embodiment, resistance is applied to both the inspiration and expiration phase of the respiratory cycle, but the functional measurement is only carried out on one of the two phases. In another preferred embodiment, resistance is applied to both the inspiration and expiration phase of the respiratory cycle, and the functional measurement is carried out on one or more expirations, and subsequently, one or more inhalations. The functional measurement typically comprises analysis of the time constant.

[0036] **Resistance:** Typically, a resistor is used for imparting resistance. The resistor may be any convenient device for modifying the flow of inhaled or exhaled air. For example, the resistor may simply comprise a piece of tubing. However, it is important that the characteristics of the tubing are known and can be accounted for.

[0037] The resistor may form part of a device that imparts variable resistance at the mouth and measures the time constant at the airway opening. The resistor may comprise, for example a pneumotach type flow device or an impeller flow measurement device with an additive resistance or restriction through which the air must flow.

[0038] In another embodiment the resistor comprises a valve, such as an iris valve.

[0039] The resistor may impart a constant level of resistance. Alternatively, the resistor may impart variable resistance. On one embodiment, multiple resistors, each of different resistance may be attached to a manifold so that the resistance can be changed.

[0040] **Imaging:** The lung imaging may be any convenient two dimensional or three dimensional lung imaging means including X-ray velocimetry, CTXV, Xe-CT (contrast), hyperpolarised He-MRI scanning (optimally with N₂ wash-outs), EIT, or the imaging method described in WO 2011/032210.

[0041] The lung imaging could provide, for example, multiple independent regions of the lung (ie as many as 2,000 to 1,000,000) allowing a functional measurement to be made at each of the 2,000 to 1,000,000 localities imaged, instead of being averaged over the entire lung.

[0042] In particular, the lung imaging method described in WO 2011/032210 (Fouras & Dubsky) would be particularly preferred X-ray technique for the method of the present invention because it would provide a lower radiation dose to the subject as compared with other methods. The preferred non-X-radiation technique is He-MRI scanning however it provides general function information instead of the regional information provides by the technique of WO 2011/032210

[0043] With particular reference to the imaging technique described in WO 2011/032210, in another aspect of embodiments described herein there is provided a method for investigation of a subject lung, the method comprising the steps of:

- (i) applying resistance to respiration of the subject lung,
- (ii) carrying out a functional measurement of the lung,
- (iii) carrying out imaging of the lung by,
 - (a) recording images encoding data for the lung in terms of coordinates,
 - (b) reconstructing a 2D or 3D data field from the information encoded in the recorded images,
 - (c) segmenting an image of the lung, and
 - (d) associating each segment with regions of the 2D or 3D data field wherein the reconstruction is performed without first reconstructing 2D or 3D images,
- (iv) correlating the functional measurement with the imaging,

wherein steps (iii) and (iv) are automated.

[0044] It will be readily apparent to the person skilled in the art that any suitable coordinate system could be used for the imaging and data could be converted from one

coordinate system to another. For example, Cartesian, cylindrical or polar coordinates could be used, or local coordinates that are oriented to the relevant anatomical features of the lung. The term 'region' or 'regional' is used in the sense of functional information pertaining to an area or locale (such as, for example, a part of the lung, such as a lobe) and may be used in contradistinction to functional information derived from a combination or average of data from multiple regions (such as, for example the entire lung). The term region or regional may also be based on geometrical or any arbitrary markers and not based on anatomical markers, for example a region may for example be a slice or a block based on image co-ordinates or any co-ordinate system. Thus, the present invention may be used to present functional information that is commonly used in scientific and clinical practice but has not hitherto been available regionally, in a manner that is useful and relevant to medical practitioners and clinicians.

[0045] The present invention permits the extraction and manipulation of data to allow presentation of functional information in a format that is easy to compare and interpret. In particular, it can be made easy to interpret for medical and clinical practitioners, who have become accustomed over time to certain metrics and methods of presentation. In particular it can be used for presentation of regional functional information.

[0046] It should be apparent to a person skilled in the art that this invention is well suited for use in methods of imaging respiratory time constants. Such methods commonly include wash-in and wash-out of gases during CT and MRI imaging. This provides regional information on respiratory time constants within the lungs. For instance this invention may be used in making multiple measurements of respiratory time constants throughout a subject lung for each of several different resistances imposed at the subject's mouth or at a specific location within the lungs. In this manner one or more time constants can be obtained for one or more locations in a subject lung.

[0047] In addition this invention may also be used for 2D imaging methods such as fluoroscopy, or even a 2D variant of a CTXV system. A 2D imaging system is ideally suited to applications where fast imaging is required and patient cooperation is limited, such as in the paediatric environment. A 2D system will provide information of regional lung function, at extremely low radiation dose, and is thus acceptable for use in

paediatrics. This technique can also be used in a CTXV scanner as a screening test prior to the full CTXV scan or even during a CTXV scan.

[0048] **Correlation:** Correlation of the functional measurement with the imaging may be carried out, for example, by making a first functional measurement of expiration then changing the expiratory resistance (eg by adding an extra resistor at the subject's mouth during expiration) and making a second functional measurement. The measurements can be expressed as pairs of simultaneous equations and solved for both the compliance and the resistance of the lung at every location imaged.

[0049] The results of correlating the functional measurement with the imaging can be presented in any convenient format including text, graphics or a combination of text and graphics.

[0050] The method of the present invention may further include the use of a lung model. For example, the one or more images recorded may be applied to a multidimensional lung model so that a multidimensional image field of the subject lung can be reconstructed. If a lung model is used, the extra information provided by the images adds extra degrees of freedom (parameters) to the model. For example, the resistance and compliance (two parameters of the expiratory time constant C) can be represented for each region of the subject lung. Carrying out measurements with and then without resistance allows the resistance and compliance terms to be separated. Alternatively, the resultant output may be averaged across the whole lung.

[0051] In a further aspect of embodiments described herein there is provided a method for investigation of a subject lung, the method comprising the steps of:

- (i) applying resistance to respiration of the subject lung,
- (ii) carrying out a functional measurement of the subject lung,
- (iii) recording at least one in vivo image of the subject lung in one or more regions;

- (iv) applying said at least one in vivo image to a multidimensional lung model,
- (v) reconstructing a multidimensional image field of the subject lung, and
- (v) correlating the functional measurement with the multidimensional image field to obtain information regarding regional lung function.

[0052] In yet a further aspect of embodiments described herein there is provided a system when used for the method of the present invention, the apparatus comprising:

- (a) a means for applying expiratory resistance to the subject,
- (b) one or more energy sources for imaging; and
- (c) one or more detectors for recording images created by energy from the one or more energy sources passing through a sample;

wherein in use, the subject is located intermediate the energy sources and detectors and at least one image is recorded at each of a single, or a plurality of energy projection angles simultaneously with the application of expiratory resistance to the subject.

[0053] Any convenient range of projection angles may be used from 1° to 360°. However, typically the range of projection angles does not reach the extremes of this range. For example, projection angles spaced over as little as 30° or as much as 180° are likely to be suitable. The different energy projection angles may be achieved by moving the subject relative to the energy sources and detectors, or by moving the energy sources and detectors relative to the subject, or a combination thereof.

[0054] In addition to at least one energy source and detector, the apparatus for use with the method of the present invention may include a number of other components including, for example, (i) systems for modulating and aligning the source, the target and/or the detector, (ii) systems for image capture, processing and analysis, and (iii) a convenient user interface

[0055] Other aspects and preferred forms are disclosed in the specification and/or defined in the appended claims, forming a part of the description of the invention.

[0056] In essence, embodiments of the present invention stem from the realization that improved information relating to lung health can be obtained by changing expiratory resistance of the lung in concert with the use of an imaging technique. More specifically the present invention stems from the realisation that direct in vivo measurement of lung tissue motion (with concomitant accurate measurement of volume and flow, with improved spatial resolution) coupled with a change in resistance, can be used to obtain values for both compliance and resistance of the lung. In particular, the measurements can be obtained for individual regions or locations instead of being averaged out over the entire lung.

[0057] Advantages provided by the present invention comprise the following:

- simple and easy to implement,
- can be adapted to existing lung imaging systems,
- allows measurement of the lung health at multiple locations,
- provides more detailed information on lung function and health,
- can directly measure in vivo lung tissue motion coupled with change in resistance to provide data on both compliance and resistance of the lung.

[0058] Further scope of applicability of embodiments of the present invention will become apparent from the detailed description given hereinafter. However, it should be understood that the detailed description and specific examples, while indicating preferred embodiments of the invention, are given by way of illustration only, since various changes and modifications within the spirit and scope of the disclosure herein will become apparent to those skilled in the art from this detailed description.

BRIEF DESCRIPTION OF THE DRAWINGS

[0059] Further disclosure, objects, advantages and aspects of preferred and other embodiments of the present application may be better understood by those skilled in the relevant art by reference to the following description of embodiments taken in conjunction with the accompanying drawings, which are given by way of illustration only, and thus are not limitative of the disclosure herein, and in which:

Figure 1 illustrates a plot of expiratory time constants calculated using 2D X-ray PIV data for seven rabbit pups with data averaged over each lung, which is equivalent to carrying out measurements at the mouth as per traditional spirometry of the prior art.

Figure 2 includes plots showing the variation of measured lung time constant with lung height for a preterm rabbit pup under four levels of expiratory resistance with corresponding maps showing regional time constants calculated using X-ray PIV imaging.

DETAILED DESCRIPTION

[0060] The lung is a complex and non-homogeneous system. Exhaling through the resistor causes varying changes through out different regions of the lung. The present invention is based on the placing of an external resistor adjacent the lung, varying the degree of resistance and monitoring the effect on the lung. Imaging is a particularly effective means for monitoring the effect. This may be done for example, by carrying out a normal scan, then subsequent scans after each change in resistance.

[0061] The method of the present invention was applied to a group of seven rabbit pups (n=7). Figure 1 illustrates a plot of expiratory time constants calculated using 2D X-ray PIV data for the seven pups but with data averaged over each lung. The pups are indicated as follows: Pup 1 $\diamond$; Pup 2 $\blacksquare$, Pup 3 $\blacktriangle$; Pup 4 $\times$; Pup 5 $+$; Pup 7 $\bullet$; and Pup 8 $+$.

[0062] The data obtained is equivalent to carrying out measurements at the mouth as per traditional spirometry of the prior art. Different degrees of airway resistance were applied by having the pups breath through tubes of different lengths.

[0063] Figure 2 includes graphs showing the variation of measured lung expiratory time constant (x-axis) with lung height (y-axis) for (i) low, (ii) moderately low, (iii) normal and (iii) high additional airway resistance. Each graph is adjacent a corresponding map showing regional time constant calculated via X-ray PIV imaging methodologies.

[0064] Figure 2 illustrates how, as resistance is increased there is decreasing homogeneity of the lung, with air taking longer to expire from the top of the lungs (apex) than the bottom (base). This relationship allows us to solve for the resistance and compliance of the lung on a regional basis. A minimum of only two resistance measurements are actually required.

[0065] A large number of unknowns may be involved. Accordingly, efforts have been made to see which unknown changes with each change in resistance. This is a first step in creating a useful mathematical model of the lung.

[0066] With respect to the results shown in Figures 1 and 2, the expiratory time constant has been measured at the same time as carrying out imaging sequences. The expiratory time constant is the time taken to expel 63% of lung volume. In rabbit lungs this has shown a shift in behaviour which can be used to measure resistance (r) and compliance (c) – two parameters of the expiratory time constant (C). The value C is relatively constant across the lung. Potentially, C could be measured across the lung from the aforementioned method, especially if the properties of resistance across the lung are known.

[0067] A spatial model for r and c can be calculated throughout the lung. For example r may vary from one part of the lung to another and trending can be used. Accordingly, it is not necessary to make large numbers of scans in multiple regions because predictive or trending tools can be used.

[0068] While this invention has been described in connection with specific embodiments thereof, it will be understood that it is capable of further modification(s). This application is intended to cover any variations uses or adaptations of the invention following in general, the principles of the invention and including such departures from the present disclosure as come within known or customary practice within the art to which the invention pertains and as may be applied to the essential features hereinbefore set forth.

[0069] As the present invention may be embodied in several forms without departing from the spirit of the essential characteristics of the invention, it should be understood that the above described embodiments are not to limit the present invention unless otherwise specified, but rather should be construed broadly within the spirit and scope of the invention as defined in the appended claims. The described embodiments are to be considered in all respects as illustrative only and not restrictive.

[0070] Various modifications and equivalent arrangements are intended to be included within the spirit and scope of the invention and appended claims. Therefore, the specific embodiments are to be understood to be illustrative of the many ways in which the principles of the present invention may be practiced. In the following claims, means-plus-function clauses are intended to cover structures as performing the defined function and not only structural equivalents, but also equivalent structures.

[0071] "Comprises/comprising" and "includes/including" when used in this specification is taken to specify the presence of stated features, integers, steps or components but does not preclude the presence or addition of one or more other features, integers, steps, components or groups thereof. Thus, unless the context clearly requires otherwise, throughout the description and the claims, the words 'comprise', 'comprising', 'includes', 'including' and the like are to be construed in an inclusive sense as opposed to an exclusive or exhaustive sense; that is to say, in the sense of "including, but not limited to".

CLAIMS

1. A method for investigating a subject lung, the method comprising the steps of (i) applying resistance to respiration of the lung, (ii) carrying out a functional measurement of the lung and (iii) correlating the resistance applied with the functional measurement to obtain information regarding lung function.
2. A method according to claim 1 wherein at least steps (i) and (ii) are repeated with the application of different resistance.
3. A method according to claim 2 wherein at least one of the different resistances applied is zero
4. A method according to claim 1 wherein the information obtained is a measure of lung compliance expressed as a record of volume flow versus resistance.
5. A method for investigating a subject lung according to claim 1, wherein the functional measurement comprises imaging of the lung to obtain information regarding lung function.
6. A method for investigating a subject lung according to claim 5 wherein the information obtained is a measure of one or more time constants at one or more locations in the lung.
7. A method for investigating a subject lung according to claim 2 wherein step (iii) comprises 2D imaging and the information obtained is regional lung function.
8. A method according to claim 1 wherein steps (i), (ii) and (iii) are carried out simultaneously or in sequence.
9. A method for investigation of a subject lung, the method comprising the steps of:
 - (i) applying resistance to respiration of the subject lung,

- (ii) carrying out a functional measurement of the subject lung comprising imaging,

and

- (iii) correlating the functional measurement with the imaging to obtain information regarding lung function.

10. A method according to claim 9 wherein the steps are repeated with a different resistance applied at each repetition.

11. A method for investigation of a subject lung according to claim 9 wherein the imaging is carried out by

- (a) recording images encoding data for the lung in terms of coordinates,
- (b) reconstructing a 2D or 3D data field from the information encoded in the recorded images,
- (c) segmenting an image of the lung, and
- (d) associating each segment with regions of the 2D or 3D data field wherein the reconstruction is performed without first reconstructing 2D or 3D images,

wherein steps (ii) and (iii) are automated.

12. A method for investigation of a subject lung, the method comprising the steps of:

- (i) applying resistance to respiration of the subject lung,
- (ii) carrying out a functional measurement of the subject lung,

- (iii) recording at least one in vivo image of the subject lung in one or more regions;
- (iv) applying said at least one in vivo image to a multidimensional lung model,
- (v) reconstructing a multidimensional image field of the subject lung, and
- (vi) correlating the functional measurement with the multidimensional image field to obtain information regarding regional lung function .

13. A system for investigating a subject lung according to the method of claim 3, system comprising:

- (a) a means for applying expiratory resistance to the subject,
- (b) one or more energy sources for imaging; and
- (c) one or more detectors for recording images created by energy from the one or more energy sources passing through a sample;

wherein in use, the subject is located intermediate the energy sources and detectors and at least one image is recorded at each of a single, or a plurality of energy projection angles simultaneously with the application of expiratory resistance to the subject.

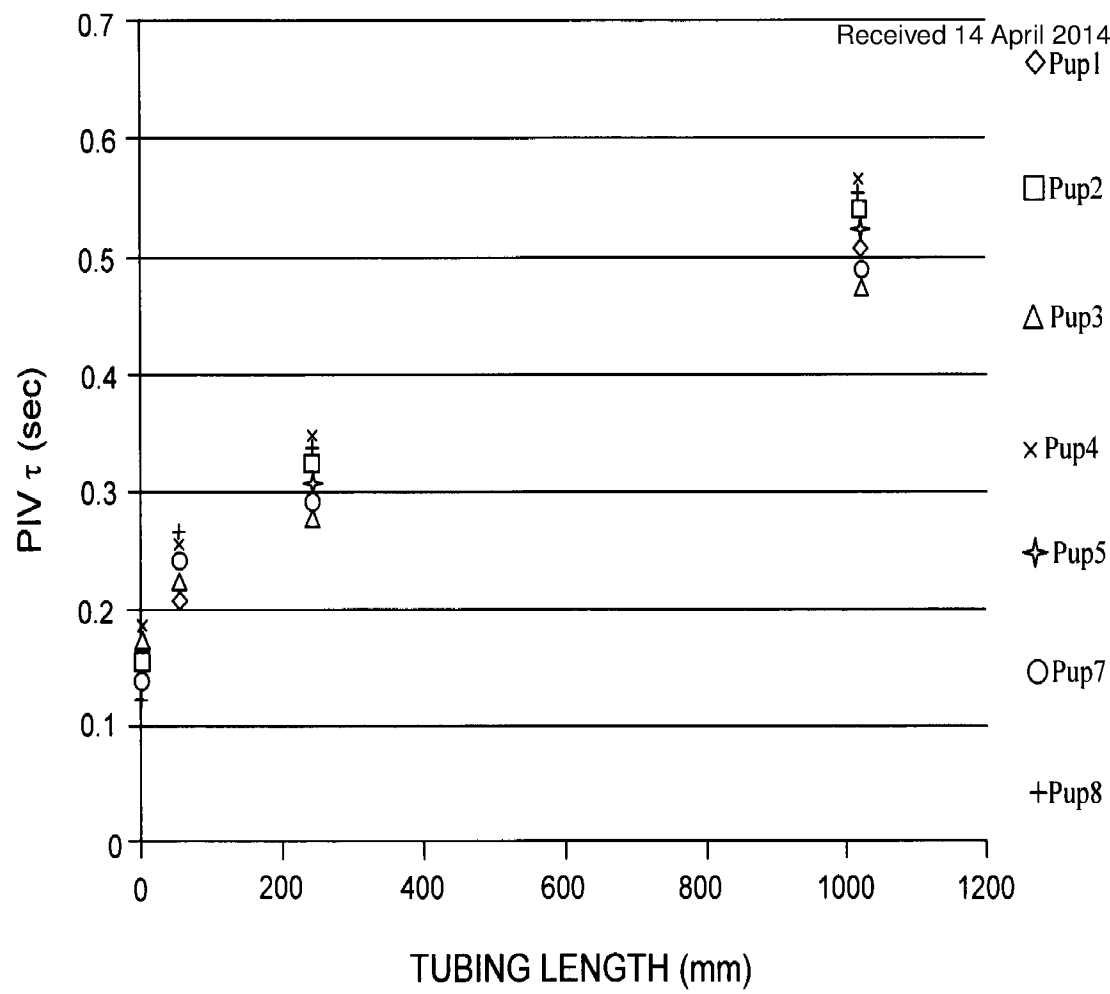


Figure 1

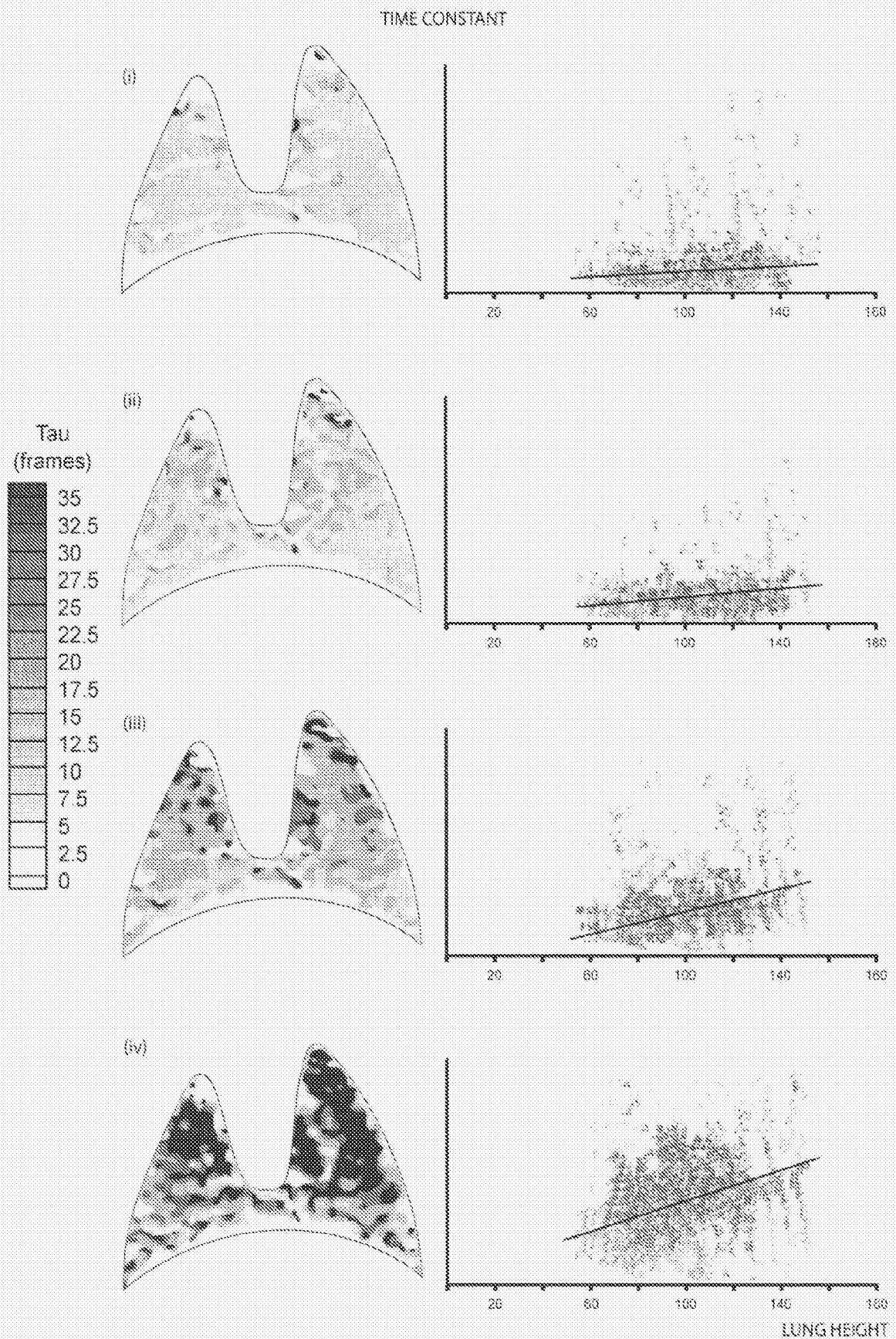


Figure 2

INTERNATIONAL SEARCH REPORT

International application No.

PCT/AU2014/000042

A. CLASSIFICATION OF SUBJECT MATTER

A61B 5/08 (2006.01) A61B 5/091 (2006.01) A61B 6/02 (2006.01) A61M 16/00 (2006.01)

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)

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)

WPI, EPODOC and IPC A61B5, A61B6- and keywords and phrases such as: pulmonar+, lung, air, bronchi, forced, compliance, resistance, elastic, monitor, display, model, fitting, registration, region, ROI, projection, image, pixel, voxel, resistance load and the like.

Google Scholar inclusive of Google Patents with search keywords and phrases: air resistance, compliance, lung, functionality, 2D, 3D, registration, segmentation, expiratory resistance, model, PIV, multiple projections and the like.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	Documents are listed in the continuation of Box C	

☒ 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	"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
"E" earlier application or patent but published on or after the international filing date	"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
"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)	"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
"O" document referring to an oral disclosure, use, exhibition or other means	"&" document member of the same patent family
"P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search 31 March 2014	Date of mailing of the international search report 31 March 2014
Name and mailing address of the ISA/AU AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA Email address: pct@ipaustralia.gov.au Facsimile No.: +61 2 6283 7999	Authorised officer Viara Van Raad AUSTRALIAN PATENT OFFICE (ISO 9001 Quality Certified Service) Telephone No. + 61 2 62223643

INTERNATIONAL SEARCH REPORT		International application No.
C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		PCT/AU2014/000042
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 6631716 B1 (ROBINSON et al.) 14 October 2003 Abstract, Figs. 2-A, 3-A, 3-B; Figs. 7-A to 7-C and col. 6, ln. 8-col. 7, ln. 57; Figs. 8 and 9; col. 7, ln. 58-col. 8. Ln. 46	1-10
Y	Abstract, Figs. 2-A, 3-A, 3-B; Figs. 7-A to 7-C	13
X	KACZKA, D. et al. 'Analysis of Regional Mechanics in Canine Lung Injury Using Forced Oscillations and 3D Image Registration,' Annals of Biomedical Engineering, 2011, Vol. 39, No. 3, pages 1112-1124 Abstract, Figs. 3-8, page 1116; parts 'Introduction,' 'Method,' 'Results'; part 'Discussion' esp. Figs. 7 and 5	1, 9
X	WO 2011/032210 A1 (MONASH UNIVERSITY) 24 March 2011 Abstract, page 6, ln. 25-33, page 7, ln. 13-page 12, ln. 3, Figs. 1-11c, esp. page 9, ln. 6-page 13, ln. 23; flow-chart on page 11; 'Example 1' on pages 24-26 and part 'Velocity Reconstruction' page 30, ln. 15-32	1, 4-6, 9, 11, 12
Y	Abstract, entire document	13

Form PCT/ISA/210 (fifth sheet) (July 2009)

INTERNATIONAL SEARCH REPORT

International application No.

PCT/AU2014/000042

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. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
the subject matter listed in Rule 39 on which, under Article 17(2)(a)(i), an international search is not required to be carried out, including
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:

See Supplemental Box for Details

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 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.

INTERNATIONAL SEARCH REPORT	International application No. PCT/AU2014/000042
Supplemental Box	
Continuation of: Box III This International Application does not comply with the requirements of unity of invention because it does not relate to one invention or to a group of inventions so linked as to form a single general inventive concept. This Authority has found that there are different inventions based on the following features that separate the claims into distinct groups: • Claims 1-4 and 8 are directed to a method for investigating a subject lung, the method comprising the steps of (i) applying resistance to respiration of the lung, (ii) carrying out a functional measurement of the lung and (iii) correlating the resistance applied with the functional measurement to obtain information regarding lung function. The feature of the investigation of subject's lung by application of resistance to the respiration of the lung, carrying out functional measurements and correlating the resistance applied with the functional measurement to obtain information regarding lung function is specific to this group of claims. • Claims 9-12 and 5-7(append to claim 1) are directed to a method (or methods) for investigation of subject's lung by applying resistance to respiration of subject's lung, carrying out a functional measurement of the subject's lung comprising imaging and using this imaging and the functional measurements at different regions of the lung to demonstrate the information about the functionality of these regions of the subject's lung that correlate the applied resistance by using 2D or 3D imaging to the functional measurements. The feature of the correlation between the applied resistance to the subject's lungs and the regionally imaged functional measurements of the lung to obtain information about lung's function is specific to this group of claims. • Claim 13 is directed to a system for investigating a subject's lung that is capable to be used in the method of claim 3, comprising: a means for applying expiratory resistance to a subject; one or more energy sources for imaging; one or more detectors for recording images created by energy from the energy sources passing through a sample and when in use the subject being located intermediate the energy sources and detectors and at least one image is recorded at each of a single or plurality of energy projection angles simultaneously with the application of expiratory resistance to the subject. The feature of the said system providing the means for application of expiratory resistance to a subject's lung simultaneously with the recording of the image at either single or multiple projection angles, when the subject is positioned intermediate the energy source the detector, providing repeated and different expiratory resistances to the subject's lung to obtain information about the lung's function is specific to this group of claims. PCT Rule 13.2, first sentence, states that unity of invention is only fulfilled when there is a technical relationship among the claimed inventions involving one or more of the same or corresponding special technical features. PCT Rule 13.2, second sentence, defines a special technical feature as a feature which makes a contribution over the prior art. When there is no special technical feature common to all the claimed inventions there is no unity of invention. In the above groups of claims, the identified features may have the potential to make a contribution over the prior art but are not common to all the claimed inventions and therefore cannot provide the required technical relationship. The only feature common to all of the claimed inventions and which provides a technical relationship among them is a method for investigation of lungs by applying resistance to the lung and taking functional measurements to obtain information about lung's function However this feature does not make a contribution over the prior art because it is disclosed in: D1: US 6631716 B1 (ROBINSON et al.) 14 October 2003 (Figs. 7-A to 7-C and col. 6, ln. 8-col. 7, ln. 57) or D2: KACZKA, D. et al. "Analysis of regional mechanics in canine lung injury using forced oscillations and 3D image registration," Annals of biomedical engineering, 2011, Vol. 39, No. 3, pages 1112-1124 (Abstract, part "Discussion" pages 1118-1122); D3 WO 2011/032210 A1 (MONASH UNIVERSITY) 24 March 2011 - entire document. Therefore in the light of this document this common feature cannot be a special technical feature. Therefore there is no special technical feature common to all the claimed inventions and the requirements for unity of invention are consequently not satisfied <i>a posteriori</i>. Form PCT/ISA/210 (Supplemental Box) (July 2009)	

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Supplemental Box	
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INTERNATIONAL SEARCH REPORT Information on patent family members		International application No. PCT/AU2014/000042	
This Annex lists known patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.			
Patent Document/s Cited in Search Report		Patent Family Member/s	
Publication Number	Publication Date	Publication Number	Publication Date
US 6631716 B1	14 Oct 2003	None	
WO 2011/032210 A1	24 Mar 2011	AU 2010295229 A2	20 Sep 2012
		CA 2790588 A1	24 Mar 2011
		EP 2478379 A1	25 Jul 2012
		JP 2013504394 A	07 Feb 2013
		SG 179151 A1	27 Apr 2012
		US 2012237104 A1	20 Sep 2012
		US 2013070062 A1	21 Mar 2013
		WO 2011032210 A1	24 Mar 2011
End of Annex			
Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001. Form PCT/ISA/210 (Family Annex)(July 2009)			