Abstract: A respiration implant system for a patient with impaired breathing includes one or more temperature sensors configured for placement into an inner wall tissue along an airway passage of the patient and configured to measure temperature in the inner wall tissue in order to produce a temperature signal based on the measured temperature. The system further includes a pacing processor configured to receive the temperature signal from the temperature sensor and to generate a respiration pacing signal based on the temperature signal that is synchronized with a breathing cycle of the patient and a stimulating electrode configured to deliver the respiration pacing signal from the pacing processor to respiration neural tissue of the patient to facilitate breathing in the patient. The respiration implant system may be used as a laryngeal pacemaker system.
Respiration Sensors for Recording of Triggered Respiratory Signals in Neurostimulators

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] The present application claims priority to U.S. Provisional Patent Application No. 61/984,914 filed April 28, 2014, the disclosure of which is incorporated by reference herein in its entirety.

TECHNICAL FIELD

[0002] The present invention relates to respiration implant systems such as implantable respiration pacing systems and sleep apnea treatment systems.

BACKGROUND ART

[0003] The larynx is located in the neck and is involved in breathing, producing sound (speech), and protecting the trachea from aspiration of food and water. Figure 1A shows a posterior view of the anatomy of a human larynx 100 and Figure 1B shows the larynx as viewed from above, including the epiglottis 101, thyroid cartilage 102, vocal folds/ligaments 103, cricothyroid muscle 104, arytenoid cartilage 105, posterior cricoarytenoid (PCA) muscle 106, vocalis muscle 107, cricoid cartilage 108, recurrent laryngeal nerve (RLN) 109, transverse arytenoid muscle 110, oblique arytenoid muscle 111, superior laryngeal nerve 112, hyoid bone 113 (note: the hyoid bone is not usually considered part of the larynx and is included in Figures 1A and 1B strictly as an aid to orientation), thyrohyoid membrane 117, and thicker lower portion of elastic membrane or conus elasticus 118. Figure 1C shows a lateral view and Figure 1D shows a sagittal sectional view of head and neck regions showing the larynx 100 and its structures, trachea 114, esophagus 115 and pharynx 116, including cricoarytenoid joint 119, cricothyroid joint 120, and tongue 121.

[0004] The nerves and muscles of the larynx 100 abduct (open) the vocal folds 103 during the inspiration phase of breathing to allow air to enter the lungs. And the nerves and muscles of the larynx 100 adduct (close) the vocal folds 103 during the expiration
phase of breathing to produce voiced sound. At rest, respiration frequency typically varies from 12 to 25 breaths per minute. So, for example, 20 breaths per minute result in a 3 second breath duration, with 1.5 sec inspiration, and 1.5 sec exhalation phase (assuming a 50/50 ratio). The breathing frequency changes depending on the physical activity.

[0005] Unilateral and bilateral injuries or ruptures of the recurrent laryngeal nerve (RLN) 109 initially result in a temporal partial paralysis of the supported muscles in the larynx (and the hypolarynx). A bilateral disruption of the RLN 109 causes a loss of the abductor function of the posterior cricoarytenoid (PCA) muscle 106 with acute asphyxia and life-threatening conditions. This serious situation usually requires surgical treatment of the bilateral vocal cord paralysis such as cordotomy or arytenoidectomy, which subsequently restrict the voice and put at risk the physiologic airway protection.

[0006] Another more recent treatment approach to RLN injuries uses a respiration implant that electrically stimulates (paces) the PCA muscle 106 during inspiration to abduct (open) the vocal folds 103. During expiration, the vocal folds 103 relax (close) to facilitate voicing. In these respiration implant systems, the patient can adjust (vary) the pacing/respiration frequency (breaths per minute) according to his or her physical state (e.g., at rest, normal walking, stairs, etc.) by manually switching the stimulation frequency of the pacer device, the assumption being that the human body may adapt to the artificial externally applied respiration frequency - within some locking-range. Thus, the patient and the respiration pacemaker can be described as free running oscillators at almost the same frequency but without phase-matching (no phase-locking). At some time, both systems will be in phase, but at other times the systems will be out of phase and thus benefit for the patient will be reduced.

[0007] Besides laryngeal pacemakers for RLN injuries, there also are respiration implant neurostimulators that electrically stimulate the hypoglossal nerve that innervates the root of the tongue for treatment of sleep apnea. These sleep apnea treatment systems use a respiration sensor that is implemented to trigger on the inhaling phase of breathing, for example, using a bioimpedance measurement or a pressure sensor in the pleural gap.
SUMMARY

[0008] Embodiments of the present invention are directed to a respiration implant system (e.g., laryngeal pacemaker systems) for a patient with impaired breathing. The system includes one or more temperature sensors configured for placement into an inner wall tissue along an airway passage of the patient, e.g., inside the mucosa along the laryngeal walls, and configured to measure temperature in the inner wall tissue in order to produce a temperature signal based on the measured temperature. The system further includes a pacing processor configured to receive the temperature signal from the temperature sensor and to generate a respiration pacing signal based on the temperature signal that is synchronized with a breathing cycle of the patient, and a stimulating electrode configured to deliver the respiration pacing signal from the pacing processor to respiration neural tissue of the patient to facilitate breathing in the patient.

[0009] Embodiments of the present invention are also directed to methods of using a respiration implant system in order to develop a respiration pacing signal in a patient with impaired breathing to promote breathing in the patient. The method includes using one or more temperature sensors implanted into an inner wall tissue along an airway passage of the patient to measure temperature in the inner wall tissue along the airway passage and developing a temperature signal based on the measured temperature and a breathing cycle of the patient. The method further includes generating a respiration pacing signal based on the temperature signal that is synchronized with the breathing cycle of the patient and delivering the respiration pacing signal to respiration neural tissue of the patient to facilitate breathing in the patient.

[0010] In related embodiments, the temperature sensors may be placed subglottically inside the inner wall tissue along the airway passage. For example, the temperature sensors may be placed into the thyrohyoid membrane between the cricoid cartilage and the thyroid cartilage of the patient. Preferably, the temperature sensors have a reaction time of about 1°C change per 5 ms or faster and have a temperature resolution of about 0.05°C or smaller. The temperature sensors may be coupled to the stimulating electrode. The measured temperature may be based on inspired air in the airway passage and/or expired air in the airway passage. The stimulating electrode may be configured to deliver the respiration pacing signal to posterior cricoarytenoid muscle in the larynx.
The respiration implant system may be used as a laryngeal implant system and the stimulating electrode may deliver the respiration pacing signal to posterior cricoarytenoid muscle in the larynx, the hypoglossal nerve, and/or the internal superior laryngeal nerve (iSLN).

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1A shows a posterior view and Figure 1B shows a superior view of the anatomy of a human larynx. Figure 1C shows a lateral view and Figure 1D shows a sagittal sectional view of head and neck regions showing the larynx, trachea, and esophagus.

Figure 2 shows a respiration implant system with a stimulating electrode placed into posterior cricoarytenoid (PCA) muscle according to embodiments of the present invention.

Figure 3 shows one vocal fold opening during stimulation with a respiration implant system according to embodiments of the present invention.

Figure 4 shows waveforms for the temperature change and breathing cycle for a temperature sensor compared to reference signal waveforms.

DETAILED DESCRIPTION

Various embodiments of the present invention are directed to improved respiration implants that use one or more temperature sensors implanted into an inner wall tissue along an airway passage (e.g., along the pharynx, the larynx and/or the trachea) of the patient and configured to measure temperature in the inner wall tissue along the airway passage. For example, the inner wall tissue may change temperature based on the temperature of the inspired and/or expired air within the airway passage. Based on this measured temperature, a temperature signal is produced and used to generate a respiration pacing signal that is synchronized with a breathing cycle of the patient. A stimulating electrode then delivers the respiration pacing signal to respiration neural tissue, e.g., posterior cricoarytenoid muscle in the larynx of the patient, the hypoglossal nerve and/or
internal superior laryngeal nerve, to facilitate breathing in the patient. Such respiration implant systems include, for example, laryngeal pacemaker systems.

[0017] Embodiments of the present invention utilize the underlying effect that the air in the airway passage varies in temperature depending on the phase of the breathing cycle. For example, in general, inspired air is colder than the airway passage and is thus heated up in the airway passage during the inhalation phase of breathing. Therefore, under most circumstances, there is a temperature difference between inhaled and exhaled air so that colder air is inhaled than exhaled. These temperature differences can be easily measured inside the inner wall tissue of the airway passage from the nose/mouth until the lungs e.g., along the tracheobronchial tree. This necessary heat exchange during inspiration comes from the mucosa, or inner wall tissue that covers the muscles of the larynx, along the surface of the airway passage that heats up the colder air. Heat moves from the mucosa to the incoming air as a direct function of the temperature difference that exists between the airstream and the mucosa throughout the airway passage. During expiration, the process reverses. The air exiting the alveoli is now warmer than the mucosa and during its passage to the mouth, heat from the air is continuously given back to the airway passage surface. Thus, the inner wall tissue changes temperature based on the temperature of the inspired and/or expired air within the airway passage.

[0018] Figure 2 shows one embodiment of a respiration implant system 130 having one or more temperature sensors 132 implanted along an airway passage of the patient. The temperature sensor(s) 132 are configured to measure the temperature in the inner wall tissue along the airway passage (i.e., along the pharynx, the larynx and/or the trachea) in order to produce a temperature signal based on the measured temperature. Preferably, the temperature sensor(s) have a fast reaction time (e.g., 1°C change per 5ms or faster) which is very short compared to the inhalation and exhalation periods and good temperature resolution (e.g., 0.05°C or smaller) so that the drop in temperature is detected by the temperature sensor(s) 132 at the onset of the inhalation phase, and similarly the rise in temperature is detected by the temperature sensor(s) 132 at the onset of the expiration phase. Preferably, the temperature sensor(s) 132 are placed into the thyrohyoid membrane (mucosa) 117 subglottically between the cricoid cartilage 108 and the thyroid cartilage 102, e.g., along the black arrow as shown in Figure 1C. Placing the temperature sensor(s) 132
subglottically (below the separation between trachea 114 and oesophagus 115) provides the benefit of minimizing the effects produced when drinking hot beverages and should reduce any artefacts when sensing respiration.

[0019] The respiration implant system 130 further includes a pacing processor 134 configured to receive the temperature signal from the temperature sensor(s) 132 and configured to generate a respiration pacing signal based on the temperature signal that is synchronized with a breathing cycle of the patient. The pacing processor 134 delivers the respiration pacing signal via a processor lead 138 to a stimulating electrode 136 implanted in a target respiration neural tissue to facilitate breathing in the patient. For example, Figure 3 shows vocal fold opening during the inhalation phase when stimulating the PCA muscle by the stimulating electrode 136. The stimulating electrode 136 maybe implanted in the respiration neural tissue using a variety of insertion techniques. For example, U.S. Patent No. 8,136,532 to Lindenthaler et al., incorporated by reference herein in its entirety, discloses various methods of introducing a stimulating electrode to interface with laryngeal structures, such as the PCA muscle. The placement of the temperature sensor(s) 132 inside the mucosa may be along the same insertion path as the stimulating electrode 136. Therefore, the temperature sensor(s) 132 may be placed on the outer surface of the stimulating electrode 136, so that no additional temperature sensor electrode is necessary, and no additional branch off of the stimulating electrode 136 with the temperature sensor(s) is necessary either. In this case, the stimulating electrode 136 and temperature sensor(s) 132 are located on one electrode, with no separation of functionality on another branch of the electrode, which permits the placement of the stimulating electrode 136 without the problems of sensing and stimulating the same physical position. In other embodiments, the temperature sensor(s) 132 and the stimulating electrodes 136 may be on separate electrode branches.

[0020] Figure 4 shows waveforms for the temperature change and breathing cycle for a temperature sensor placed intramucosally or within the inner wall tissue along the airway passage compared to a reference signal waveform. The first (top) waveform was formed with a temperature signal from a temperature sensor placed subglottically inside the mucosal wall. The second (bottom) waveform was formed with a Spirometer reference signal to define inspiration and expiratory cycles. The two vertical dashed lines near the
beginning of the waveforms show the start of each inspiration cycle. The temperature signal shows a high correlation in temperature decrease during inspiration and temperature increase during expiration. The measured delay between temperature sensors placed intratracheal and intramucosal was around 100-300 ms depending on the respiratory pattern. This delay maybe due to the fact that tissues need more time to be cooled down by the airstream than the airstream itself. The amplitude of temperature difference measured was around 0.2-0.4 °C between inspiration and expiration. This demonstrates that a temperature sensor with high sensitivity (e.g., resolution of about 0.05°C or smaller) placed within the mucosal wall can detect the breathing cycle and can be used as a trigger for any respiratory neurostimulator.

[0021] The pacing processor 134 can use signal processing of the temperature signal from the temperature sensor 132 to detect the onset of inspiration. For example, the peak or change point of the temperature signal can be used as a stimulation trigger for a stimulation pulse for patients with unilateral or bilateral vocal fold paralysis. The stimulation trigger signal defines a specific time point during the respiration cycle to initiate stimulation of the target neural tissue. The time point may specifically be the start or end of the inspiratory or expiratory phase of breathing, or any other defined time point. The respiration pacing signal is then generated to synchronize the respiration implant system 130 to the breathing cycle of the patient.

[0022] In addition to the temperature sensor(s) 132, the respiration implant system 130 may also include other sensors that may be used to detect the breathing cycle and the onset of inspiration in order to synchronize the timing of the respiration implant system 130 to the breathing cycle of the patient. These sensors may include, for example, various microphones, accelerometer sensors, and pressure sensors (positioned in the pleura gap). For example, a three-axis acceleration movement sensor (not shown) may be located within the housing of the pacing processor 134 and maybe used to generate a movement signal. Electromyogram (EMG) measurements may also be used to detect the onset of inspiration. These respiration sensors may be used to generate a respiration signal and/or movement signal that is used in conjunction with, or instead of, the temperature signal in order to detect the breathing cycle and the onset of inspiration. For example, in an environment where the surrounding air has about the same temperature as the body itself,
the temperature sensor(s) 132 may not provide reliable sensor signals if there is no
temperature difference to detect. In this case, one or more additional respiration sensors
may provide the respiration implant system 130 with alternative sensor(s) to detect the
breathing cycle, and the pacing processor 134 may generate the respiration pacing signal
based on the temperature signal, the respiration signal and/or the movement signal in order
to synchronized the respiration implant system 130 with the detected breathing cycle of
the patient. Alternatively, or in addition, the respiration implant system 130 may be
configured to switch to a sensorless operation mode in which the stimulation rate for
opening the vocal folds is predetermined or is derived from previous sensing cycle(s).

[0023] Embodiments of the invention may be implemented in part in any conventional
computer programming language such as VHDL, SystemC, Verilog, ASM, etc.
Alternative embodiments of the invention maybe implemented as pre-programmed
hardware elements, other related components, or as a combination of hardware and
software components.

[0024] Embodiments can be implemented in part as a computer program product for use
with a computer system. Such implementation may include a series of computer
instructions fixed either on a tangible medium, such as a computer readable medium (e.g.,
a diskette, CD-ROM, ROM, or fixed disk) or transmittable to a computer system, via a
modem or other interface device, such as a communications adapter connected to a
network over a medium. The medium may be either a tangible medium (e.g., optical or
analog communications lines) or a medium implemented with wireless techniques (e.g.,
microwave, infrared or other transmission techniques). The series of computer
instructions embodies all or part of the functionality previously described herein with
respect to the system. Those skilled in the art should appreciate that such computer
instructions can be written in a number of programming languages for use with many
computer architectures or operating systems. Furthermore, such instructions may be
stored in any memory device, such as semiconductor, magnetic, optical or other memory
devices, and may be transmitted using any communications technology, such as optical,
infrared, microwave, or other transmission technologies. It is expected that such a
computer program product may be distributed as a removable medium with accompanying
printed or electronic documentation (e.g., shrink wrapper software), preloaded with a
computer system (e.g., on system ROM or fixed disk), or distributed from a server or electronic bulletin board over the network (e.g., the Internet or World Wide Web). Of course, some embodiments of the invention may be implemented as a combination of software (e.g., a computer program product), hardware, and/or firmware. Still other embodiments of the invention may be implemented as entirely hardware, or entirely software (e.g., a computer program product).

[0025] Although various exemplary embodiments of the invention have been disclosed, it should be apparent to those skilled in the art that various changes and modifications can be made which will achieve some of the advantages of the invention without departing from the true scope of the invention.
CLAIMS

What is claimed is:

1. A respiration implant system for a patient with impaired breathing, the system comprising:
   - one or more temperature sensors configured for placement into an inner wall tissue along an airway passage of the patient and configured to measure temperature in the inner wall tissue in order to produce a temperature signal based on the measured temperature;
   - a pacing processor configured to receive the temperature signal from the temperature sensor and to generate a respiration pacing signal based on the temperature signal that is synchronized with a breathing cycle of the patient; and
   - a stimulating electrode configured to deliver the respiration pacing signal from the pacing processor to respiration neural tissue of the patient to facilitate breathing in the patient.

2. The system according to claim 1, wherein the one or more temperature sensors are configured for placement subglottically inside the inner wall tissue along the airway passage.

3. The system according to claim 2, wherein the one or more temperature sensors are configured for placement into thyrohyoid membrane between cricoid cartilage and thyroid cartilage of the patient.

4. The system according to any one of claims 1 to 3, wherein the one or more temperature sensors have a reaction time of about 1°C change per 5 ms or faster.

5. The system according to any one of claims 1 to 4, wherein the one or more temperature sensors have a temperature resolution of about 0.05°C or smaller.

6. The system according to any one of claims 1 to 5, wherein the one or more temperature sensors are coupled to the stimulating electrode.
7. The system according to any one of claims 1 to 6, wherein the measured temperature is based on inspired air in the airway passage, expired air in the airway passage, or a combination thereof.

8. The system according to any one of claims 1 to 7, wherein the stimulating electrode is configured to deliver the respiration pacing signal to posterior cricoarytenoid muscle in the larynx.

9. The system according to any one of claims 1 to 7, wherein the stimulating electrode is configured to deliver the respiration pacing signal to hypoglossal nerve and/or internal superior laryngeal nerve.

10. A method of developing a respiration pacing signal in a patient with impaired breathing to promote breathing in the patient, the method comprising:
   - using one or more temperature sensors implanted into an inner wall tissue along an airway passage of the patient to measure temperature in the inner wall tissue along the airway passage;
   - developing a temperature signal based on the measured temperature;
   - generating a respiration pacing signal based on the temperature signal that is synchronized with a breathing cycle of the patient; and
   - delivering the respiration pacing signal to respiration neural tissue of the patient to facilitate breathing in the patient.

11. The method according to claim 10, wherein the one or more temperature sensors are implanted subglottically inside the inner wall tissue along the airway passage.

12. The method according to claim 11, wherein the one or more temperature sensors are implanted into thyrohyoid membrane between cricoid cartilage and thyroid cartilage of the patient.

13. The method according to any one of claims 10 to 12, wherein the one or more temperature sensors have a reaction time of about 1°C change per 5 ms or faster.

14. The method according to any one of claims 10 to 13, wherein the one or more temperature sensors have a temperature resolution of about 0.05°C or smaller.
15. The method according to any one of claims 10 to 14, wherein a stimulating electrode delivers the respiration pacing signal to the respiration neural tissue of the patient, and the one or more temperature sensors are coupled to the stimulating electrode.

16. The method according to any one of claims 10 to 15, wherein the measured temperature is based on inspired air in the airway passage, expired air in the airway passage, or a combination thereof.

17. The method according to any one of claims 10 to 16, wherein the respiration neural tissue of the patient includes posterior cricoarytenoid muscle in the larynx.

18. The method according to any one of claims 10 to 16, wherein the respiration neural tissue of the patient includes hypoglossal nerve and/or internal superior laryngeal nerve.
## INTERNATIONAL SEARCH REPORT

**A: CLASSIFICATION OF SUBJECT MATTER**

**IPC(8)** - A61N 1/36 (2015.01)

**CPC** - A61N 1/361

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)

CPC: A61N 1/361; IPC(8): A61N 1/36 (2015.01); USPC: 607/42

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

CPC: A61B 17/22, A61B 5/4818, A61B 5/08, A61B 5/0816, A61N 1/361 1, A61N 1/3605, A61N 1/0519; IPC(8): A61B 19/00 (2015.01); USPC: 607/2 (keyword limited; terms below)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

PatBase; Google (Web, Patents, Scholar) Search Terms Used: Respiration implant breathing temperature sensor thermometer airway passage respiration pacing breathing cycle pulse electrode stimulation neural tissue nerve axon muscle subglottic inner wall tissue thyrohyoid membrane cricoid cartilage thyroid

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
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<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
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<tr>
<td>X</td>
<td>US 5,056,519 A (Vince), 15 October 1991 (15.10.1991), entire document, especially FIGURE; col 1, ln 47-60; col 3, ln 5-31</td>
<td>1-2, 4, 10-11 and 13</td>
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<td>Y</td>
<td>US 8,136,532 B2 (Lindenthaler et al.), 20 March 2012 (20.03.2012), entire document, especially Fig. 3 and 5; col 7, ln 13-18; col 13, ln 33 to col 14, ln 4</td>
<td>3 and 12</td>
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Further documents are listed in the continuation of Box C.

* 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 07 June 2015 (07.06.2015)

Date of mailing of the international search report 02 JUL 2015

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US, Commissioner for Patents

P.O. Box 1450, Alexandria, Virginia 22313-1450

Facsimile No. 571-273-8300

Authorized officer: Lee W. Young

PCT/ISA/2 10 (second sheet) (January 2015)
INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 15/24018

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:

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<td>1</td>
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<td>because they relate to subject matter not required to be searched by this Authority, namely:</td>
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<td>2</td>
<td></td>
<td>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:</td>
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<tr>
<td>3</td>
<td></td>
<td>5-9 and 14-18 because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).</td>
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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:

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<td>As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.</td>
</tr>
<tr>
<td>2</td>
<td>As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.</td>
</tr>
<tr>
<td>3</td>
<td>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.:</td>
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<tr>
<td>4</td>
<td>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.:</td>
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Remark on Protest

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<td>The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.</td>
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Form PCT/ISA/2 10 (continuation of first sheet (2)) (January 2015)