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(54) Title: SEIZURE DETECTION

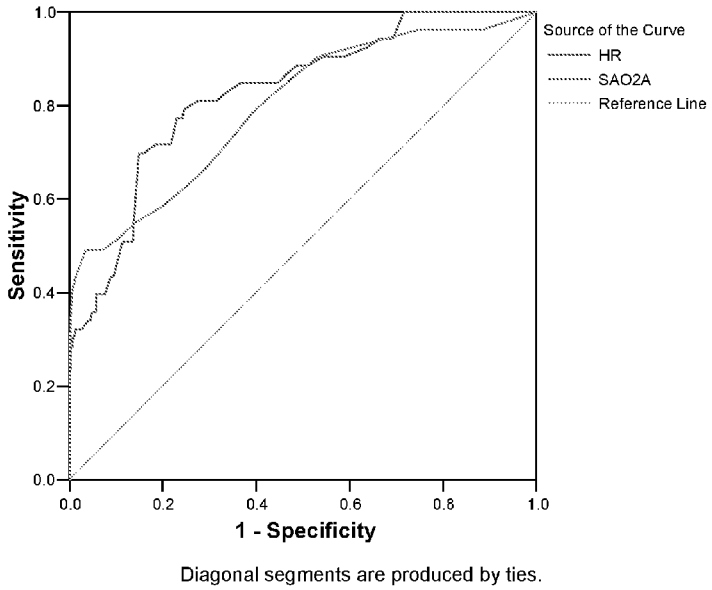

Figure 1

(57) Abstract: The present invention provides methods, procedures and systems which may find application in the detection of seizures including, for example epileptic seizures. The methods of the present invention comprise the step of determining the percentage difference between heart rate measurements of a subject, wherein a percentage difference between heart rate measurements indicates that a seizure is about to occur or is occurring. The systems of the present invention comprise means for determining the percentage difference between heart rate measurements of a subject, wherein if the heart rates differ, the system reports the occurrence of a seizure. This invention also provides devices comprising a system according to this invention.

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SEIZURE DETECTION

FIELD OF THE INVENTION

The present invention provides methods and systems for use in the detection and/or diagnosis of seizures including, for example epileptic seizures.

BACKGROUND OF THE INVENTION

Around 1,000 deaths related to epilepsy occur in the UK each year. Most of these deaths are un-witnessed; the detection of nocturnal seizures is a particular problem. Indeed, it is not uncommon for a parent to find a child in the morning having convulsed for an unknown length of time during the night.

Prolonged undetected seizures can lead to brain damage due to lack of oxygen and in some cases death. This type of brain damage has a major impact on the individual and their families, often resulting in the epilepsy becoming worse and more difficult to control with medication.

Several types of seizure alarm systems are currently commercially available. Nine different types of seizure alarm systems provided by various manufacturers or charities are considered. Systematic reviews on the reliability of these types of seizure alarms are not found in the literature. Each manufacturer advertising an epileptic seizure alarm claims reliability.

'Support Dogs' is a registered charity, which was established in 1992 and is based in Sheffield. They train rescued dogs to alert their owner of an imminent seizure and to warn them in a positive manner, by raising a paw or barking twice. This allows the person to get into a safe place (Strong 1999). Incredibly, some dogs can sense a seizure between 20-45 minutes prior to it taking place and this gives people living with epilepsy the confidence to lead more independent lives (Stephens 1997). It is believed that the dogs sense chemical changes which are unique to seizure activity. They are trained to alert their owners of these chemical changes, which warn them that a seizure is about to occur.

The cost of training a dog to detect a seizure and warn their owner of an imminent seizure is around £1500. The cost of this training is funded from donations and sponsorship and is not charged to the person who needs the trained dog.

However, the charity does not provide dogs for every person with epilepsy. Generally, children are not included because they are not old enough to be responsible for the dog. The prospective owner also has to be old enough to work closely with the charity and the dog in residential training for a minimum of 170 hours (Support Dogs 1997).

Commercially, two devices tend to be used in detecting seizures in the home. The first is a baby monitor, so that parents or carers can hear a seizure occurring. Seizure detection then depends on the parents not sleeping through the seizure or the seizure not being silent.

The second type of seizure alarm most commonly used is a bed movement alarm. Various manufacturers make this type of alarm e.g. Medpage Ltd, Emfit by Safety Systems Distribution Ltd and Sensorium providing the Sensalert (www.sensorium.co.uk) and the sensor

can be adjusted to what the parents believe so it would not miss true seizures or collect unwanted false alarms from child restlessness. A similar type of bed movement alarm system called Epson alarm (no longer available) but used the same technology was found to have a high level of false alarms of 10:1 (Brotherstone 1992). This type of monitor assumes that the seizure would cause a lot of shaking motion. This type of monitor would not be appropriate for someone who has restricted physical movement or has the type of seizures that does not result in clonus.

A similarly intended device measures electromyographic activity (EMG) via sensory electrodes placed on one arm and one leg. The attached device then indicates a seizure by the increased EMG activity, particularly oscillatory activity. This again assumes clonic action during the seizure. It may also be unpleasant being wired up every night or restrictive on changing position during sleep. Detection of shaking (frequency 2-5Hz) using gyroscopes, accelerometers and computer algorithms have been developed for a mobile phone App called "EpDetect" can be downloaded free onto a compatible mobile phone. If it detects shaking of the wearer for more than 10 seconds, it will send a message to carer's pre-set phone numbers and give a GPS location of the person who triggered the EpDetect App (www.EpDetect.com, 2012). Another similar device is the "SmartWatch" from SmartMonitor that detects abnormal movements within 7-10 seconds and alerts carers by mobile phone (www.Smart-Monitor.com, 2012).

Oxygen saturation monitoring seems to be rarely used in the home, yet clinically our attention is often drawn to a patient having a seizure on the ward because of this type of monitor.

Another type of commercially available system is the 'wristcare' monitor, which collects data for pulse, skin temperature, movement and sweat. It is largely used for the elderly in sheltered accommodation and detects cardiac events, hypothermia and epileptic seizures. When triggered it automatically sends a signal to a warden who can then go and assist or call for emergency back up. The accuracy of this device in detecting seizures will depend on pulse during the seizure.

An apnoea monitor is sometimes used in detecting seizures and it will alarm if the person stops breathing for at least 10 seconds. False alarms can be problematic if the body position moves off the pressure sensor mat. In a previous study the apnoea monitor detected 21% of seizures and had a high false alarm rate of 5:1 (Brotherstone 1992).

The remaining devices commercially available are the enuresis alarm supplied by Alert-it.co.uk and a pressure mat placed on the floor. The enuresis alarm assumes that incontinence occurs during every seizure, which is clearly not the case. Finally, the pressure mat is dependent on the person rolling out of bed during a seizure and landing conveniently on the placed mat! Alert-it monitors also supply bed movement with breathing sensor and bed vacation sensors.

SUMMARY OF THE INVENTION

The present invention provides methods, procedures and systems which may find application in the detection of seizures including, for example epileptic seizures. Many seizures occur at night (nocturnal seizures) and are difficult to detect or predict; without prompt intervention, a seizure can lead to oxygen starvation (hypoxia) in the brain (causing brain damage) and in some cases death. As such, this method facilitates the detection of a seizure in progress.

Methods of "detection" of this invention may include methods of detecting the imminent or pending occurrence of a seizure. In some cases, this invention may find application in diagnostic procedures and as such, the term "method of detection" may also encompass methods of diagnosis. In those territories where *in vivo* methods (or at least methods directly applied to the human or animal body) are excluded from patentability, the various parameters analysed in the detection of a seizure (for example heart rate measurements and/or oxygen saturation measurements) are provided by subjects to be tested.

Accordingly, a first aspect of this invention provides a method of detecting a seizure, said method comprising the step of determining the percentage difference between heart rate measurements of a subject, wherein a percentage difference between heart rate measurements indicates that a seizure is about to occur or is occurring.

This invention is based on methods which exploit a percentage change in heart rate. This is advantageous over prior art methods (which may simply focus on an absolute increase in heart rate) as it takes into account age dependant heart rate variability (neonatal hearts beat much faster than adult hearts). The methods (and devices and systems) described herein calculate changes in heart rates as a proportional change and can be compared for all ages. As described in more detail below, detection of a seizure is triggered by comparison of the percentage changes in heart rate measurements from a subject being monitored and certain threshold/predetermined percentage changes in heart rate.

Methods of this invention may exploit sensors to facilitate the detection and/or measurement of heart rates and/or the subsequent calculation of a percentage difference between heart rate measurements. The methods may exploit one or more sensors. The sensors may be attached to or worn against or around a body part. For example, a sensor may be fixed to a wrist, ankle, part of the chest, scalp, head, finger or toe. A sensor suitable for use in the methods of this invention may be formed and adapted to collect, record and/or transmit information useful in the measurement of a heart rate and/or calculation of a percentage heart rate difference. A sensor may be formed and adapted to detect and/or compute a heart rate and/or a percentage difference between heart rate measurements.

It should be understood that the term "seizure" may include any form of disturbed brain activity and includes the seizures known as generalised tonic-clonic seizures, tonic seizures, atonic seizures, complex focal seizures, temporal lobe complex focal seizures, prolonged frontal

lobe seizures, temporal lobe seizures, absences and myoclonus. In addition, the term "seizure" embraces any seizure which might occur as a consequence of an underlying medical disease, condition and/or syndrome. For example, the methods and procedures described herein may be used to detect seizures and/or seizures occurring in subjects having brain structural abnormalities associated with seizures (for example mesial temporal lobe sclerosis and/or sclerosis of the hippocampus). In addition the term "seizure" includes seizures associated with, for example, Rassmussen's syndrome, stroke, space-occupying lesions, sub-cortical band heterotopia, encephalitis, cortical damage, ischaemic encephalopathy, Ohtahara's syndrome, Aicardi syndrome, Autism, Asperger's syndrome, lennox Gastaut Syndrome, progressive polymorphic epilepsy of Dravet and Myoclonic Astatic Epilepsy (AME). The various aspects and embodiments of this invention may be applied to the detection of one or more specific seizures as described herein.

In view of the above, the subject may be a human subject known to suffer (or suspected as suffering) from seizures and/or a disease, condition or syndrome associated with seizures. In other embodiments, the subject may be a human subject predisposed or susceptible to seizures.

The successful detection of a seizure in a subject may rely upon the detection of at least two heart rate measurements (designated herein as the "first" and "second" heart rate measurements). A seizure and/or the imminent occurrence of a seizure can be detected by means of a difference between, for example, a first heart rate measurement and a second heart rate measurement. It should be understood that the term "difference" as applied to the first and second heart rate measurements encompasses any increase or decrease in the second heart rate measurement relative to the first heart rate measurement.

Accordingly, the invention provides a method of detecting a seizure, said method comprising the step of determining the percentage difference between a first and a second heart rate of a subject, wherein if there is a percentage difference between a second heart rate of the subject and a first heart rate of the subject, a seizure is occurring or is about to occur. The second heart rate measurement may be regarded as "different" from the first heart rate measurement if the second heart rate measurement is slower or faster than the first heart rate measurement.

For example, if the first and second heart rates differ by at least about 15%, a seizure is occurring or is about to occur.

As such, a method of this invention (namely a method of detecting a seizure) may comprising the step of determining the percentage difference between a first and a second heart rate of a subject, wherein if the first and second heart rates differ by at least about 15%, a seizure is about to occur or is occurring.

It should be understood that while methods of this invention may be based upon the detection of a percentage difference between heart rate measurements, the magnitude of that

percentage difference may be varied. For example, while the method may be based upon the detection of a percentage difference of at least about 15%, other methods may be based upon percentage differences (between heart rates) of at least about 15-20% (and any % value therebetween), at least about 25%, at least 30%, at least 35%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, at least 99%,at least about 100%, at least about 105%, at least about 110%, at least about 150%, at least about 200%, at least about 250%, at least about 300%, at least about 350%, at least about 400%, at least about 450% or at least about 500% (and any specific % heart rate change therebetween). Typically, the methods may be based upon the detection of heart rate measurements which differ by at least about 15% to about 30%, for example at least about 16%, 17%, 18%, 19%, 20%, 21%, 22%, 23%, 24%, 25%, 26%, 27%, 28%, 29% or 30%. For example, certain types of seizure may be associated with specific percentage heart rate changes and therefore, the various aspects (methods, devices and systems) of this invention may be modified so as to specifically detect or monitor for certain types of seizure. The data and detailed description of this specification identifies a number of relationships between percentage heart rate changes and seizures – all of these relationship's may be exploited in this invention and may be used to form the basis of the parameters monitored by or in the methods, devices and/or systems of this invention.

It should be noted that the terms "at least" and "at least about" embraces a variation of anywhere between + /- 0.1%-0.9%, for example +/- from the stated % heart rate.

A heart rate measurement (for example a second heart rate measurement) which differs from another heart rate measurement (for example a first heart rate measurement) by at least 15%, may be at least 15% greater or less than the other (first) heart rate measurement. Similarly, a heart rate measurement (for example a second heart rate measurement) which differs from another heart rate measurement (for example a first heart rate measurement) by at least 20%, at least 30% or at least 50% may be at least 20%, at least 30% or at least 50% (respectively) greater or less than the other (first) heart rate measurement.

Accordingly, the detection procedure provided by this invention may be based upon the detection of a heart rate measurement which is at least 15% greater or less than another heart rate measurement. The heart rate measurements may be first and second heart rate measurements, and the detection method may be based upon the detection of a second heart rate measurement which is at least 15% greater or less than a first heart rate measurement. As noted above, the precise % difference between first and second heart rate measurements which forms the basis of the detection procedures provided by this invention may vary and may, in some circumstances require detection of a percentage difference of at least 20%, at least 30%, at least 40% or at least 50% (or any other % therebetween or as described above).

Further, it should be understood that the precise parameters used in the methods of this invention – for example the difference between heart rates which is to be indicative of a seizure and/or imminent seizure may be varied depending on the subject. For example specific

parameters may be used depending on a subject's age, sex, medical status, medical history and/or the type and/or frequency of the seizures experienced by the subject. The parameters used in the methods of this invention may therefore be "personalised" to ensure efficient seizure detection in any given patient.

Prior art methods of diagnosing seizures are unable to properly distinguish between clinically insignificant and clinically significant seizures; as such, they are prone to false detection – that is to say, a high proportion of seizures detected by prior art methods are clinically insignificant seizures.

In contrast, the inventor has discovered that methods of seizure detection based upon a percentage change between heart rate measurements, in particular methods based on the detection of a % (for example at least a 15%) change between separate or distinct (for example first and second) heart rate measurements are less prone to false detection – that is to say, a high proportion of seizures detected using the methods described herein are clinically significant seizures.

One of skill will appreciate that methods which reliably detect clinically significant seizures represent a considerable advantage over the prior art. The methods described herein facilitate the reliable, accurate and precise detection of clinically significant seizures e.g. generalised tonic clonic seizures and substantially avoid detection of (or ignore) clinically insignificant seizures e.g. absences or single myoclonus.

The method of this invention may be based upon a heart rate which is measured or determined at one time point and a further or additional heart rate which is measured or determined at another or different time point. For example, a method of this invention may involve measuring or determining a first heart rate at a first time point, measuring or determining a second heart rate at a second time point and calculating the percentage difference between the two.

One of skill will appreciate that a "heart rate" is a measure of the number of beats of a heart in a specified period of time. For example, a heart rate may be expressed as a particular number of beats per minute.

As such, a method of this invention may comprise a step in which heart rates are calculated by counting the number of beats of a subject's heart over predetermined or specific periods of time. The predetermined or specific period of time used to calculate a heart rate (including, for example, the first and/or second heart rates exploited by the methods of this invention) may be referred to as a "sampling period".

The sampling period over which a one (perhaps a first) heart rate is calculated may be distinct from the sampling period over which another (perhaps a second) heart rate is calculated.

The sampling periods over which heart rates (for example first and/or second heart rates) are determined may overlap. For example, a heart rate may be determined over a

sampling period which runs concurrently with part of the sampling period used to determine another heart rate. For example, the latter part of a sampling period used to determine a first heart rate may run concurrently with the beginning of a sampling period used to determine a second heart rate.

The duration of the sampling periods used to determine heart rates (including first and second heart rates as required by the methods of this invention) may be the same or different.

The sampling periods may comprise anywhere between about 2 and about 60 seconds (s). Typically, the sampling periods may comprise 3s, 4s, 5s, 6s, 7s, 8s, 9s, 10s, 15s, 20s, 25s, 30s, 35s, 40s, 45s, 50s, 55s or 60s. One of skill will appreciate that the maximum duration of a sampling period may equate to the duration of a seizure. In this regard, it is noted that the average seizure lasts about 3 minutes. Thus a sampling period may comprise any length of time between about 3 seconds and 3 minutes (and all times therebetween). As stated, the duration of a sampling period for determining a first heart rate may differ (may be longer or shorter than) the duration of a sampling period during which a second heart rate is calculated. Whatever the duration of the sampling period(s), a heart rate for use in the methods of this invention (for example the first and second heart rates) may be calculated as:

$$\frac{\text{number of heart beats (n)}}{\text{sampling period duration (time)}}$$

The methods provided by this invention may comprise the step of determining the first and second heart rates over two distinct sampling periods. The sampling periods may (each) comprise, consist essentially, or consist of, for example, three seconds. As such, a first heart rate may be calculated as the number of heart beats/per three seconds and the second heart rate may be calculated as the number of heart beats/three seconds. The first heart rate may be calculated over one three second sampling period and the second heart rate may be calculated over a second (or distinct/different) three second period. As stated, these sampling periods may be distinct or run at least partially concurrently (i.e. overlap) with each other. In a method of this invention, these two heart rates are then compared to determine whether or not there is a percentage difference (of, for example, at least 15%) between the two heart rate measurements, if there is a percentage difference (of, for example, at least 15%) a seizure is occurring or about to occur. If these two heart rates do not differ by at least, for example 15% (or some other predetermined % difference threshold) either the first and/or second heart rate may be compared with another heart rate or different first/second heart rate measurements will be compared. The method of this invention may require that analysis of first and second heart rate measurements continues for at least the duration of the seizure or at least until two heart rates which differ by at least 15% (or some other predetermined % difference threshold) are identified – at which point the method may report to a user that a seizure is occurring or is about to occur. If (as explained in more detail below) the method is executed by an automated system, for example a system worn by a subject known to suffer from or predisposed/susceptible to,

seizures, the detection of two heart rates which differ by at least about 15% (or some other predetermined % difference threshold) may trigger some form of alarm to alert third parties as to the occurrence or likely/imminent occurrence of a seizure

The sampling periods used to calculate the (for example first and second) heart rates, may be separated by a non-sampling time period. The duration of the non-sampling period(s) may equal the duration of one or more sampling period(s). In other embodiments, the duration of the non-sampling period may be different from (i.e. longer or shorter than) the duration of a sampling period. Where the method exploits at least two sampling periods to determine at least two heart rates (which are compared with the aim of detecting a percentage difference), the non-sampling period be may equal to or different from (i.e. longer or shorter than) either or both of the sampling periods.

By way of example, where the duration of the sampling periods is equal, the duration of the non-sampling period (which separates the sampling periods) may be the same or substantially the same. Therefore where the duration of the sampling periods is three seconds, the duration of the non-sampling period may also be three seconds.

As such, the detection procedures of this invention may comprise at least a first sampling period, a non-sampling period and a second sampling period. Where the duration of the sampling periods and non-sampling periods is three seconds, the total duration of the detection procedure described herein may be nine seconds, the procedure comprising a first sampling period of 3 second duration, a non sampling period of 3 second duration and a second sampling period of 3 second duration.

A detection cycle of the method of this invention may comprise a sampling period used to detect or measure a heart rate and a further sampling period used to detect or measure a further heart rate. The sampling periods may be of equal or different duration. Optionally, the sampling periods may be separated by a non-sampling period, the duration of which may equal or be different from, either or both of the sampling periods. As such, where, for example, the sampling periods and non-sampling period comprise three seconds, the detection cycle may comprise nine seconds. The methods of this invention may comprise a plurality of detection cycles which run in parallel, continuously, contiguously, consecutively and/or (at least partially) concurrently.

It should be understood that the duration of the detection cycle depends on the duration of both sampling periods (used to calculate, for example, the first and second heart rates), the presence of any overlap between the end of the first sampling period and beginning of the second sampling period or the duration of any non-sampling period separating sampling periods.

In addition, it should be understood that during a seizure, one or more detection cycles may be used. Moreover, the detection cycles may repeat for the duration of the seizure and/or

until two heart rates which differ by some predetermined % difference threshold (for example at least 15%) are identified.

The methods provided by this invention may be automated, that is to say, a computer or other machine analyses or monitors a subject's heart rate and detects/calculates and/or reports any percentage difference between heart rate measurements.

The methods of this invention may exploit one or more sensors each adapted to measure a heart rate. The one or more sensors may be fixed to one or more body parts. The sensor may comprise or be part of a device adapted to measure a wearer's pulse. The sensor may comprise for example, a pulse oximeter device.

Upon detection of a first and second heart rate which differ, an alert may be triggered or activated. Where the method relies upon the detection of heart rates which differ by at least, for example 15%, the detection of heart rates which differ by at least 15% triggers or activates an alert.

The alert may comprise an audible, visual and/or oscillating (movement type) alarm.

In one embodiment, the methods described in this invention, in particular, the automated methods described herein, may continually monitor the heart rate of a subject. In such cases, in order to compare heart measurements, a heart rate calculated over one sampling period is compared to a heart rate calculated over a different sampling period. In the methods of this invention, any two heart rate measurements may be compared with the aim of detecting a percentage difference, for example a percentage difference of at least 15%, therebetween. The heart rate sampling method is continually updated calculating percentage heart rate changes from sampling measurements, for example consecutive heart rate measurements (optionally separated by non-sampling periods) on a real time basis. In this way, even though the heart rate of a subject is being continually monitored, specific time periods can be sampled to determine whether there is a percentage difference between any two heart rate measurements. In addition, if the percentage difference between one set of first and second heart rate measurements does not meet predefined criteria, for example they do not differ by at least 15% (or some other predetermined % difference threshold), a second or further set of heart rate measurements can be analysed. This process may be repeated and upon detection of two heart rate measurements which differ by the requisite predetermined % change threshold (for example at least 15%), an alarm, for example an audible, visible and/or oscillating (movement type) alarm or alert may be triggered or activated indicating (to a third party for example) that a seizure may be occurring or is about to occur.

In a second aspect, this invention provides a system for detecting the occurrence of a seizure, the system comprising means for determining the percentage difference between heart rate measurements of a subject, wherein if the heart rates differ, the system reports the occurrence of a seizure.

A system according to the second aspect of this invention may comprise a sensor for determining and/or measuring heart rates. The definition of the term "sensor" as used in the second aspect of this invention corresponds to the definition of "sensor" as used in connection with the first aspect of this invention. For example, the system may comprise one or more sensors fixed to one or more body parts. The sensors may independently determine or measure heart rates. The sensor or sensors may comprise a device capable of measuring a wearer's pulse, for example a pulse oximeter device. The heart rates measured or determined by each sensor may be compared with heart rates measured or determined by the same sensor or by (an)other sensor(s).

For example, if the heart rates (for example first and second heart rate measurements) differ by at least about 15% (or by some other predetermined % change threshold), the system reports the occurrence of a seizure. It should be understood that definitions applied to features of the first aspect of this invention may apply to the corresponding features of the second aspect of this invention. Accordingly, the magnitude of the difference between heart rates which is indicative of a seizure or imminent seizure may vary from a difference of at least about 15% to a difference of at least about 100% (as defined above).

It will be appreciated that the system provided by the second aspect of this invention may find particular application as a system for monitoring the status of a subject known to suffer from seizures, or subjects suspected of, or predisposed to, developing seizures. Systems of this type may be used to alert others to the occurrence of a seizure in a subject.

By way of example, the system provided by this invention may be used by anyone wishing to monitor the status of a subject known to suffer from seizures, subjects suspected of harbouring diseases or conditions characterised by, causing or contributing to seizures, or subjects thought to be predisposed to seizures. For example, the systems described herein may be used by hospital staff, carers, parents, and/or teachers.

Systems of the type described herein may comprise means to report the occurrence of a seizure in a subject, to a third party (for example a member of hospital staff, carers, parent and/or teachers). It should be understood that the term "report" may be taken to encompass, for example, the emission of an audible, and/or visual signal and/or an oscillating (vibrate or movement type) alarm.

Audible, visual and/or oscillation type alarms or signals suitable for use with the systems described herein may comprise one or more sounds such as, for example, bells, buzzers, beeps and the like and/or one or more visual signals such as, for example lights which flash or in some other way attract the attention of a third party. Oscillating alarms may comprise vibration type alerts.

The systems described herein may comprise or further comprise means to transmit or deliver data and/or an alarm signal to a remote third party (i.e. a third party who is not in the vicinity of a subject being monitored). The systems may comprise a remote receiver. For

example, upon detection of heart rates which differ (for example, by at least about 15%), a system of this invention may transmit data and/or an alarm signal to a remote receiver. Data and/or an alarm signal of the type emitted or generated by a method or system of this invention may be transmitted through wires and/or wirelessly to a remote receiver. A signal, for example a data signal or an alarm signal may be transmitted wirelessly using, for example radio transmission technology including radio waves. For example a signal may be transmitted wirelessly using Bluetooth technology. Bluetooth technology described herein includes wireless technology to a receiving unit whether radiopage or satellite signal.

In such cases, the remote receiver and/or a device connected thereto may be adapted to emit an alarm, for example an audible and/or visual alarm upon receipt (and analysis of) data revealing that a subject being tested is experiencing or about to experience a seizure, or the receipt of a suitable signal (generated upon detection of heart rates which differ by at least about 15%) from a system of this invention.

As stated, the systems of this invention may be adapted to wirelessly transmit data and/or an alarm to a remote receiver. A remote receiver unit may comprise a computer and/or a mobile device such as, for example, a laptop or tablet computer. The remote device may comprise a phone or smartphone. The computer or mobile device may comprise a program or application ("app") which reacts to the receipt of data and/or an alarm signal generated or emitted by a system of this invention. Upon receipt of data and/or an alarm signal, a program or app may itself generate an audible, visual and/or oscillation (vibrate) type alarm signal.

As such, this invention provides an alarm system for detecting the occurrence of a seizure. As stated, upon detection of heart rates that differ (for example by at least 15%), the system may report the occurrence, of a seizure in a subject to a third party. The invention also provides a device for detecting the occurrence of a seizure. As stated, upon detection of heart rates that differ (for example by at least 15%), the device may report the occurrence, of a seizure in a subject to a third party.

The system or device of this invention may be a wearable system or device. For example, the system or device may be formed and/or adapted to be worn on a body part, for example around a wrist or ankle. The system or device may comprise means for (for example sensors for) detecting a wearer's heart rate. The system or device may be further adapted to detect and calculate a wearer's heart rate and any percentage difference between two or more heart rate measurements. A wearable system may further comprise an alarm triggered upon detection of heart rate measurements which differ by at least the predetermined percentage threshold described herein.

As such, a third aspect of this invention may provide a device which comprises a system according to the second aspect of this invention.

A device of this invention may be worn on, against or around a body part, for example on a wrist or ankle. The device may comprise means for measuring or determining and/or recording and/or storing a wearer's heart rate. Heart rates measured and/or stored by the device may be compared with the aim of identifying heart rate measurements (perhaps consecutive heart rate measurements) which differ by at least a predetermined amount, for example by at least about 15%. The device may comprise a display, for example an LCD or OLED display, for displaying or presenting information, for example heart rate information collected by the device.

The device may comprise a sensor such as, for example, a sensor used in the first and/or second aspects of this invention. The sensor of any device of this invention may be formed and adapted to detect and/or measure (or compute) a heart rate. The device may comprise one or more sensors. A user may wear one or more devices.

The device may comprise an audible, visual and/or oscillation (vibrate or movement type) alarm which is triggered or activated upon detection of heart rates (for example consecutive heart rates) which differ by at least a predetermined (percentage) amount. The device may further comprise means for transmitting a signal, for example a wireless signal, to a remote device. The remote device may comprise an alarm (audible, visual and/or oscillation (vibrate/movement type alarm) which is activated or triggered upon receipt of an appropriate signal transmitted or emitted by the device.

In one embodiment, the methods, systems and devices of this invention may further comprise a means to report the detection of any heart rate measurement which indicates the occurrence of a life threatening event. By way of example, the methods, systems and devices described herein may be further adapted to (separately) report the detection of one or more predetermined or specific heart rates. For example the method, system or device may be adapted to report the detection of heart rates which are less than or equal to about 90 beats/min, about 70 beats/min, 60 beats/min, about 50 beats/min, about 40 beats/min, about 30 beats/min, about 20 beats/min, about 10 beats/min, about 5 beats/min or about 0 beats/min. Additionally or alternatively, the methods, systems and devices of this invention may comprise or further comprise a means to report the detection of increased heart rates. For example the methods, systems and/or devices of this invention may be configured to detect and/or report heart rates which are greater than about 90 beats/min, 100 beats/min, 110 beats/min, 120 beats/min, 130 beats/min, 140 beats/min, 150 beats/min, 160 beats/min, 170 beats/min, 180 beats/min, 190 beats/min and/or 200 beats/min. A method, system and/or device of this invention may be configured to detect and/or report occurrences of heart rates which differ from a predetermined heart rate and/or average, normal or resting heart rate by more or less than about 15%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, 150%, 200%, 250%, 300%, 350%, 400% and/or 500%.

In one embodiment, the methods, systems and/or devices described herein may be adapted to report (audibly, visually and/or via oscillation type alarm) the detection of a heart rate which is less than or equal to about 30 beats/min.

The specific or pre-determined heart rates which the methods, systems and/or devices are configured to report may be fixed and may not be altered or adjusted. Additionally or alternatively, the specific or pre-determined heart rates which the methods, systems and/or devices are configured to report may be altered, adjusted and/or set by a user. For example, the methods, systems and/or devices may comprise means allowing a user to program the method, system or device to report the detection of one or more specific or predetermined heart-rates.

The methods, systems and/or devices of this invention may be supplemented with one or more additional steps which require the analysis of a subject's oxygen saturation levels. It should be understood that the term "oxygen saturation" means the level of oxygen saturated in a subject's blood – 100% representing total or complete blood oxygen saturation.

Accordingly, a method, system and/or device of this invention may comprise steps and/or means for determining the percentage difference between heart rate measurements of a subject and a subject's oxygen saturation levels, wherein a difference between the heart rate measurements of a subject and/or a reduction in oxygen saturation below a predetermined base value, indicates that a seizure is about to occur or is occurring.

Methods, systems and/or devices supplemented with steps or means designed to detect levels of oxygen saturation are particularly useful in the detection of seizures which may contribute to, or cause, a state of hypoxia within a subject. For example, if a seizure causes the level of oxygen saturation in a subject to fall to around 85% or less, the subject may be becoming hypoxic.

Additionally though, if oxygen saturation falls to around 60%, this may indicate that the subject is experiencing, or is about to experience, a life threatening event.

As such, the methods, systems and/or devices described herein may be supplemented with steps which require the detection of oxygen saturation levels which fall to or below one or more predetermined levels. For example, if a subject's oxygen saturation level falls to around 90%-80% (specifically to around 89%, 88%, 87%, 86%, 85%, 84%, 83%, 82% or 81%), the subject may be diagnosed as experiencing (or about to experience) a state of hypoxia. If oxygen saturation falls to around 90-80% and two heart rate measurements are identified which differ (by for example at least 15%), the subject may be diagnosed as experiencing or about to experience a seizure associated with hypoxia.

If oxygen saturation falls to around 40% and two heart rate measurements are identified which differ by at least 15%, the subject may be diagnosed as experiencing or about to experience a seizure associated with life-threatening hypoxia.

In one embodiment, the methods, systems and/or devices described herein may comprise the additional step of, or means for, providing an indication of the levels of oxygen saturation in a subject to be tested.

A subject's oxygen saturation levels may be continuously monitored (or provided) by the methods, systems and/or devices of this invention. In one embodiment, the oxygen saturation level of a subject is assessed during each of the sampling periods used to calculate the first and second heart rate measurements. In other embodiments a subject's oxygen saturation levels may be assessed or provided at the same or other time points.

In view of the above, the methods, systems and devices provided by this invention may be further adapted to report (audibly, visually and/or via oscillation (vibrate/movement) type alarm) the occurrence of 90-80% oxygen saturation in a subject and/or 70-55% oxygen saturation in a subject. The methods, systems and devices described herein may be configured to report the occurrence of one or more specific oxygen saturation levels in a subject either as distinct events or as events occurring in combination (or together) with a difference, for example a 15% difference, between two heart rates.

As such, a method, system or device provided by this invention may be configured to report the occurrence of first and second heart rates which differ by at least 15% separately or together with the occurrence of between about 90%-80% oxygen saturation and/or about 70%-35 % oxygen saturation.

In one embodiment, the methods, systems and/or devices described herein may be configured to report (audibly, visually, via oscillation (vibrate/movement) type alarm, and/or via a wireless (e.g. Bluetooth link) the occurrence of either or both of: first and second heart rates that differ by at least a predetermined percentage difference in heart rates, for example a 15% difference; or oxygen saturation of less than 85%.

The methods, systems, and/or devices of this invention may exploit a combination of percentage differences between first and second heart rates and values for oxygen saturation. These parameters may be compared with threshold parameters. Such a threshold may be fixed or may be varied depending on the patient and/or assessed or calculated in an adaptive manner. A method, system and/or device of this invention may be configured to report (audibly, visually, via vibration, and/or via a wireless link) when some mathematical combination of the difference between first and second heart rates and the oxygen saturation level passes a threshold.

For example, the methods, systems and/or devices described herein may be configured to report when a condition of the following form is satisfied

$$\frac{|HRT|}{\mathrm{SAT}} \geq y$$

where HRT is the percentage heart rate change between first and second heart rates, and |HRT| denotes the absolute (i.e. non-negative) value of the percentage heart rate change; SAT is the oxygen saturation level as a percentage; and y is a combined threshold. In some

embodiments y may be around 0.25-0.35 (specifically around 0.25, 0.26, 0.27, 0.28, 0.29, 0.30, 0.31, 0.32, 0.33, 0.34, or 0.35).

The methods, systems and/or devices described herein may be configured to report according to a binary classifier with |HRT| and SAT as inputs.

The methods, systems and/or devices described herein may be configured to report when a condition of the following form is satisfied

$$|\text{HRT}| \times (101 - \text{SAT}) \geq y$$

where |HRT|, SAT, and y are as defined as above. In some embodiments, y may be around 125-135 (specifically around 125, 126, 127, 128, 129, 130, 131, 132, 132.5, 133, 134, or 135).

The methods, systems and/or devices described herein may be configured to report (audibly, visually, via vibration, and/or via a wireless link) when one or more thresholds is reached or exceeded; for example when any one or more of a percentage heart rate change threshold, oxygen saturation threshold, or combined threshold is reached or exceeded. For example, the method, system or device may be configured to report when any one or more of the following events is detected: the magnitude of the difference between first and second heart rates is greater than for example about 15% or about 25% (or indeed any other percentage change value described herein or set by the user etc); the oxygen saturation level is less than about 85%; or the combined value |HRT|x(101-SAT) is greater than or equal to 132.5.

In one embodiment, the methods, systems and/or devices described herein may be configured to report (audibly, visually, via vibration, and/or via a wireless link) when a condition of the following form is satisfied

$$|\text{HRT}| \times (101 - \text{SAT}) \geq y \text{ V } \text{SAT} \leq z$$

where |HRT|, SAT, and y are as defined as above, V is the logical "or" operator, and z is an oxygen saturation threshold. z may be configured to be around 90%-80% (specifically around 89%, 88%, 87%, 86%, 85%, 84%, 83%, 82%, or 81%).

The methods, systems and/or devices described herein may be configured to report (audibly, visually, via vibration, and/or via a wireless link) when any of one or more conditions of the following form are satisfied:

$$a|\text{HRT}| + b\text{SAT} + c|\text{HRT}|\text{SAT} \geq y$$

where a, b, and c are coefficients, and |HRT|, SAT, and y are as defined above. For example the method, system, and/or device may be configured with three conditions of said form in which the parameter vectors (a b c y) are (1 0 0 62.5), (0 -1 0 -85) and (101 0 -1 132.5). For example, the method, system and/or device may be configured to report when the percentage heart rate change is greater than 62.5%, the oxygen saturation is less than 85%, and/or the combined value |HRT|x(101-SAT) is greater than 132.5. Alternatively, only two conditions may be used, with parameter vectors of (1 0 0 25) and (0 -1 0 -85), to report when HRT changes by, for example, 25% or more, and/or oxygen saturation falls below 85%.

The methods, systems and/or devices described herein may be adapted to record and/or store information provided by or obtained from a subject. The recorded information may be transmitted, transferred or downloaded to a storage (for example digital storage) medium. As such, the methods, systems and/or devices described herein may comprise one or more ports through which stored or recorded data/information may be accessed.

The methods, systems and/or devices provided by this invention may be supplemented with additional steps, processes or means (for example sensors) which assess, determine and/or measure one or more of a subject's temperature, sweat production (impedance), movement, myoelectric (muscle) activity, cardiac activity, respiration rate and/or electrical/brain activity. The methods, systems and/or devices of this invention may comprise, for example ECG type sensors and/or electrodes and the like.

It should be understood that the methods, systems and/or devices of this invention may be set to respond to physiological parameters (for example heart rates and/or oxygen saturation levels) which are tailored or "personalised" to an individual. For example, the methods, systems and/or devices of this invention may be set (or adapted) to detect a specific percentage difference between heart rates – the magnitude of the difference being determined by, for example, a subject's age, sex, disease status and/or medical history.

A subject may be analysed in a clinic to determine the types and/or frequency of seizures they experience and one or more physiological parameters. The methods, systems and/or devices of this invention may then be adjusted or personalised in accordance with the findings of the clinical assessment. For example, in any given patient it may be found that detection of a difference of at least 20% between heart rate measurements is more suited to their age, sex, medical status and/or medical history. In such cases, the methods, devices and/or systems of this invention may be adjusted to report a seizure or imminent occurrence of a seizure upon detection of heart rates which differ by at least 20%.

The detection parameters (such as % heart rate difference and/or oxygen saturation levels) of the methods, systems and devices of this invention may be manually and/or automatically adjusted to accommodate a subject's "normal" or baseline parameters. For example, due to underlying health issues a subject may have a naturally slow heart rate and/or low blood oxygen saturation levels – in such cases, the detection thresholds of the methods, systems and devices of this invention may have to be altered.

A method, system and/or device of this invention may be further adapted to report an error and/or power supply fail (for example low/no battery). An error or the like may be reported by means of an alarm of the type described above. A system or device of this invention may transmit a signal (perhaps wirelessly via Bluetooth) indicating an error to a remote device. A signal of this type may be referred to as an "error signal". The remote device may comprise an alarm which is triggered or activated upon receipt of an error signal. Examples of errors to be

reported may include a low battery, detachment of one or more sensors, devices of the invention and/or systems of the invention from part of the body.

A device of this invention may be rechargeable.

A device of this invention may comprise a docking station into which it can be placed. When docked the device may recharge and/or download recorded data. The docking station may permit uploading of information (software/firmware) to or from the device.

A method, device or system of this invention may be adapted so as to specifically detect the occurrence or impending occurrence of different types of seizure or event. For example by monitoring for a specific set of defined parameters, for example a specific percentage change in heart rate and/or a specific level of oxygen saturation, the various methods, devices and systems of this invention can be made to specifically report the occurrence or impending occurrence of any given type of seizure or event. For example, a method, device or system that monitors for a percentage heart rate change of about 25%-40%, for example a 30%, 31%, 32%, 32.5%, 33% or 34% change in heart rate and/or oxygen saturation at about 90%, for example 85%, 90.5% or 95%, may be particularly useful in the detection of tonic-clonic type seizures. Moreover, the methods, devices and systems described herein may be further supplemented with one or more additional measures to modify, improve or alter seizure detection capability; these are:

- Corrected QT interval
- Heart Rate Variability (HRV) using a cardiac index of parasympathetic activity
- Respiration (breathing rate) derived from optical signals from the pulse oximeter or electrical signals from a separate sensor.

The following options may have the potential to improve alarm performance through modification of seizure detection thresholds and/or "normal" baselines;

- Personalised seizure alarm thresholds / settings optimised for the specific seizure types experienced by each patient (user or clinician selects from a drop down list)
- In the clinic, analyse patient seizure types and patient-specific physiological response to allow personalisation of alarm settings and/or select patients whom the device works for (ie. device may not be suitable for everyone)
- Allow different seizure threshold settings for different patients or patient groups (eg age, sex, presence of certain disease states), and/or feed this information into the seizure detection algorithm
- Baselines and/or seizure detection thresholds automatically adapt to specific user baselines through measurement of "normal" signals
- Baselines and/or seizure detection thresholds automatically adapt to specific user baselines, changing over time (eg. base heart rate may go up during fever) – ie. using a longer term average

- Different seizure threshold levels for heart rate increase and heart rate decrease
- Use instantaneous rate of change (ie. derivative of heart rate or SpO2 with time) as an input to the seizure detection algorithm
- Use second derivative (inflection points) of heart rate or SpO2 with time as an input to the seizure detection algorithm.

DETAILED DESCRIPTION

The present invention will now be described in detail with reference to the following Figures which show:

Figure 1: Receiver Operator Curve for Diagnostic Testing of Percentage Heart Rate Change and Oxygen Saturation during Clinically Significant Seizures.

Figure 2: Receiver Operator Curve for Diagnostic Testing of Percentage Heart Rate and Oxygen Saturation during Clinically Insignificant Seizures.

Figure 3: Maximum Percentage Heart Rate Changes during Generalised Seizures.

Figure 4: Maximum Oxygen Saturation during Generalised Seizures.

Figure 5: Minimum, Mean and Maximum Values of Percentage Heart Rates Changes during Focal Seizures.

Figure 6: Minimum, Mean and Maximum Values for Oxygen Saturation during Focal Seizures

Figure 7: Minimum, Mean and Maximum values of Percentage Heart Rates Changes during Normal Events.

Figure 8: Minimum, Mean and Maximum values for Oxygen Saturation during Normal Events

Figure 9: Bland & Altman plot Observer 1 Limits of Agreement on Difference in heart rate percentage change between Run 1 and Run 2 are 1.6% and -2.4% (± 2 standard deviations).

Figure 10: Box plot comparison of observer 1 R-R interval measurements and heart rate percentage change analysis of Run 1 and Run 2.

Figure 11: Bland & Altman plot Observer 2 Limits of Agreement between Run 1 & Run 2. Limits of Agreement of difference are -10 and 10 msec (± 2 standard deviations).

Figure 12: Bland & Altman plot Observer 2 Difference in heart rate percentage change between Run 1 and Run 2. Limits of Agreement of Difference is 1.04% and -2.32% (± 2 standard deviations)

Figure 13: Boxplot Observer 2 R-R Run 1, R-R Run 2, percentage changes Run 1 and percentage change Run 2.

Figure 14: Scatterplot Observer 1 Runs 1 & 2 and Observer 2 Runs 1 & 2 (R-R vs percentage heart rates change).

Figure 15: Bland & Altman plot Inter-observer difference in Run 1 R-R measurements. Limits of Agreement of Difference are 6 and -2 (± 2 standard deviations).

Figure 16: Bland & Altman plot Inter-observer difference Observer 1 and Observer 2 in Run 2 R-R measurements. Limits of Agreement are between 2 and (-2) msec (± 2 standard deviations).

Figure 17: Correlation between variables and visualisation of proposed alarm thresholds.

Figure 18: superposition of ROC curves generated from additional analysis of data. Dark blue and dark green lines represent original data, light blue and light green lines are from the new analysis.

Figure 19a and b: Data showing that a mathematical combination of heart rate change and oxygen saturation might improve algorithm performance. The triangular shape of the cluster of insignificant events suggests a multiplicative algorithm. The first promising results came from the absolute value of heart rate change divided by oxygen saturation; this gives the ROC curve shown. Maximum sensitivity and specificity occur at a threshold value of 0.3 (81%, 79%)

Figure 20a and b: Further analysis using an algorithm based on multiplication of heart rate change and oxygen saturation change. Absolute value of heart rate change multiplied by (101 – oxygen saturation). This effectively assumes a pre-seizure oxygen saturation of 100%, increased to 101% to avoid dividing by zero. Maximum sensitivity and specificity occur at a threshold value of 132.5 (sensitivity = 84%, specificity = 89%). Further improvement may be possible, eg by using a measured value for pre-seizure oxygen saturation

Figure 21: Maximum increases and maximum decreases in heart rate percentage change* during 10 clinically significant seizures from six patients. *heart rate percentage change calculated using specific algorithm.

Figure 22: Percentage oxygen saturation during 10 clinically significant seizures from six patients.

Figure 23: Maximum increases and maximum decreases in heart rate percentage change* during 18 clinically insignificant seizures from five patients. *heart rate percentage change calculated using specific algorithm.

Figure 24: Percentage oxygen saturation during 18 clinically insignificant seizures from five patients.

Example 1

Materials & Methods

Study Group Characteristics.

Fifty patients were invited to take part in this prospective and ethically approved study (Table 3). All patients were having EEG videotelemetry monitoring as part of their clinical management of their epilepsy. Not all patients in the study had seizures captured during their monitoring. The patients had an age range of 1 day (full term) to 60 years and 3 months with a mean age of 13 years and 4 months ± 13.45 years was calculated for the group. The median age of 8 years 6

months indicates that most of the patients in the group tend towards the younger paediatric age range. The gender mix was 33 Males and 17 females.

Eleven patients had structural abnormalities (not including mesial temporal sclerosis or sclerosis of the hippocampus); 1 patient had Rassmussen's Syndrome, 3 patients had a history of stroke, 2 patients had space-occupying lesions, 1 patient had a double cortex (or sub-cortical band heterotopia), two patients had a history of an encephalitis with subsequent cortical damage, 1 patient was microcephalic and one patient was a neonate with a severe ischaemic encephalopathy.

Several different syndromes were included in the group. One patient had Ohtahara's syndrome, 2 patients were Aicardi syndrome, 2 patients were Austistic Spectrum Disorder, 2 patients had Lennox Gastaut syndrome, 1 patient had progressive polymorphic epilepsy of Dravet and 1 patient had Myoclonic Astatic Epilepsy (MAE).

The general seizure type of the group in this study were as follows; 21 patients had a history mainly of complex focal seizures, 24 patients had a history of mainly generalised tonic-clonic seizures and 5 patients had a history purely of focal seizures.

Anti-convulsant medication was used either as a monotherapy or in combination with other anti-convulsants in the attempt to control frequent seizures. In this group of patients, the most commonly used anti-convulsant was Sodium Valproate, which was prescribed for 17 patients (34%). The next most commonly used anti-convulsant was Carbamazepine, which was prescribed for 13 patients (26%) of the study group. Lamotrigine (9: 18%), Topiramate (8: 16%), Phenytoin (6: 12%) and Phenobarbitone (5:10%), were used less commonly. The least commonly used anti-convulsant therapies prescribed for the group were Nitrazepam (2: 4%), Keppra (2: 4%), Vigabatrin (2: 4%) and Ethosuximide (1: 2%). Rescue medication (Diazepam) is not included in this analysis.

The videotelemetry provided valuable information for the clinical management for all patients. Based on the results, 10 (20%) patients had their medication changed or were commenced on anti-convulsants for the first time because of evidence of epilepsy.

From the adult cohort, videotelemetry supported complex focal seizures consistent with neuro-imaging in two patients being assessed for epilepsy surgery.

Analysis Methodology

Statistical analysis was performed using Minitab version 14 for percentage heart rate change and oxygen saturation for the total seizure group and also for the total normal event group. These two groups were then sub-divided into separate seizure types and normal event types. Further analysis is performed on the data by splitting the seizure data into 'clinically significant' seizures and 'clinically insignificant' seizures. Finally diagnostic testing was performed on the data using Statistical Package for Social Sciences (SPSS) software version 12 on each category of seizure data.

Results

527 seizures were analysed in the total seizure group. This was composed of 36 absences (4 patients), 102 simple focal (6 patients), 229 frontal lobe seizures (10 patients), 11 generalised tonic-clonic seizures (6 patients), 28 myoclonus (5 patients), 31 temporal lobe seizures (11 patients) and 90 tonic seizures (7 patients). In addition, 83 sub-clinical seizures (7 patients) and 10 neonatal seizures were analysed.

A mean difference of 21.8% in heart rate is calculated for the total seizure group during seizures compared to baseline measurements and is highly statistically significant (*p<0.001*). Mean differences in oxygen saturation are small (2.1) dropping mean oxygen saturation to 96.1, which is clinically not significant but is statistically significant (*p<0.001*).

t-tests	N	Mean	St.Deviation	SE Mean	P<
%HR	527	21.803	29.799	1.303	0.001
SAO2					0.001
BEFORE	494	98.253	1.944	0.088	
DURING	494	96.107	5.336	0.240	
Difference	494	2.146	4.964	0.223	

Table 1: Descriptive Statistics for Percentage Heart Rate Change One Sample t-test and Oxygen Saturation Percentage Paired t-test during Total Seizure Group.

Clinically Significant Seizure Group.

All seizures in this study were self-resolving and did not require medication intervention to stop any prolonged seizures. However, some seizures were more 'clinically significant' than others. The seizures that were categorised as being clinically significant were generalised tonic-clonic seizures, prolonged frontal lobe seizures with significant hypoxia and some temporal lobe seizures that caused cardiological changes e.g. diminished T-wave etc. Generally, seizures that were dramatic in nature and posed an obvious clinical threat to the patient and where an alarm system would be beneficial in alerting someone to the fact that the seizure was occurring, were included in this group.

Results for Clinically Significant Seizure Group.

One sample t-tests were performed using Minitab version 14 on percentage change in heart rate and paired t-tests for oxygen saturation percentage during 61 clinically significant seizures. These seizures were composed of frontal lobe seizures (13), complex focal (2), temporal lobe complex focal (25), generalised tonic-clonic seizures (11), tonic seizures (9), epileptic spasms (1).

t-test	N	Mean	StDeviation	SE Mean	P<
%HR	61	40.69	33.85	4.41	0.001
SAO2					0.001
BEFORE	49	97.286	2.739	0.391	
DURING	49	86.918	11.047	1.578	
Difference	49	10.368	11.394	1.628	

Table 2 Descriptive Statistics for Percentage Heart Rate One Sample t-test and Oxygen Saturation Percentage Paired t-tests for Clinically Significant Seizures.

Interpretation of Results.

The best compromise between the best level of correctly identified seizures (sensitivity) and keeping false alarms to a minimum due to normal events (false positives) appears to be when the trigger level is set to a percentage heart rate change of 25.5%. This level gives a sensitivity of 0.792 (79%), which is almost 80% accurate seizure detection. This trigger level gives a specificity of 1-0.246 (75%), which will correctly identify heart rate changes due to normal events that would not trigger the alarm. This leaves a false alarm rate of 25%, which is possibly a little high i.e. 1:4 ratio of false alarms.

To minimise the proportion of false alarms, a lower sensitivity of true positive seizure detection would occur. If parents were given the choice they would probably ask for better seizure detection rate and accept that 1 alarm out of 4 may be a false alarm.

Clinically Insignificant Seizure Group.

Many epileptic seizures are very brief in nature. Bystanders may not even be aware that someone has had an absence attack. These types of attacks can interrupt concentration and affect school performance. However, in terms of a seizure alarm device it would neither be useful to the parent or beneficial to the patient if it triggered every time an absence occurred.

Some people may have a mixture of absence attacks and generalised tonic-clonic seizures. In this situation, it would be useful for an alarm system to trigger during the tonic-clonic seizure but not during an absence.

Results for Clinically Insignificant Seizure Group.

466 epileptic events were included in the clinically insignificant seizure group. This group is composed of frontal lobe seizures (214), atonic seizure (1), complex focal seizures (95), temporal lobe complex focal seizures (16), absences (35), myoclonus (27) and tonic seizures (78).

t-test	N	Mean	St.Deviation	SE Mean	P<
% HR	466	14.727	16.560	0.780	0.001
SAO2	430				0.001
BEFORE		98.42	1.778	0.0858	
DURING		97.21	2.664	0.1285	
Difference		1.209	2.1107	0.1018	

Table 3 Descriptive statistics for percentage heart rate change one sample t-test and oxygen saturation percentage paired t-test for clinically insignificant seizures.

Statistical significance *($p<0.001$)* occurs in both heart rate percentage change and oxygen saturation during clinically insignificant seizures. Insignificant seizures have a mean heart rate change of 14.7% compared to baseline with a standard deviation of 16.5%. The mean oxygen saturation of 97% and is a normal value and not clinically significant for a patient but is statistically significant in this group because the majority of clinically insignificant seizures have a slight alteration in oxygen saturation during the seizure of around 1%.

Statistical significance does not equate to clinical significance in this instance and diagnostic testing is required to assess whether insignificant seizures can be distinguished from normal events using percentage heart rate and oxygen saturation as parameters for a seizure alarm.

Results

Overall, percentage heart rate change during clinically insignificant seizures, are not distinguishable from normal events. The best compromise seen from diagnostic testing (Figure 19) is a trigger level of 14.5%. This gives a sensitivity of 45% of identifying true positives with 55% missed seizures. A similar specificity is seen of 1-0.51 (49%) true negatives (correctly identified normal events) and a high level of false alarms at 51%. This means that when the alarm triggers, it could either be almost equally due to a clinically insignificant seizure or a normal event. This trigger level is similar to the mean heart rate percentage change for the group of 14.7% seen from statistical analysis of one sample t-tests.

Oxygen saturation percentage for this group shows a similar result in diagnostic testing to heart rate percentage change and it cannot distinguish clinically insignificant seizures from normal events either. The level of sensitivity and specificity that show the best compromise is a trigger level of 97.5%. This results in a sensitivity of 41% true positives and a specificity of 1-0.53 (47% true negatives). The level of false positives (false alarms) is 53%. Again an alarm system triggering at this level may or may not be a seizure with an almost equal probability.

An alarm system based on percentage heart rate change and oxygen saturation which is set at a trigger level specific in detecting clinically significant seizures, will be unlikely to be triggered due to a clinically insignificant seizure or normal event.

ROC Analysis was performed for individual seizure types with sensitivity and specificity values. Results are given in Tables 7,8,10 &11.

Sensitivity: combined triggered percentage Heart Rate change & Oxygen Saturation.

	Triggered Parameter	Non-Triggered Parameter	**Total**
% heart rate change	49	16	65
Oxygen saturation	22	43	65
Total	71	59	130

Table 4: Cross Tabulation of Triggered Parameter & non-Triggered Parameters in the detection of seizures using Percentage heart rate change and oxygen saturation.

Sensitivity- proportion of independently correctly triggered events

% heart rate change: 49/65= 75%

oxygen saturation: 22/65= 34%

Agreement in parameter identification of triggered seizures (both parameters triggered during same event) =14/65 = 22%

Combined result of either triggered parameter in identified seizures (either or both parameters triggered during total events) = 56/65 = 86%

False negatives:

Total of missed events using optimum trigger levels in percentage heart rate change = 16/65 = 25%

Total of missed events using optimum trigger levels in oxygen de-saturation = 43/65 = 66%

Combined parameters false negatives (events missed completely by both triggers) = 9/65 = 14%

Depending on both percentage heart rate change at 25.5% and oxygen saturation of 85% reaching these trigger levels together lowers the sensitivity to 24% but improves specificity to 99%. Oxygen saturation on its own can only identify 38% of seizures but correctly ignores non-events to 99.5%. However, when the data is combined with one/ other/ both parameters reaching their trigger levels, the sensitivity improves further to **91%** and specificity stays the same at 75%. This result indicates that if a seizure alarm was triggered because of either percentage heart rate change or oxygen saturation parameters triggered either independently or together then 91% of clinically significant seizures would be detected. As before, one triggered alarm in every four would be false.

Seizure Type	N	Mean	St.Deviation	SE.Mean	P<
Generalised Tonic-Clonic Seizures	11	53.363	24.068	7.257	0.001
Tonic Seizures	90	18.956	15.422	1.626	0.001
Absences	35	3.36	7.14	1.19	0.008
Myoclonus	28	2.178	12.350	2.334	0.359

Table 5 Summary of Descriptive Values of One Sample T-Test for Percentage Heart Rate Change during Generalised Seizures.

Seizure Type	N	Mean	St.Deviation	SE.Mean	P<
Generalised Tonic-Clonic Seizures Difference	8	91.2	4.926	1.742	0.018
Tonic Seizures Difference	89	94.7	3.894	0.413	0.001
Absence Seizures Difference	35	94.8	1.32	0.22	0.378
Myoclonus Difference	28	93.2	4.02	0.76	0.001

Table 6 Summary of Descriptive Values of Paired T-tests for Oxygen Saturation during Generalised Seizures

Seizure Type	Proposed Trigger Level	Sensitivity True Positives	Sensitivity False Negatives	Specificity True Negatives	Specificity False Postives
Generalised Tonic-Clonic Seizures	32.5%	88	12	85	15
Tonic Seizures	32.5%	78	22	85	15
Absences	8.5% (or higher to miss events)	31	69	31	69
Myoclonus	9.5% (or higher to miss events)	36	64	34	66

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Table 7: Summary of Diagnostic Testing of Percentage Heart Rate Changes during Generalised Seizures.

Seizure Type	Proposed Trigger Level.	Sensitivity True Positives	Sensitivity False Negatives	Specificity True Negatives	Specificity False Positives
Generalised Tonic-Clonic Seizures	90.5%	50	50	95	5
Tonic Seizures	95.5%	44	56	71	29
Absence Seizures	95.5% (or lower to miss events).	66	34	71	29
Myoclonus	85% (to miss events).	7	93	100	0

10 Table 8: Summary of Diagnostic Testing & Proposed Trigger levels of Oxygen Saturation during Generalised Seizures

Seizure type	N	Mean	St.Deviation	SEMean	P<
Frontal Lobe	229	28.332	15.424	1.019	0.001
Right Frontal Lobe	13	53.615	39.794	11.037	0.001
Left Frontal Lobe	214	26.86	11.081	0.757	0.001
Temporal Lobe	31	28.484	30.121	5.409	0.001
Right Temporal Lobe	15	43.467	22.944	5.924	0.001
Left Temporal Lobe	16	14.438	29.804	7.451	0.072
Neonatal	10	8.10	13.89	4.39	0.098
Sub-clinical seizure	83	2.349	9.342	1.025	0.025

Table 9: Summary of Descriptive Values of One Sample t-tests for Percentage Heart Rate during Focal Seizures.

Seizure type	Proposed Trigger Level	Sensitivity True Positives	Sensitivity False Negatives	Specificity True Negatives	Specificity False Positives
Frontal Lobe Seizures	30.5%	83	17	82	18
Temporal Lobe Seizures	25.5%	75	25	75	25
Neonatal Seizures	15.5%	43	57	51	49
Sub-clinical seizures	>25.5 % (to ignore events)	3	97	75	25

Table 10: Summary of Diagnostic Testing & Proposed Percentage Heart Rate Change Trigger Levels in Focal Seizures.

Seizure type	Proposed Trigger Level	Sensitivity True Positives	Sensitivity False Negatives	Specificity True Negatives	Specificity False Positives
Frontal Lobe Seizures	89.5%	67	33	97	3
Temporal Lobe Seizures	88.5%	29	71	99	1
Neonatal Seizures	98.5%	100	0	26	74
Sub-clinical seizures	86.5% (to ignore events)	0	100	100	0

Table 11: Summary of Diagnostic Testing & Oxygen Saturation Proposed Trigger levels in Focal Seizures

Summary of Maximum Changes in Percentage Heart Rate Change and Oxygen Saturation during Focal Seizures.

Summary of Mean Values (during normal events).

Normal Physiological Event Group	Mean % Heart Rate Change	n	One sample t-test *p</=*	Mean Oxygen Saturation (during)	n	Paired t-test *p</=*
Total	16.5	496	0.001	96.4	462	0.001
Arousal	21.0	190	0.001	96.2	174	0.049
Coughing	6.4	34	0.001	96.0	33	0.513
Crying	13.0	15	0.001	97.1	11	0.132
Laughing	5.0	22	0.001	97.1	22	0.732
Stretching	14.8	36	0.001	96.2	36	0.258
Sneezing	15.3	10	0.001	97.0	10	0.177
Turning over in bed.	20.9	141	0.001	96.7	133	0.132
Yawning	0.5	48	0.728	97.7	44	0.269

Table 12 Summary of Mean Values during Normal Events

Maximum, Mean and Minimum Values

Intra & Inter-observer Error

Observer 1	Run1 (% change)	Run 2 (% change)	Difference	Average
n	24	24	24	24
Mean	(-3.01)	(-3.01)	0	-3.01
Standard Error of Mean	5.04	5.15	0.266	5.1
Standard Deviation	24.7	25.2	1.3	24.9
Minimum	(-72.5)	(-76.8)	-2.4	-74.6
Q1	(-17.9)	(-17.0)	-0.6	-17.4
Median	4.8	4.8	0	4.8
Q3	12.7	12.7	0	12.7
Maximum	29.2	29.2	4.3	29.2
Range	101.6	105.9	6.8	103.8

Table 13 Descriptive statistics Observer 1 percentage change Run 1 and Run 2.

A close relationship is found between Run 1 and Run 2 for observer 1 measurements (n=146) (Table 39) with a mean difference of 0 milliseconds and mean percentage change difference of (-0.001) % Limits of agreement are 8 msec and (-12) msec, 1.6% and (-2.4) % (±2 standard deviations).

Observer 2

Observer 2	Run1 (msec)	Run 2 (msec)	Difference (msec)	Average (msec)
Total count n (R-R intervals)	146	146	146	146
Mean	630.8	630.9	-0.1	630.9
Standard Error of Mean	11.0	11.0	0.5	11.0
Standard Deviation	133.2	133.1	6.875	133.1
Minimum	448	448	-18	448
Q1	520	520	-0.25	516
Median	608	608	0	608
Q3	712	707	0.5	709.5
Maximum	1040	1024	24	1032
Range	592	576	42	584

Table 14 Descriptive statistics Observer 2 Run 1 and Run 2.

Observer 2	Run1 (% change)	Run 2 (% change)	Difference	Average
n	24	24	24	24
Mean	1.7	1.8	-0.1	1.7
Standard Error of Mean	4.2	4.3	0.4	4.2
Standard Deviation	20.8	21.1	2.2	20.9
Minimum	(-44.3)	(-43.4)	(-7.5)	(-43.9)
Q1	(-15.1)	(-14.0)	(-0.8)	(-14.5)
Median	5.5	5.0	0	5.3
Q3	14.6	16.2	0.8	14.5
Maximum	41.2	41.2	6.1	41.2
Range	85.5	84.6	13.7	85.1

Table 15 Descriptive statistics for Observer 2 percentage change Run 1 and Run 2.

A close relationship is also found between Run 1 and Run 2 for Observer 2 measurements (n=146) with a mean difference of (-0.1) milliseconds and mean percentage change difference of (-0.144) % Limits of agreement are very similar to Observer 1, at 10 msec and (-10) msec and 1.04% and (-2.32) % (±2 standard deviations).

Inter-observer Analysis

Inter-observer	Run 1 Difference Observer 1 minus Observer 2	Run 1 Average Observer 1 plus Observer 2	Run 2 Difference Observer 1 minus Observer 2	Run 2 Average Observer 1 plus Observer 2
Total count n (R-R intervals)	146	146	146	146
Mean	0.3	631.0	0.5	631.1
Standard Error of Mean	0.2	11.0	0.3	11.0
Standard Deviation	3.0	132.8	3.2	133.1
Minimum	(-16.0)	448	(-12.0)	448
Q1	0	520	0	520
Median	0	608	0	608
Q3	0	712	0	706.5
Maximum	16.0	1035	18.0	1024
Range	32	587	30	576

Table 16 Descriptive statistics for Inter-observer analyses.

Inter-observer analysis demonstrates a close relationship with a mean difference of 0.3 msec between observer 1 and observer 2 for Run 1 and 0.5 msec mean difference for Run 2 . Narrow limits of agreement for Run 1 of 6 msec and (-2) msec mean 95% differences between observer 1 and observer 2 are within 8 msec range.

Similarly, Run 2 shows narrow limits of agreement of 2 and (-2) msec with 95% of inter-observer agreement within 4 msec range.

Discussion

The diagnosis of epilepsy carries an excess mortality that is 2-3 times higher than the general population (Cockerall et al 1994) and official statistics report around 1000 deaths due to epilepsy in the UK each year. In chronic epilepsy sudden unexplained death in epilepsy is the main cause of excess mortality and risk of premature death from SUDEP in individuals with intractable epilepsy is 1:200/year (Nashef et al 1995). Reported risk factors for Sudden Unexplained Death in Epilepsy include young age, uncontrolled epilepsy and seizures occurring in sleep (Shorvon 1997).

Despite these statistics, inadequate seizure alarms are commercially available for identifying nocturnal seizures. This remains a problem for people with epilepsy and their families or carers. The incidence of seizures occurring at night are probably under-estimated because so many attacks are un-witnessed and the person having the seizures may not remember having them due to post-ictal amnesia, are unable to communicate the problem if they have age related communication difficulties or who may be learning disabled, or experience loss of consciousness following the seizure. It is well documented that sleep itself increases the occurrence of seizures. 'Surveys suggest that in 10-45% of patients [with epilepsy] overall, have

seizures that may occur predominantly or exclusively in sleep or in relation to sleep deprivation' (Walker et al 2004).

Undetected prolonged nocturnal seizures can be fatal or result in significant morbidity due to hypoxic brain damage. This leaves an indescribable burden of guilt on families living with epilepsy and they have voiced the need for a reliable alarm system. In a professional capacity, 'one still sees the catastrophe of the child who is found by his parents in the morning having convulsed half the night in compensated status and who is left with permanent hemiplegia' (Brown et al 1991). Compensated status epilepticus is continual convulsive status where the body compensates to cope with oxygen and glucose demands metabolically by switching to anaerobic respiration physiological mechanisms. This usually occurs after 30 minutes of continual seizure activity. The brain requirements for oxygen are very high especially during a seizure. During convulsive status, blood flow increases by approximately 400% to meet oxygen and glucose demands of neuronal activity. Areas of brain structures most damaged by status epilepticus are the hippocampal regions, Purkinje cells in the cerebellum, thalamus and then resultant laminar necrosis of the cortex (Brown et al 1991).

Some seizures resulting in death are accidental and death could have been avoided if someone was alerted to the situation and intervened with rescue medication and body re-positioning to prevent an obstructed airway (Langan et al 2000).

Other seizures resulting in death due to SUDEP may not have been prevented even with intervention (Dashief et al 1986). Whether in cases of SUDEP or seizures amenable to intervention, if parents were given the choice of having an alarm system which would alert them of a seizure taking place or not having an alarm system, I am certain that parents and carers would prefer to know when a seizure was occurring. A reliable alarm system would result in carers doing everything possible to prevent bodily injury, brain damage or even a fatality.

The knowledge that we are dealing with two separate problems, of death in epilepsy namely 'extrinsic factors' of circumstantial compromise e.g. suffocation due to obstructive apnoea or drowning and 'intrinsic factors' of SUDEP, have been considered for over one hundred years. 'Epileptologists at the turn of the century were well aware of the dangers from seizures and recognised that seizure deaths could be accidental or due to intrinsic mechanisms during a single seizure or serial seizures and status' (Nashef 2000). However, very little is understood of what exactly these 'intrinsic' mechanisms are and much research is active in this area.

An increased risk of SUDEP is reported in a young age group. These patients are most vulnerable at night when seizures are most likely to be un-witnessed. A high percentage of nocturnal seizures occur in this age group. 'More nocturnal seizures recur in children, adolescents and young adults than daytime seizures (82%). The most likely timescale for recurrent GTCS are within 6 months of first seizure' (Martinovic et al 1997).

Another risk group for undetected nocturnal seizures are the elderly, often living alone with no immediate assistance during a seizure event. The incidence rate is 1 per 1000 of the general population but this figure is set to rise with the growing elderly population of recent times and is regarded as a significant public health issue with epilepsy being the third most common neurological disorder in old age after dementia and stroke (Sander et al 2004).

There is already a need to understand the physiological mechanisms involved during seizures and a necessity to devise a reliable alarm system. A reliable alarm system may not prevent true SUDEP cases but many seizures that are amenable to intervention, if detected, will be prevented from causing bodily injury, hypoxic brain damage and in some cases death. My view is supported by others ' timely assistance at the time of a seizure is likely to reduce the risk of death or injury' and 'unwitnessed seizures carry a higher risk of death' (Nashef 2000) and 'positioning of the patient or stimulation of respiration may prevent a fatal outcome in some cases. This raises the important issue of supervision' (Langan et al 2000).

A wide age range of patients, were recorded in this study from a 1 day old neonate to a 60 year old pensioner. A baseline heart rate in a neonate is generally much higher e.g. 210/ min compared to that of an elderly person with a heart rate generally of around 60/min. It is because of this age dependant heart rate fundamental that heart rate 'percentage change' is analysed instead of absolute heart rate. Any changes in heart rate before an event and during an event were calculated as a proportional change and can be compared for all ages.

An alarm system based on percentage heart rate would have to show a significant proportional change during an epileptic seizure for all ages. In a neonate or young child who has a resting heart rate of 200/min, a 20% increase in heart rate would result in a rate of 240/min. In an adult with a resting heart rate of 60/min, a 20% increase in heart rate would result in a rate of 72/min. Both analogies show a mild proportional change in both patients. If we were to consider an absolute heart rate increase of 40/min of a neonate or young child and add that to an adult rate of 60/min, we would see a significant tachycardic state of the adult at 100/min. Clearly, this would be a significant increase in heart rate for the adult, not a mild change. Therefore, absolute heart rate changes are not appropriate and do not offer an ideal measurement when considering and comparing heart rate changes during a wide age range of patients.

Percentage heart rate and optionally oxygen saturation during epileptic seizures were identified and clinically categorised using electroencephalographic videotelemetry. The rationale for choosing to examine these parameters was based on the general belief amongst researchers that there is a fundamental involvement of cardiac and respiratory changes during a seizure. These changes in heart rate and respiratory changes resulting in possible hypoxaemia may either be a centrally driven channelopathy effect or simply the physiological response to physical effort during the seizure with heart rate increase. An alarm system based

on heart rate change and oxygen saturation could also measure vital signs and alarm if someone's life was threatened.

Percentage Heart Rate Changes and Oxygen Saturation in Seizures.

The results of percentage heart rate changes during clinically significant seizures in this study are distinctly different from those of clinically insignificant seizures and normal events. This is an encouraging result with good sensitivity (79%) and specificity values (75%) when a proposed trigger level of percentage heart rate change of 25.5% is used. This would suggest that a device based on percentage heart rate and perhaps oxygen saturation would identify the type of seizures, which ought to attract assistance. It also suggests that the alarm would have a minimal number of false alarms due to normal events (1:4 ratios). A factor to bear in mind with these results is that none of the 'clinically significant' seizures required medication intervention and were self-resolving. I would postulate that the sensitivity and specificity values may even be higher during more clinically prolonged seizures.

The results for detecting generalised tonic-clonic seizures give a higher sensitivity of 88% and specificity of 85%. This means that most tonic-clonic seizures would be identified and very few false alarms would occur. A proposed percentage heart rate change trigger level for detecting generalised tonic-clonic seizures is 32.5%. In this group oxygen saturation was only useful in detecting 50% of this type of seizure but is a useful additional trigger parameter with very few false alarms (5%) when a trigger level of 90.5% is used.

When data is combined with one/ other/ both parameters reaching their trigger levels, the sensitivity improves further to 91% and specificity stays the same at 75%. This result indicates that if a seizure alarm was triggered because of either percentage heart rate change or oxygen saturation parameters triggered either independently or together then 91% of clinically significant seizures would be detected. As before, one triggered alarm in every four would be false.

Changes in percentage heart rate occurring during epileptic seizures showed statistical significance of $p<0.001$ for generalised tonic-clonic seizures, tonic seizures, frontal lobe seizures and temporal lobe seizures. Statistical significance was slightly lower in absence seizures ($p=0.008$) and not significant during episodes of myoclonus ($p=0.359$).

Analysis of statistical significance for oxygen saturation was high for tonic seizures ($p<0.001$) and slightly lower for generalised tonic-clonic seizures ($p=0.018$). Absence seizures did not show statistically significant changes in oxygen saturation ($p=0.378$).

Statistical significance does not necessarily equate to clinical significance. Although statistical significance of $p<0.001$ is also seen for percentage heart rate change during many types of normal events; arousal, coughing, crying, laughing, sneezing and turning over in bed, the maximum percentage heart rate changes are distinctly lower than that seen during seizures. Changes in oxygen saturation as a group reached high statistical significance ($p<0.001$) but

generally were less statistically significant when analysed separately; arousal p=0.049, coughing p=0.513, crying p=0.132, laughing p=0.732, sneezing p=0.177, turning over in bed p=0.132 and yawning p=0.269.

The alarm system based on these parameters would be ideally pre-set to trigger appropriately to the type of seizure the patient is known to have. It may be necessary to collect data individually for that patient to build their own unique range of normal values so the device could be as accurate as possible.

An ideal system would analyse percentage heart rate change and oxygen saturation using an epoch data sampling time of 9 seconds. This would be necessary to average out any normal sinus arrhythmia, which can be marked in children. A separate safety trigger level within the device (which should not be altered) would act as a 'safety-net' to indicate life-threatening vital signs. This trigger would be based on minimum pulse rate and oxygen saturation. If levels dropped to this level then the safety net trigger would indicate that life may be threatened.

Hemisphere Lateralisation Effects on Percentage Heart Rate and Oxygen Saturation.

A difference is seen when comparing percentage heart rate changes during seizures arising from the right hemisphere and seizures arising from the left hemisphere. Major differences are seen when data is divided into right and left frontal lobe seizures in terms of percentage heart rate changes. The mean percentage heart rate change for the right hemisphere is twice (53.6%) the mean heart rate change seen from the left hemisphere (26.8%). Similarly, more dramatic data of mean oxygen saturation changes are seen from seizures derived from the right hemisphere (83.7%) compared to the left hemisphere (98.3%). High statistical significance is seen (p<0.001) for heart rate changes occurring in frontal lobe seizures derived from either hemisphere.

A similar difference is seen when percentage heart rate changes are examined separately for right and left temporal lobe seizures. Much higher changes in mean percentage change occurs from seizures arising from the right temporal lobe (43.5%) compared to the mean percentage heart rate changes from seizures arising from the left temporal lobe (14.4%). High statistical significance (p<0.001) is seen for heart rate change from right temporal lobe seizures. A marginally lower statistical significance is seen from heart rate changes during left temporal lobe seizures (p=0.072).

Reports of sinus arrest have been secondary to seizures arising from the right temporal region. Other reports have been cases of severe bradycardia secondary to seizures arising from the left temporal lobe (Vaughn et al 1997).

A different result is obtained however when the oxygen saturation changes are studied for right temporal lobe seizures and left temporal lobe seizures. Clinically significant changes in mean oxygen saturation (86.1%) occurred from left temporal lobe seizures with a high statistical significance of p<0.001. Mean oxygen saturation changes appear less clinically significant with

mean values of 91.8% from right temporal lobe seizures was not statistically significant (p=0.072).

The general differences in heart rate change recorded when comparing seizures arising from the right and left hemispheres in this study are explained by other studies on physiological differences of innervation pathways. 'There is clinical evidence of lateralization in neurocardiac control' Intra-operative stimulation of the insula and amygdala has demonstrated that the right cerebral hemisphere mainly modulates sympathetic activity (Cheung et al 2000).

The insular cortex is the continuation of cortex between the frontal/parietal and temporal lobes forming the in-going C-shape on either hemisphere. Historically, many seizures arising from the insular cortex are mistaken for temporal lobe seizures as they share similarities of auras described as a 'rising sensation from the stomach' (Brotherstone 2002). Chronotopic organization studies of the insular cortex have shown that the anterior portion is more likely to cause tachycardia compared to any other cortical area (Opherk et al 2002). Lateralisation of effect on heart rate is documented. 'Stimulation of the left anterior insula causes a bradycardia whereas stimulation of the right insular cortex induces tachycardia' (Nouri et al 2004).

Hypoxia occurs during some seizures and not others. In the study, hypoxia occurred with clinically significant levels of 71%. A wide range of seizure types of focal and generalised seizures, were associated with hypoxia. A focal seizure involving the right frontal lobe resulted in oxygen saturation levels down to 71%. Hypoxia was also recorded during a left temporal lobe seizure with oxygen saturation levels down to 75%. Several generalised seizures were associated with hypoxia. One period of hypoxia was recorded during a series of epileptic spasms with oxygen saturation recorded down to 81%. Another generalised epileptic myoclonic drop attack resulted in oxygen saturation level of 84%.

One group that did not show any change in oxygen saturation at all in this study group, were the neonates demonstrating focal seizures. A possible explanation for this is that the neonate has a very high concentration of red blood cells. In the womb, the baby depends on oxygen supply via the umbilical cord, which provides comparatively lower oxygen than that obtained during spontaneous respiration. The high concentration of red blood cells maximise the absorption of all available oxygen molecules. Therefore, the neonatal haemoglobin copes better with low oxygen availability compared to the older infant, child and adult. During a neonatal seizure, the baby may have a suppressed respiratory effort but it would take much longer for oxygen saturation levels to drop significantly. In animal studies, 'immature animals appear to tolerate hypoglycaemia and anoxia better than the more mature' Young animals have a 'higher energy reserve' and a 'lower metabolic rate' (Mayman 1971).

Accidental death during seizures can result from suffocation. The prevalence figures of this cause is somewhat disputed but various reports indicate that suffocation has either occurred due to unfortunate body position and obstructive apnoea or simply the possibility that after a seizure in an unconscious state, the person has suffocated because they have been

unable to turn over or move their face to breathe and have consequently suffocated. This is distinctive from death during seizures (SUDEP) where the person has happened to be in a prone position during a sudden 'electrical accident' and that respiratory failure was secondary to another main cause of death.

Several reports describe people being 'found face down onto his pillow' the following morning (Martin 2005). Clearly, there may be several factors involved in determining the fundamental cause or combinations of factors why death can occur during seizures. However, anti-suffocation ventilated pillows may prevent suffocation in some instances and are advertised on the 'The National Society for Epilepsy' website. An alarm system based on oxygen saturation would also alert someone to a seizure and allow intervention.

A more common reason for respiratory problems during seizures appears to be an 'intrinsic' one. ' There is strong evidence in favour of hypoventilation being a common occurrence in epileptic seizures and this is likely to be a significant mechanism in SUDEP' with ' central apnoea observed commonly during seizures, including complex partial seizures' (Nashef 2000).

Mechanically many seizures cause a change in breathing pattern particularly during generalised tonic-clonic or tonic seizures where not just the limbs are involved in tetanic contraction but the intercostal respiratory muscles are also contracted which leads to cyanosis (James 1991). In this study most of the patients having apparent generalised tonic-clonic seizures had a reduction of oxygen saturation down to 85.5%.

Apnoea and hypoxia during seizures are described during many types of seizures by several authors (Brown & Hussain 1991, James et al 1991, Jallon 1997, Langan et al 2000, Nashef et al 1997 and Opherk et al 2002). Seizures may cause a physical restriction to the respiratory muscles by tetanic contraction but others appear to be caused by an'intrinsic' mechanism. Langan et al 2000 reports, 'hypoventilation, which was primarily central in nature, occurred in the context of both generalised and partial seizures.' Animal studies may give some insight as to possible mechanisms of seizure related apnoea and hypoventilation. A study by Williams et al 1989, concentrated on stimulation of sites within the fastigial nucleus of anaesthetised cats. Stimulation rates of 20Hz, 50Hz and 200Hz caused respiratory inhibition and apnoea. They found that the higher the frequency of stimulation the longer the period of apnoea occurred.

The effect of repeated seizures on cardiac muscle and the response to hypoxia have been indicated as further risk factors of SUDEP. Opherk suggests that repeated autonomic stimulation because of frequent seizures could structurally damage the heart leaving it more susceptible to arrhythmias or ischaemia.

Example 2

Method

Thirteen participants were recruited as part of an on-going study in the clinical evaluation of a novel device in the detection of epileptic seizures. Consenting participants wear a finger sensor which records pulse and oxygen saturation every 1/3 second. This data is then analysed by the novel device which performs a calculation based on a specified moving window of percentage heart rate change and percentage oxygen saturation.

The participant wears the finger sensor during a planned videotelemetry admission which also involves 23 scalp electrodes to record electroencephalographic activity and a time synchronised video in order to identify and classify the types of seizures and normal physiological events. Each event is documented and the time in hh:mm:ss are listed. The same times are identified on the spreadsheets created by the device and the results entered onto a paper case report form (pCRF). Final statistical analysis is performed using a tamper proof data base.

Results

Clinically significant seizures in this study refer to seizures that the participant may require assistance in body re-positioning or the supply of oxygen and may, if un-identified or prolonged, lead to hypoxic brain injury or cardiac dysrhythmia.

Ten clinically significant seizures were recorded from six patients: left temporal complex focal seizures (2) from two patients; right frontal complex focal seizures (2) from two patients; right temporal complex focal with secondary generalisation (2) from 1 patient and simple focal seizures (4) from one patient.

Clinically insignificant seizures in this study refer to seizures that are either brief or are of no consequence to the participant. In many cases, the participant may not even be aware of an event occurring and a seizure detection system would not be required to alarm in that instance.

Eighteen clinically insignificant seizures were recorded from five patients: Complex focal left temporal (1) from one patient; focal left temporal seizures (1) from one patient; myoclonus (12) from 1 patient and simple focal seizures (4) from two patients.

Discussion

The device can distinguish clinically significant seizures from clinically insignificant seizures and most normal physiological events.

The results demonstrate that the two clinically significant seizures (right frontal complex focal seizure and simple focal seizure) that have low changes in % heart rate of 12.5% and -14.7% (Figure 1) had oxygen desaturations of 76% and 78% respectively (Figure 22). A seizure detection device based on a combination of % heart rate change and oxygen desaturation would trigger during those events.

Conversely two clinically significant seizures (left temporal complex focal seizures) which did have high %heart rate changes of 63.9% and 104.2% (Figure 21) did not have oxygen desaturations of 94% and 95% respectively (Figure 22). Therefore the method of heart rate percentage change can identify some clinically significant seizures without oxygen saturation.

Claims:

1. A method of detecting a seizure, said method comprising the step of determining the percentage difference between heart rate measurements of a subject, wherein a percentage difference between heart rate measurements indicates that a seizure is about to occur or is occurring.

2. The method of claim 1, wherein the seizure comprises disturbed brain activity.

3. The method of claim 1 or 2, wherein the seizure is one or more selected from the group consisting of:

(i) generalised tonic-clonic seizures;
(ii) tonic seizures;
(iii) atonic seizures;
(iv) complex focal seizures;
(v) temporal lobe complex focal seizures;
(vi) prolonged frontal lobe seizures;
(vii) temporal lobe seizures;
(viii) absences; and
(ix) myoclonus.

4. The method of any one of claims 1 or 2, wherein the seizure is any seizure occurring as a consequence of an underlying medical disease, condition and/or syndrome.

5. The method of claim 4, wherein the underlying medical disease, condition and/or syndrome is one or more selected from the group consisting of:

(i) stroke;
(ii) space-occupying lesions;
(iii) sub-cortical band heterotopia;
(iv) encephalitis;
(v) cortical damage;
(vi) ischaemic encephalopathy;
(vii) Ohtahara's syndrome;
(viii) Aicardi syndrome;
(ix) Autism;
(x) Asperger's syndrome;
(xi) lennox Gastaut Syndrome;
(xii) progressive polymorphic epilepsy of Dravet;
(xiii) Rassmussen's syndrome;

(xiv) Myoclonic Astatic Epilepsy (AME);

(xv) Mesial temporal lobe sclerosis; and

(xvi) Sclerosis of the hippocampus.

6. The method of claim 1, wherein the method is applied to heart rate measurements provided by a human subject predisposed or susceptible to seizures.

7. A method of detecting a seizure, said method comprising the step of determining the percentage difference between first and second heart rate measurements of a subject, wherein if there is a percentage difference between a second heart rate measurement of the subject and a first heart rate measurement of the subject, a seizure is occurring or is about to occur.

8. The method of claim 7, wherein the detection of a percentage difference of at least about 15% between a second heart rate measurement of the subject and a first heart rate measurement of the subject, indicates that a seizure is occurring or is about to occur.

9. The method of claim 7 or 8, wherein the detection of a percentage difference of at least about at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, at least about 95%, at least about 99%,at least about 100%, at least about 105%, at least about 110%, at least about 150%, at least about 200%, at least about 250%, at least about 300%, at least about 350%, at least about 400%, at least about 450% and/or at least about 500% between a second heart rate measurement of the subject and a first heart rate measurement of the subject, indicates that a seizure is occurring or is about to occur

10. The method of any one of claims 7-9, wherein the first heart rate measurement is determined at one time point the second heart rate is measured or determined at another or different time point.

11. The method of any one of claims 7-10, comprising measuring or determining a first heart rate at a first time point and a second heart rate at a second time point and calculating the percentage difference between the two.

12. The method of any preceding claim, wherein a heart rate is a measure of the number of beats of a heart in a specified period of time.

13. The method of any preceding claim wherein the heart rates are calculated by counting the number of beats of a subject's heart over predetermined or specific periods of time.

14. The method of any preceding claim, wherein the heart rates are calculated by counting the number of beats of a subject's heart over a predetermined or specific sampling period.

15. The method of claim 14, wherein the sampling period over which a one, for example a first, heart rate is calculated is distinct from the sampling period over which another, for example a second, heart rate is calculated.

16. The method of claim 14 or 15, wherein the sampling periods over which heart rates are determined or measured overlap.

17. The method of claim 14 or 15, wherein a heart rate is determined over a sampling period which runs concurrently with at least part of the sampling period used to determine another heart rate.

18. The method of any one of claims 14-17, wherein the sampling periods comprise anywhere between about 2 and about 60 seconds (s).

19. The method of any one of claims 14-18, wherein the sampling periods each independently comprise a time period selected from the group consisting of 3s; 4s; 5s; 6s; 7s; 8s; 9s; 10s; 15s; 20s; 25s; 30s; 35s; 40s; 45s; 50s; 55s and 60s.

20. The method of any one of claims 14-19, wherein the method comprises the step of determining the first and second heart rates over two distinct sampling periods each sampling period comprising, consisting essentially, or consisting of three seconds.

21. The method of claim 20, wherein a first heart rate may be calculated as the number of heart beats/per three seconds and the second heart rate may be calculated as the number of heart beats/three seconds.

22. The method of claim 21, wherein the first heart rate is calculated over one three second sampling period and the second heart rate is calculated over a second three second period.

23. The method of claim 22, wherein the sampling periods are distinct or run at least partially concurrently with each other.

24. The method of any one of claims 14-23, wherein the sampling periods used to calculate the heart rates, are separated by a non-sampling time period.

25. The method of any one of claims 14-24, wherein the method comprises a detection cycle comprising a sampling period used to detect or measure a heart rate and a further sampling period used to detect or measure a further heart rate.

26. The method of claim 25, wherein the sampling periods are of equal or different duration.

27. The method of claim 25 or 26, wherein the sampling periods are separated by a non-sampling period, the duration of which is equal to or different from, either or both of the sampling periods.

28. The method of any one of claims 25-27, wherein the method comprises a plurality of detection cycles which run in parallel, continuously, contiguously, consecutively and/or at least partially concurrently.

29. The method of any preceding claim, wherein the method is automated.

30. The method of any preceding claim, wherein the heart rates are measured and/or determined using one or more sensors.

31. The method of claim 30, wherein the one or more sensors may be fixed to one or more body parts.

32. The method of claim 30 or 31, wherein the sensor may comprise or be part of a device adapted to measure a wearer's pulse.

33. The method of any one of claims 30, 31 or 32, wherein the sensor comprises a pulse oximeter device.

34. The method of any preceding claim, wherein upon detection of a first and second heart rate which differ, an alert may be triggered or activated.

35. A system for detecting the occurrence of a seizure, the system comprising means for determining the percentage difference between heart rate measurements of a subject, wherein if the heart rates differ, the system reports the occurrence of a seizure.

36. The system of claim 35, wherein the system comprises a sensor for determining and/or measuring heart rates.

37. The system of claims 35 or 36, wherein the system comprises one or more sensors fixed to one or more body parts.

38. The system of claim 37, wherein the sensors independently determine or measure heart rates.

39. The system of any one of claims 36 to 38, wherein the sensor or sensors comprise a device capable of measuring a wearer's pulse.

40. The system of any one of claims 36 to 39, wherein the heart rates measured or determined by each sensor are compared with heart rates measured or determined by the same sensor or by (an)other sensor(s).

41. The system of any one of claims 35 to 40, wherein the system is configured to report the occurrence of a seizure when the heart rate measurements differ by a predetermined % change or threshold.

42. The system of claim 41, wherein the system is configured to report the occurrence of a seizure when the heart rate measurements differ by at least about 15 %.

43. The system of claim 42, wherein the system is configured to monitor the status of a subject known to suffer from seizures, or subjects suspected of, or predisposed to, developing seizures.

44. The system of any one of claims 35 to 43, wherein the system is used to alert others to the occurrence or potential occurrence of a seizure in a subject.

45. The system of any one of claims 35 to 44, wherein the system comprises means to report the occurrence or potential occurrence of a seizure in a subject, to a third party.

46. The system of claim 45, wherein the system comprises at least one of an audible, visual and/or oscillating alarm.

47. The system of any one of claims 35 to 46 wherein the system comprises a remote receiver unit.

48. The system of any one of claims 35 to 47, wherein the system comprises means to transmit or deliver data and/or an alarm signal to a remote third party.

49. The system of claim 48, wherein the system is configured to transmit data and/or an alarm signal to a remote receiver upon detection of heart rate measurements which differ.

50. The system of claims 48 or 49, wherein the system is configured to transmit a data signal and/or an alarm signal through wires and/or wirelessly to a remote receiver.

51. The system of claim 50, wherein data signal and/or an alarm signal is transmitted wirelessly using radio transmission technology.

52. The system of claim 51, wherein the signal is transmitted wirelessly using Bluetooth technology.

53. The system of any one of claims 47 to 52, wherein the remote receiver unit comprises a computer and/or a mobile device.

54. The system of claim 53, wherein the remote receiver unit comprises one of a laptop computer, a tablet computer, a phone or a smartphone.

55. The system of claims 53 or 54, wherein the computer and/or mobile device comprises a program or application configured to react to the receipt of data and/or an alarm signal generated or emitted by the system.

56. The system of claim 55, wherein the program or application is configured to generate an audible, visual and/or oscillation (vibrate) type alarm signal upon receipt of data and/or an alarm signal.

57. The system of any one of claims 35 to 56, wherein the system is a wearable system.

58. The system of claim 57, wherein the system is formed and/or adapted to be worn on a body part, such as a wrist or ankle.

59. The system of any one of claims 35 to 58, wherein the system is adapted to detect and calculate a wearer's heart rate and any percentage difference between two or more heart rate measurements.

60. A device for detecting the occurrence of a seizure, the device comprising a system according to any one of claims 35 to 59.

61. The device of claim 60, wherein the device is worn on, against or around a body part, such as a wrist or ankle.

62. The device of claims 60 or 61, wherein the device comprises means for measuring or determining and/or recording and/or storing a wearer's heart rate.

63. The device of any one of claims 60 to 62, wherein the device comprises a display for displaying or presenting information.

64. The device of any one of claims 60 to 63, wherein the device comprises a sensor formed and adapted to detect and/or measure a heart rate.

65. The device of claim 64, wherein the device comprises one or more sensors.

66. The device of any one of claims 60 to 65, wherein the device comprises means for transmitting a signal, for example a wireless signal, to a remote device.

67. The device of any one of claims 60 to 66, wherein the device comprises an audible, visual and/or oscillation alarm which is configured to be triggered or activated upon receipt of an appropriate signal transmitted or emitted by the device.

68. The method of any one of claims 1 to 34, system of any one of claims 35 to 59 or device of any one of claims 60 to 67, wherein the method, system or device is adapted to (separately) report the detection of one or more predetermined or specific heart rates.

69. The method of any one of claims 1 to 34 or 68, system of any one of claims 35 to 59 or 68 or device of any one of claims 60 to 68, wherein the method, system or device comprises additional steps and/or means for determining the percentage difference between heart rate measurements of a subject and a subject's oxygen saturation levels, wherein a difference between the heart rate measurements of a subject and/or a reduction in oxygen saturation below a predetermined base value, indicates that a seizure is about to occur or is occurring.

70. The method of any one of claims 1 to 34, 68 or 69, system of any one of claims 35 to 59, 68 or 69 or device of any one of claims 60 to 69, wherein the method, system or device

comprises additional steps and/or means for providing an indication of the levels of oxygen saturation in a subject to be tested.

71. The method of any one of claims 1 to 34, or 68 to 70, system of any one of claims 35 to 59, or 68 to 70 or device of any one of claims 60 to 70, wherein the method, system or device comprises additional steps and/or means for reporting the occurrence of first and second heart rates which differ by at least 15% separately or together with the occurrence of between about 90%-80% oxygen saturation and/or about 70%-35 % oxygen saturation.

72. The method of any one of claims 1 to 34, or 68 to 71, system of any one of claims 35 to 59, or 68 to 70 or device of any one of claims 60 to 71, wherein the method, system or device is configured to report when a condition of the following form is satisfied

$$\frac{|HRT|}{\text{SAT}} \geq y$$

where HRT is the percentage heart rate change between first and second heart rates, and |HRT| denotes the absolute value of the percentage heart rate change; SAT is the oxygen saturation level as a percentage; and y is a combined threshold.

73. The method of any one of claims 1 to 34, or 68 to 72, system of any one of claims 35 to 59, or 68 to 72 or device of any one of claims 60 to 72, wherein the method, system or device is configured to report when a condition of the following form is satisfied

$$|\text{HRT}| \times (101 - \text{SAT}) \geq y$$

where HRT is the percentage heart rate change between first and second heart rates, and |HRT| denotes the absolute value of the percentage heart rate change; SAT is the oxygen saturation level as a percentage; and y is a combined threshold.

74. The method of any one of claims 1 to 34, or 68 to 73, system of any one of claims 35 to 59, or 68 to 73 or device of any one of claims 60 to 73, wherein the method, system or device is configured to report when a condition of the following form is satisfied

$$|\text{HRT}| \times (101 - \text{SAT}) \geq y \vee \text{SAT} \leq z$$

where HRT is the percentage heart rate change between first and second heart rates, and |HRT| denotes the absolute value of the percentage heart rate change; SAT is the oxygen saturation level as a percentage; y is a combined threshold; $\vee$ is the logical "or" operator, and z is an oxygen saturation threshold.

75. The method of any one of claims 1 to 34, or 68 to 74, system of any one of claims 35 to 59, or 68 to 74 or device of any one of claims 60 to 74, wherein the method, system or device is configured to report when a condition of the following form is satisfied

$$a|\text{HRT}| + b\text{SAT} + c|\text{HRT}|\text{SAT} \geq y$$

where *a*, *b*, and *c* are coefficients; HRT is the percentage heart rate change between first and second heart rates, and |HRT| denotes the absolute value of the percentage heart rate change; SAT is the oxygen saturation level as a percentage; and *y* is a combined threshold.

76. The method of any one of claims 1 to 34, or 68 to 75, system of any one of claims 35 to 59, or 68 to 75 or device of any one of claims 60 to 75, wherein the method, system or device is supplemented with additional steps, processes or means (for example sensors) which assess, determine and/or measure one or more of a subject's temperature, sweat production (impedance), movement, myoelectric (muscle) activity, cardiac activity, respiration rate and/or electrical/brain activity.

77. The method of any one of claims 1 to 34, or 68 to 76, system of any one of claims 35 to 59, or 68 to 76 or device of any one of claims 60 to 76, wherein the method, system or device is configured to respond to physiological parameters (for example heart rates and/or oxygen saturation levels) which are tailored or "personalised" to an individual.

78. The method of any one of claims 1 to 34, or 68 to 77, system of any one of claims 35 to 59, or 68 to 77 or device of any one of claims 60 to 77, wherein the method, system or device is supplemented with one or more additional measures to modify, improve or alter seizure detection capability.

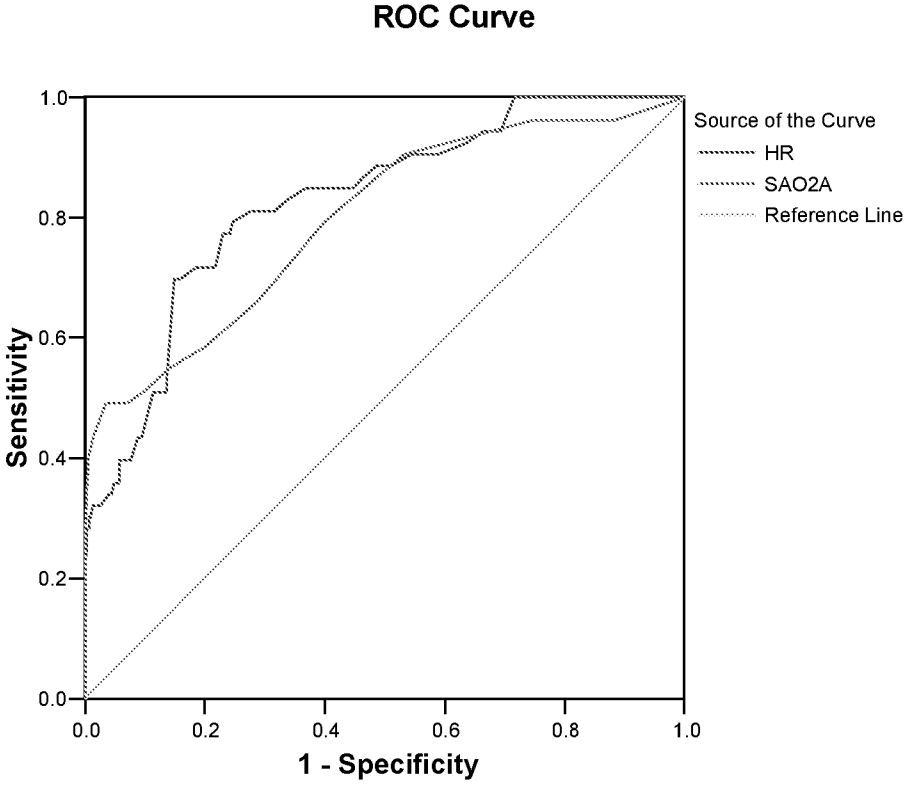

Figure 1

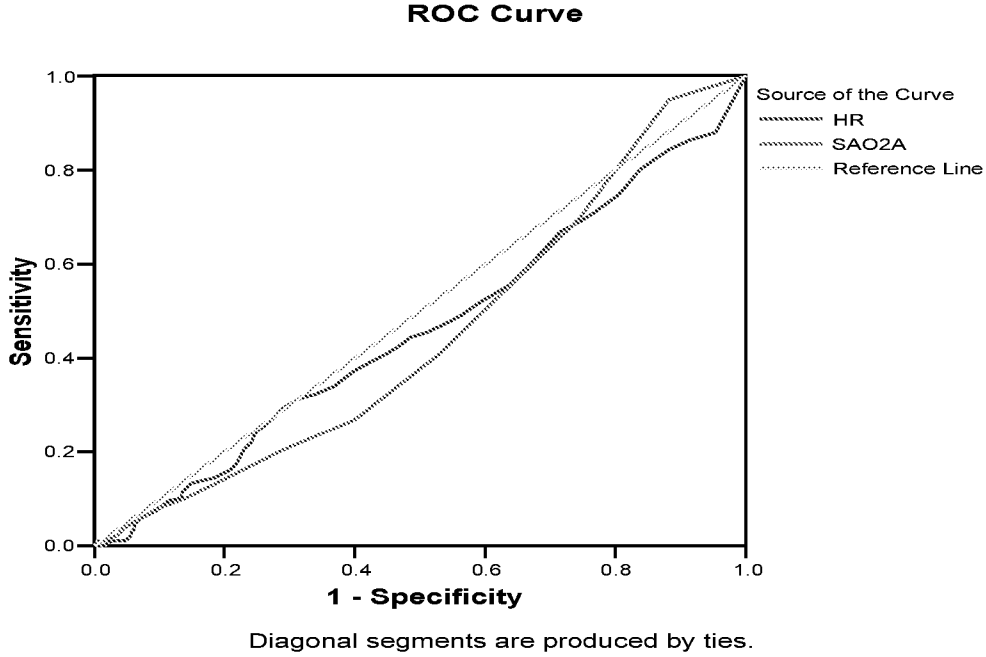

Figure 2

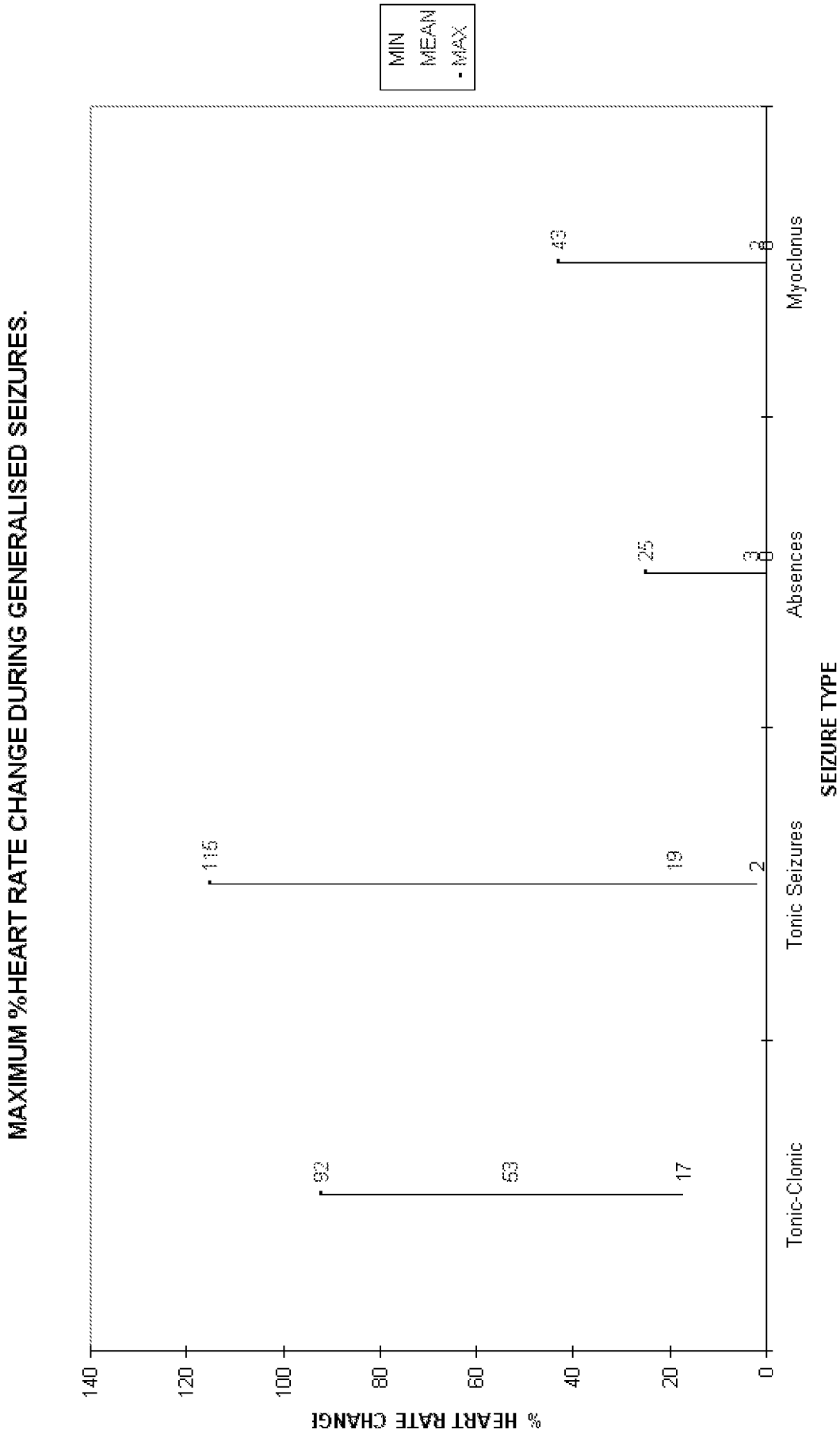
MAXIMUM %HEART RATE CHANGE DURING GENERALISED SEIZURES.
MIN
MEAN
MAX
% HEART RATE CHANGE
0
20
40
60
80
100
120
140
92
53
17
115
19
2
25
3
8
43
8
Tonic-Clonic
Tonic Seizures
Absences
Myoclonus
SEIZURE TYPE

Figure 3

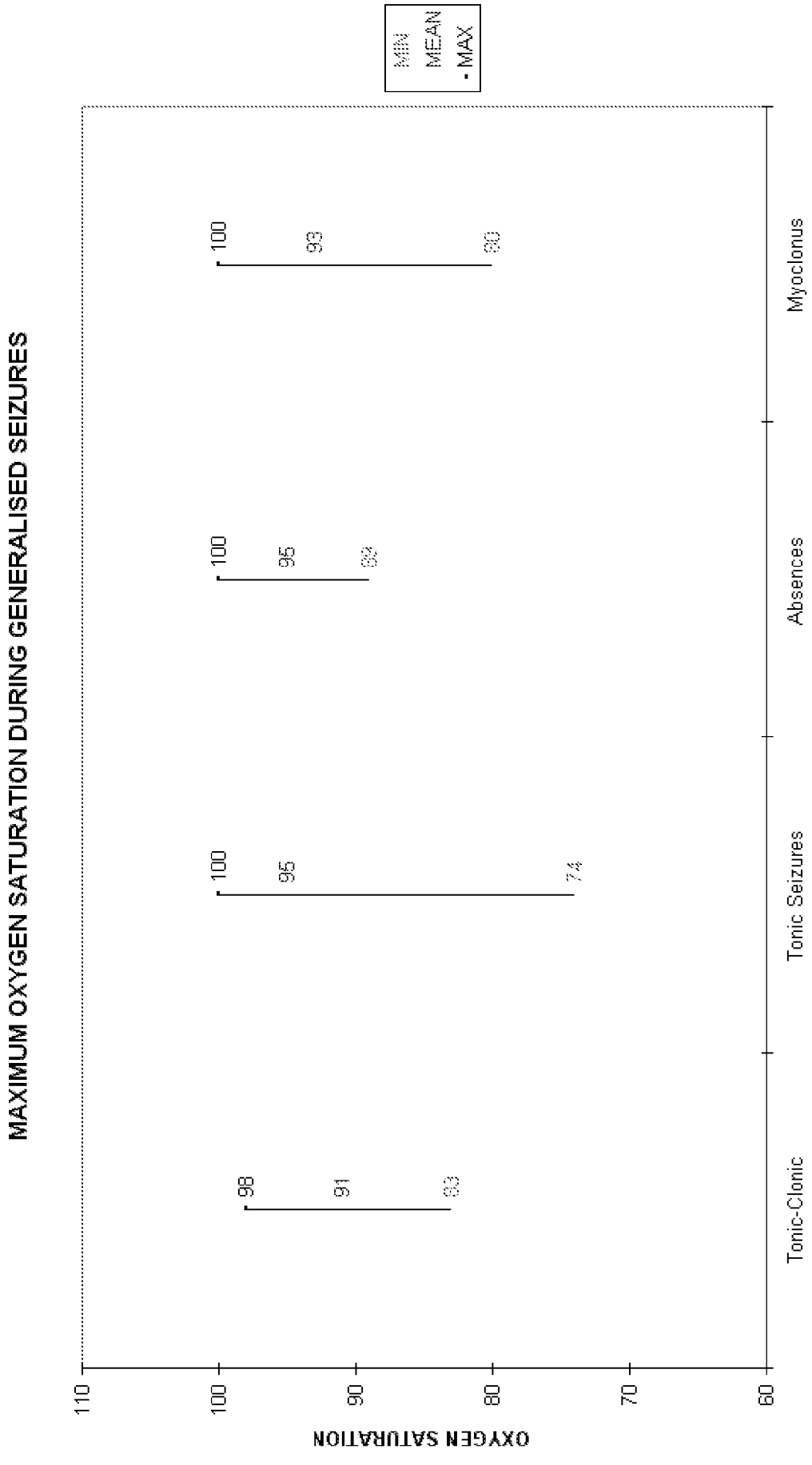
MAXIMUM OXYGEN SATURATION DURING GENERALISED SEIZURES
MIN
MEAN
MAX
OXYGEN SATURATION
110
100
90
80
70
60
98
91
83
100
95
74
100
95
82
100
93
80
Tonic-Clonic
Tonic Seizures
Absences
Myoclonus
SEIZURE TYPE

Figure 4

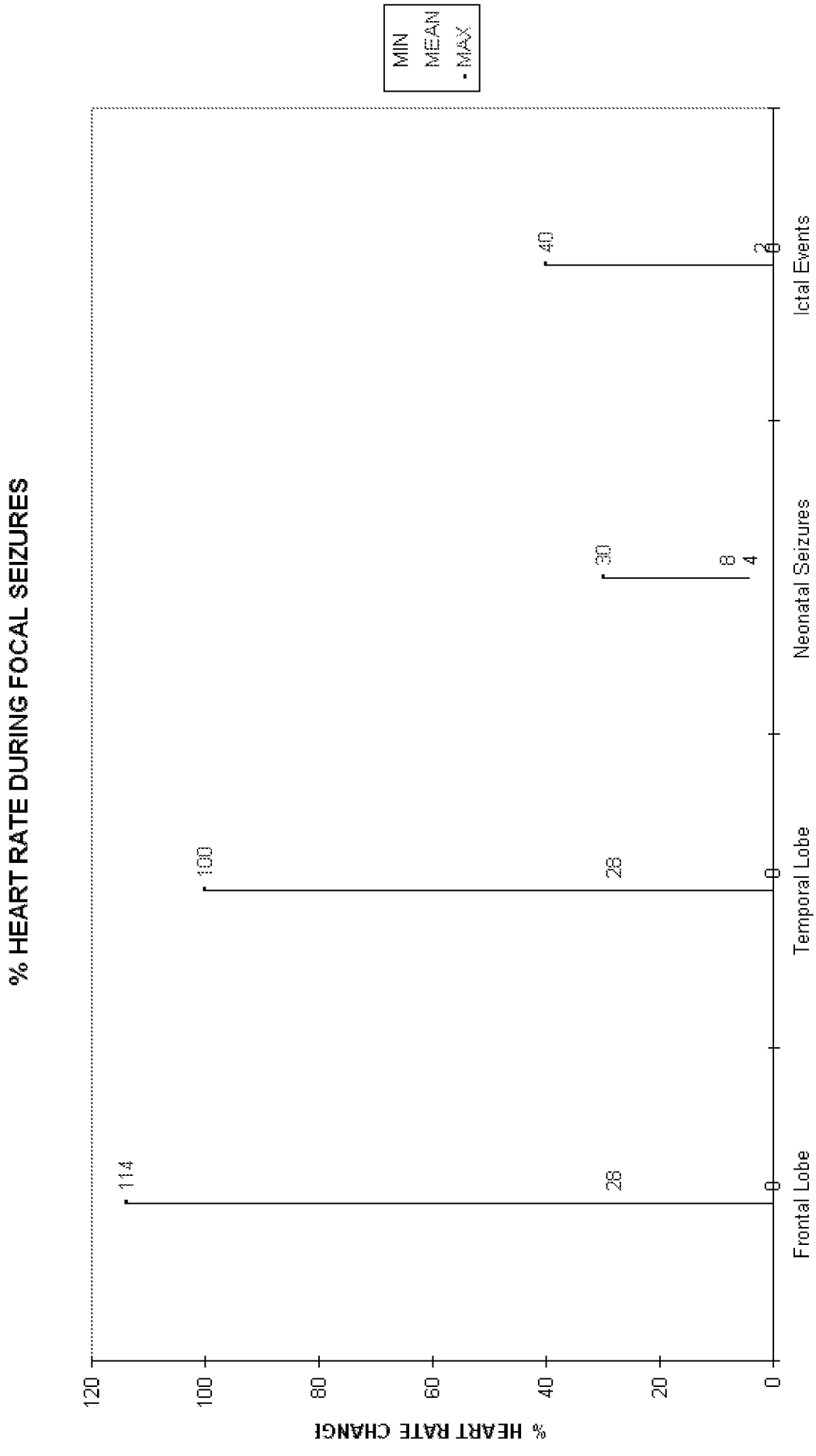
% HEART RATE DURING FOCAL SEIZURES
MIN
MEAN
MAX
% HEART RATE CHANGE
120
100
80
60
40
20
0
114
28
0
100
28
0
30
8
4
40
2
0
Frontal Lobe
Temporal Lobe
Neonatal Seizures
Ictal Events
SEIZURE TYPE

Figure 5

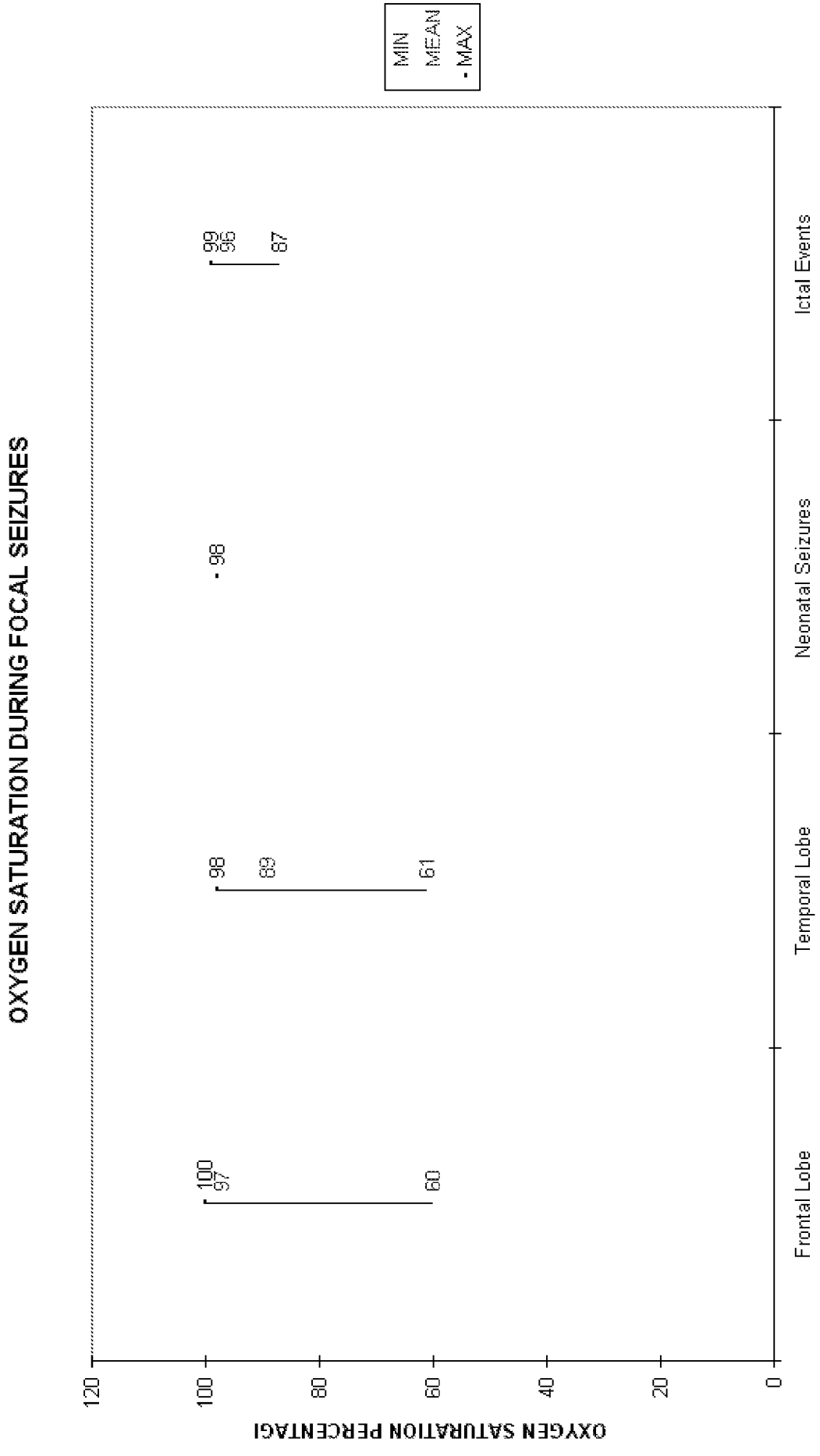
OXYGEN SATURATION DURING FOCAL SEIZURES
MIN
MEAN
- MAX
OXYGEN SATURATION PERCENTAGI
120
100
80
60
40
20
0
100
97
60
98
89
61
- 98
99
96
87
Frontal Lobe
Temporal Lobe
Neonatal Seizures
Ictal Events
SEIZURE TYPE

Figure 6

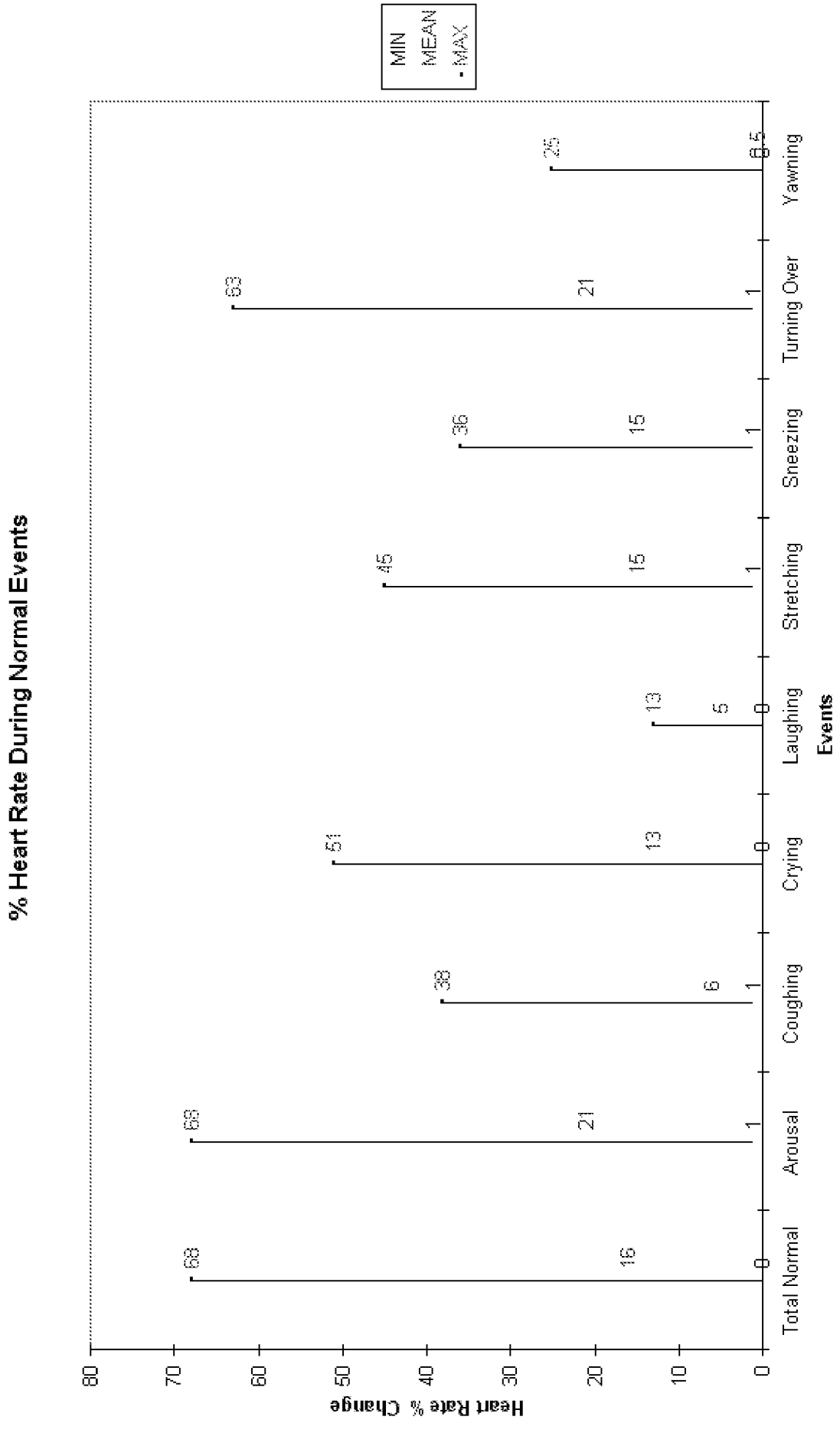
% Heart Rate During Normal Events
MIN
MEAN
MAX
Heart Rate % Change
0
10
20
30
40
50
60
70
80
Total Normal
Arousal
Coughing
Crying
Laughing
Stretching
Sneezing
Turning Over
Yawning
Events
68
16
0
68
21
1
38
6
1
51
13
0
13
5
0
45
15
1
36
15
1
63
21
1
25
8.5

Figure 7

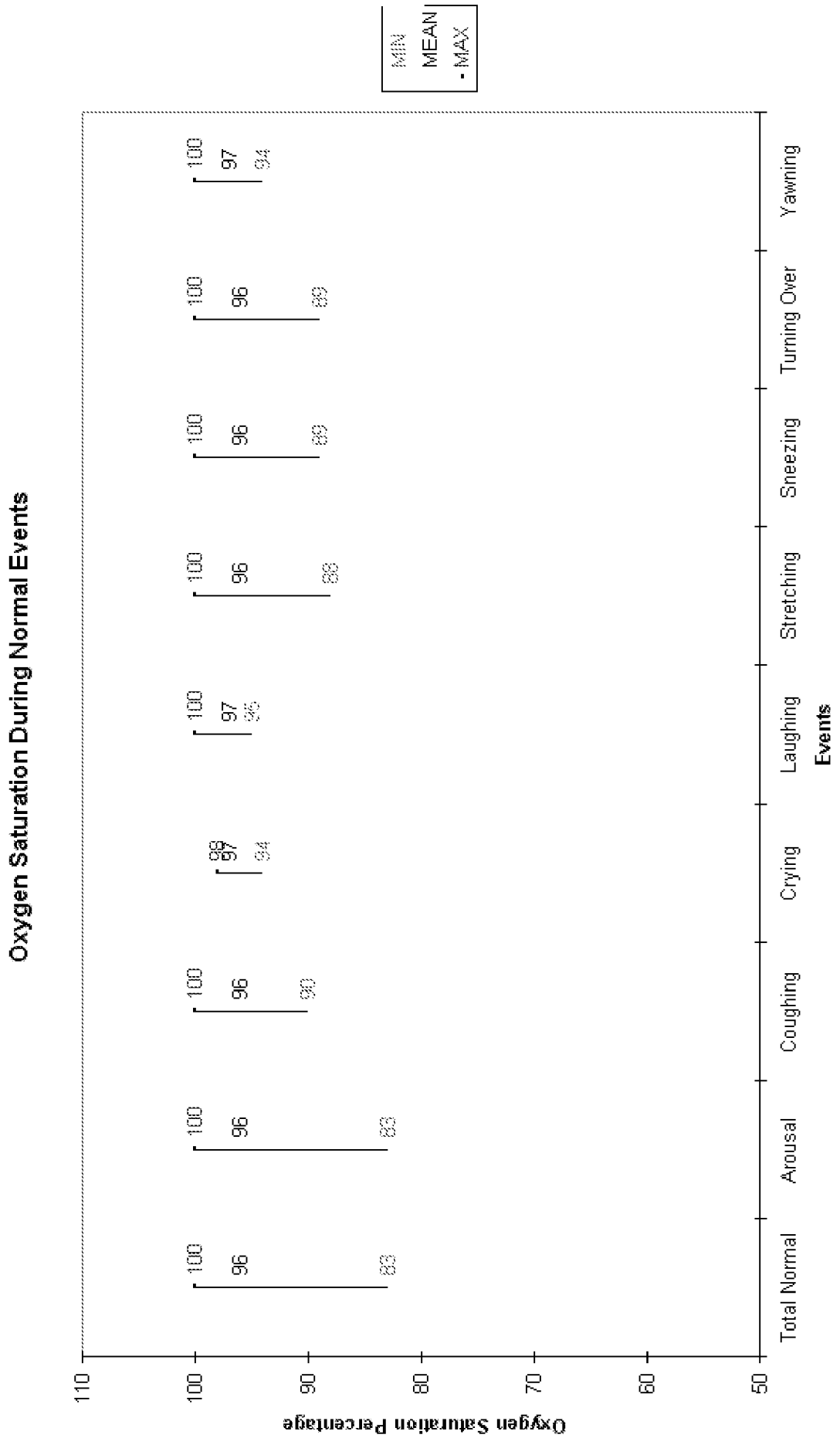
Oxygen Saturation During Normal Events
MIN
MEAN
MAX
Oxygen Saturation Percentage
110
100
90
80
70
60
50
Total Normal
Arousal
Coughing
Crying
Laughing
Stretching
Sneezing
Turning Over
Yawning
Events
100
96
83
100
96
83
100
96
90
100
97
94
100
97
95
100
96
88
100
96
89
100
96
89
100
97
94

Figure 8

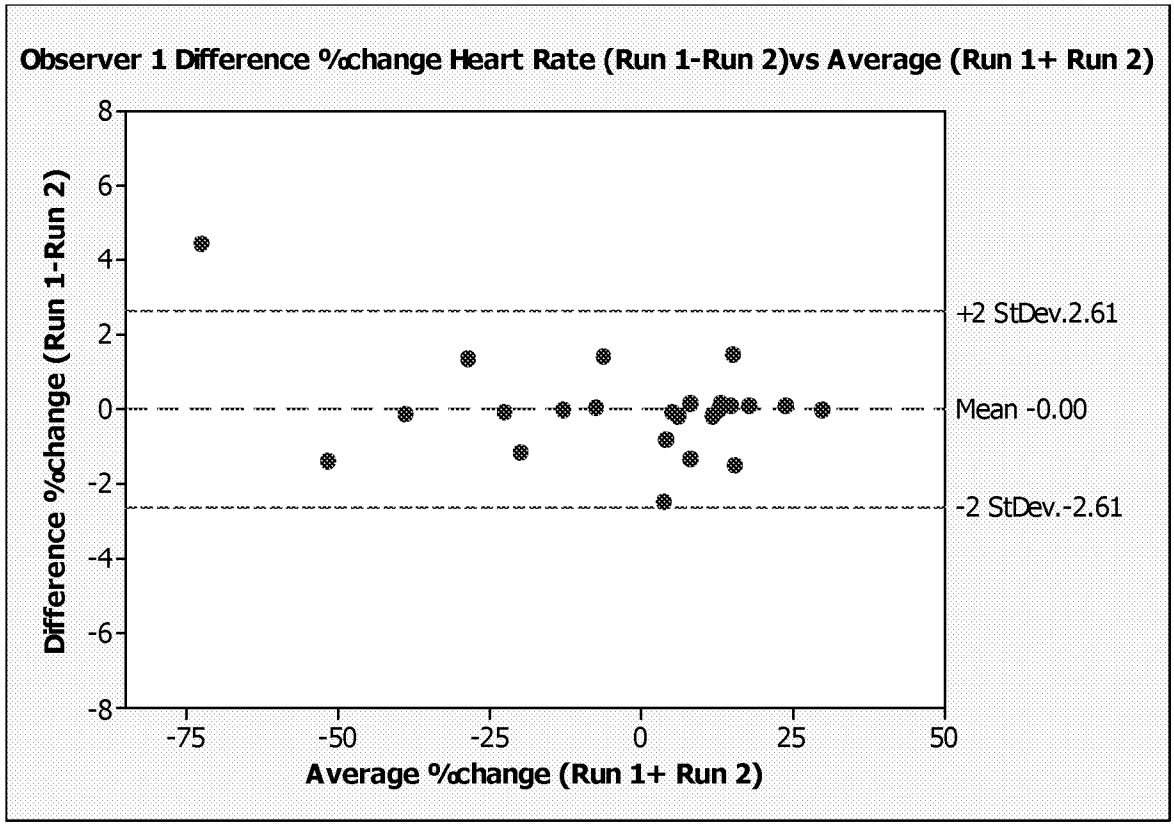

Figure 9

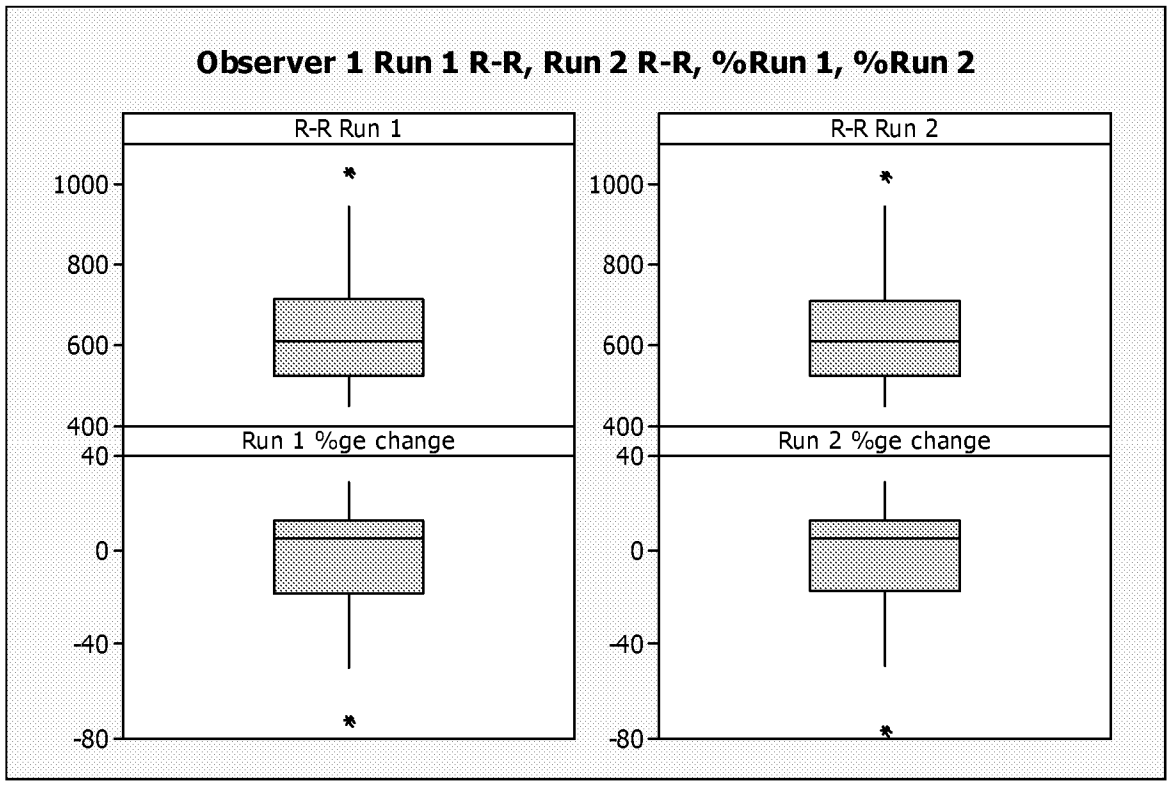

Figure 10

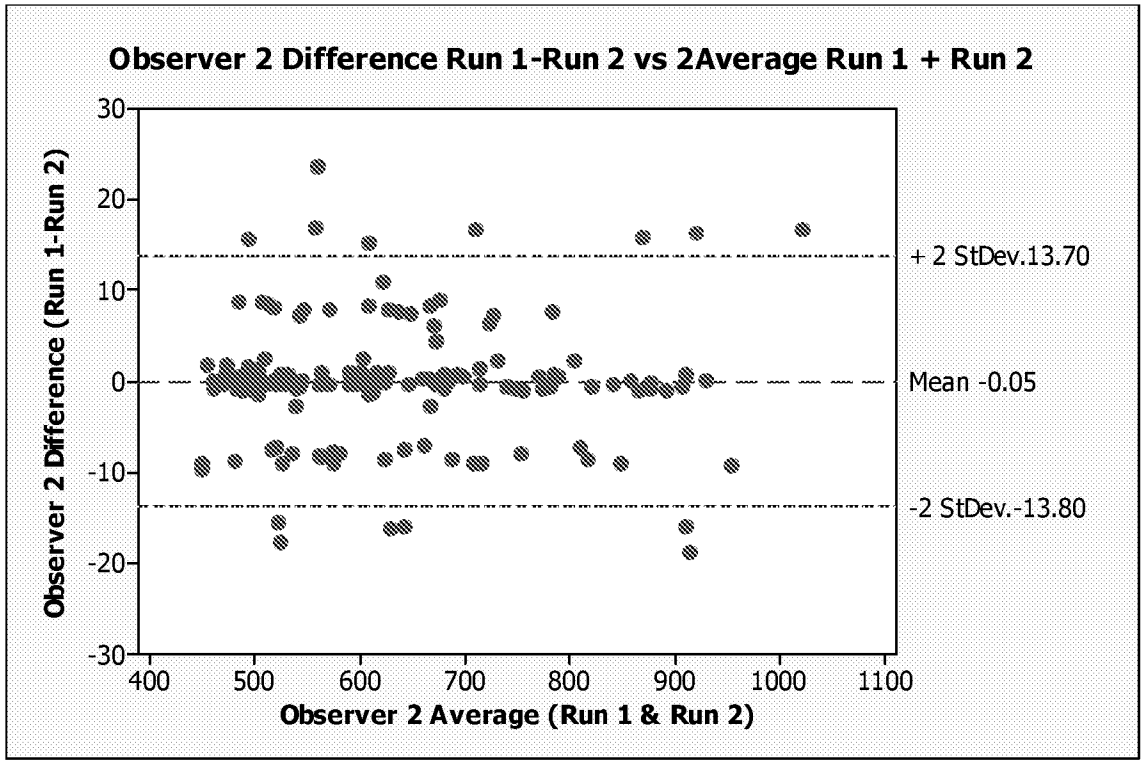

Figure 11

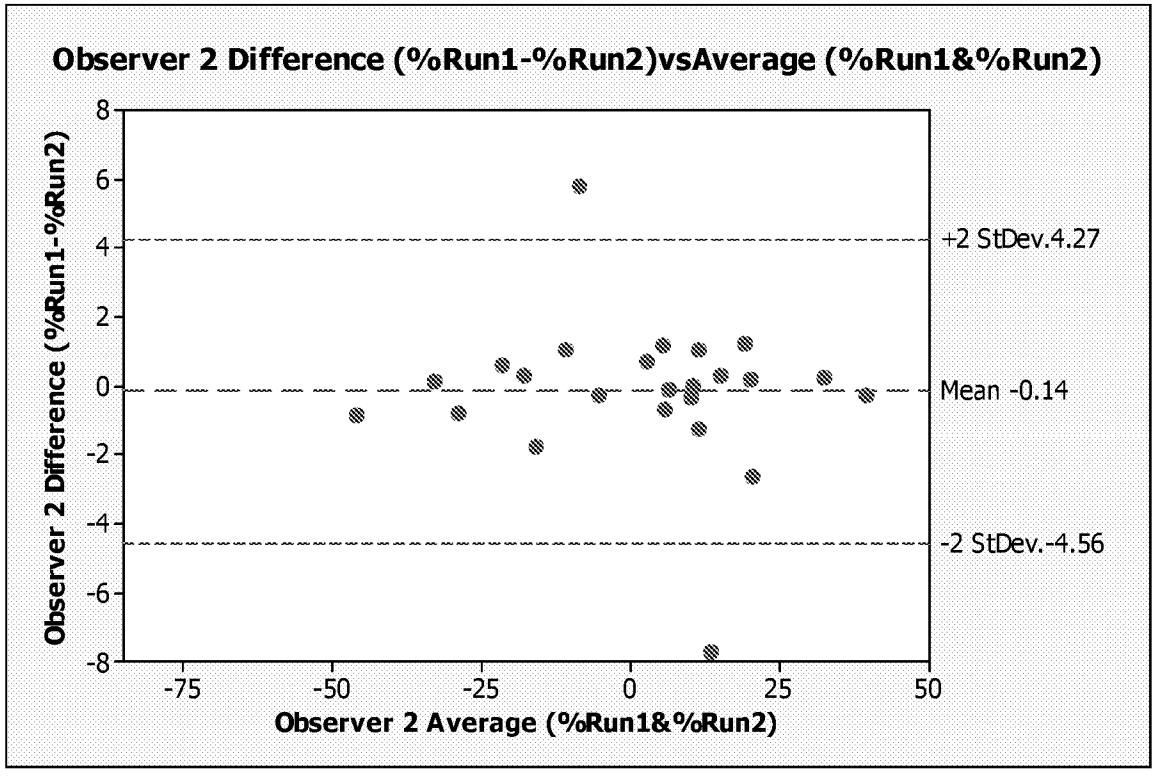

Figure 12

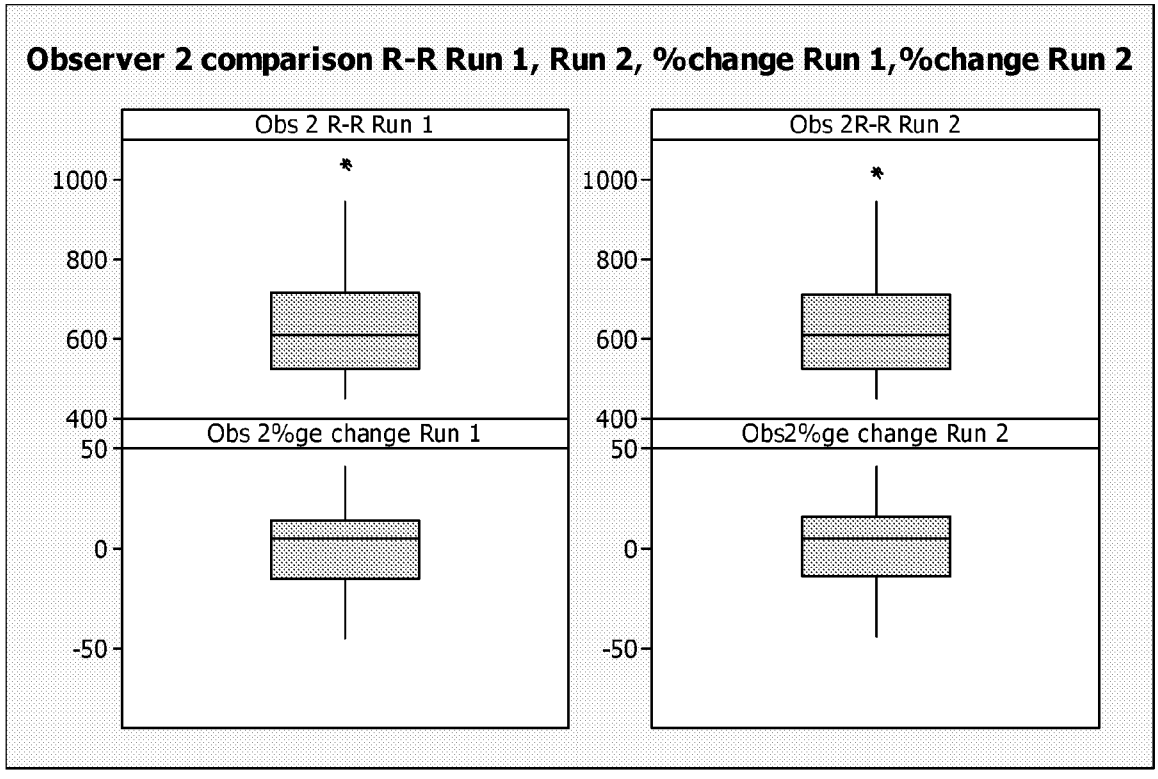

Figure 13

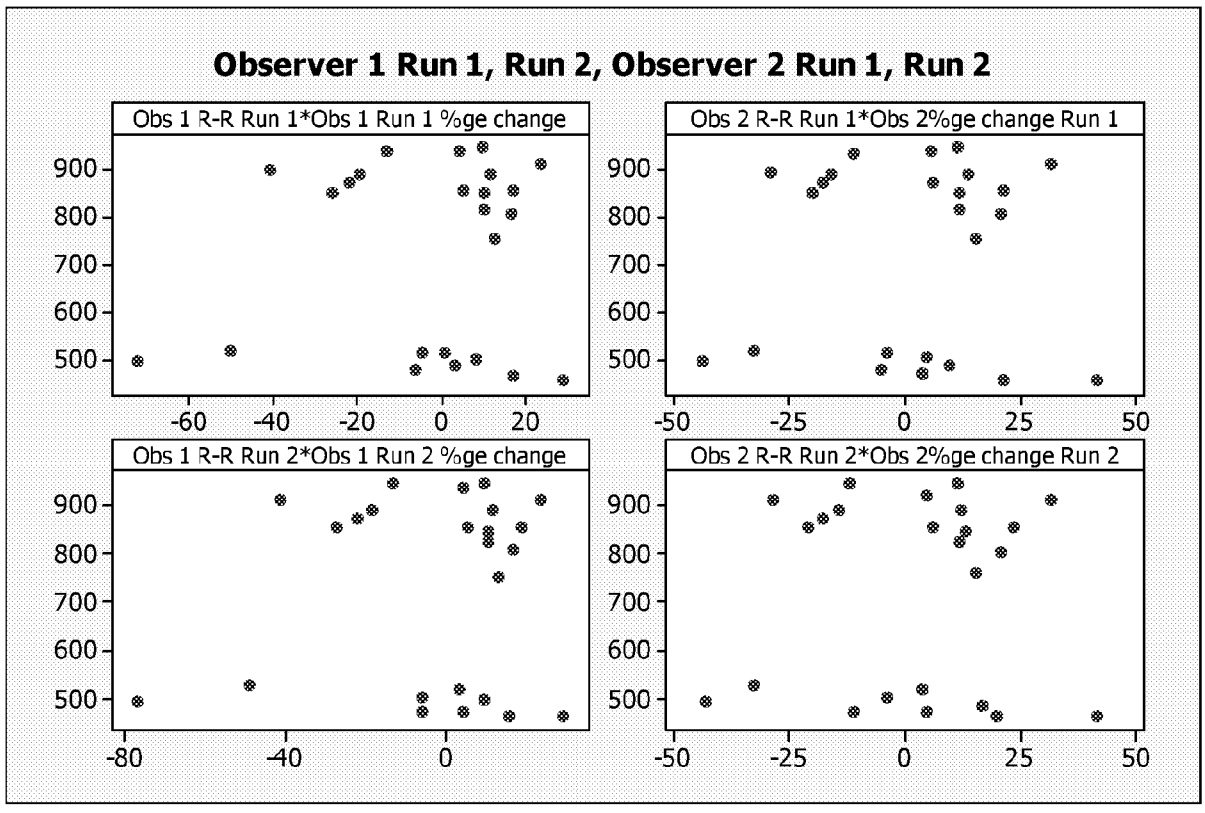

Figure 14

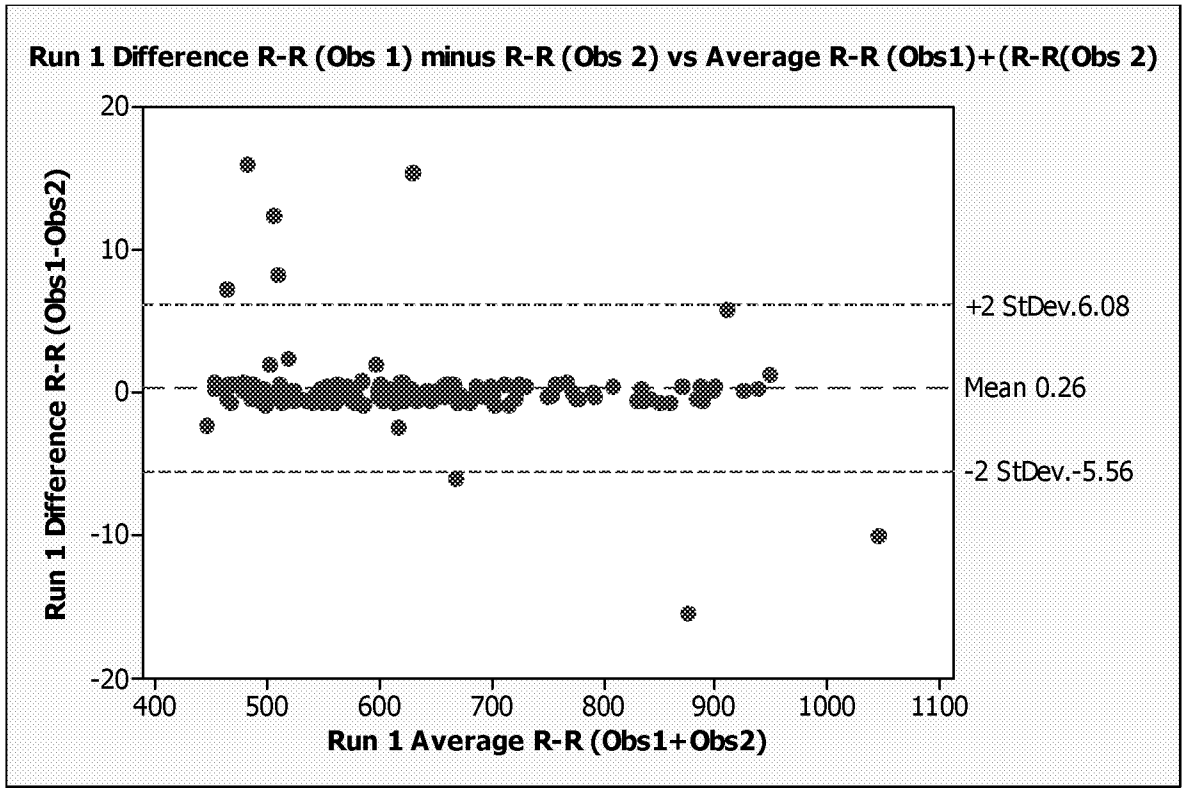

Figure 15

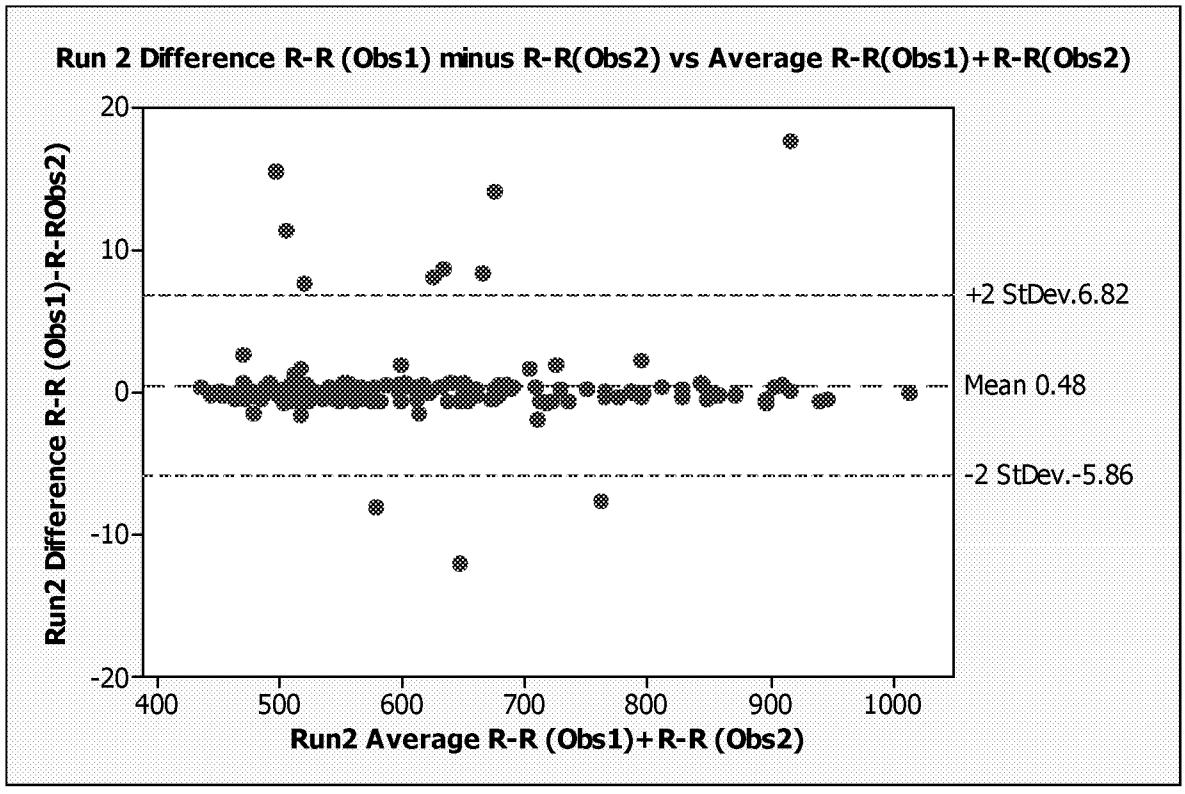

Figure 16

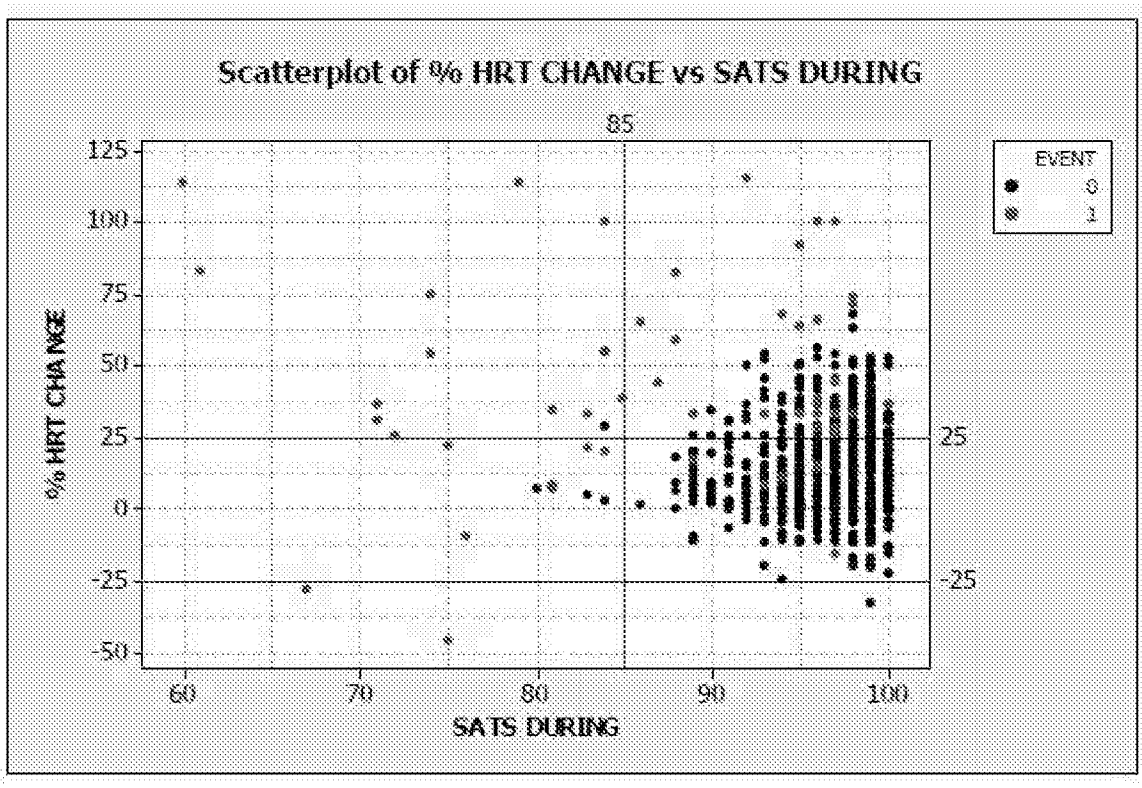

Figure 17

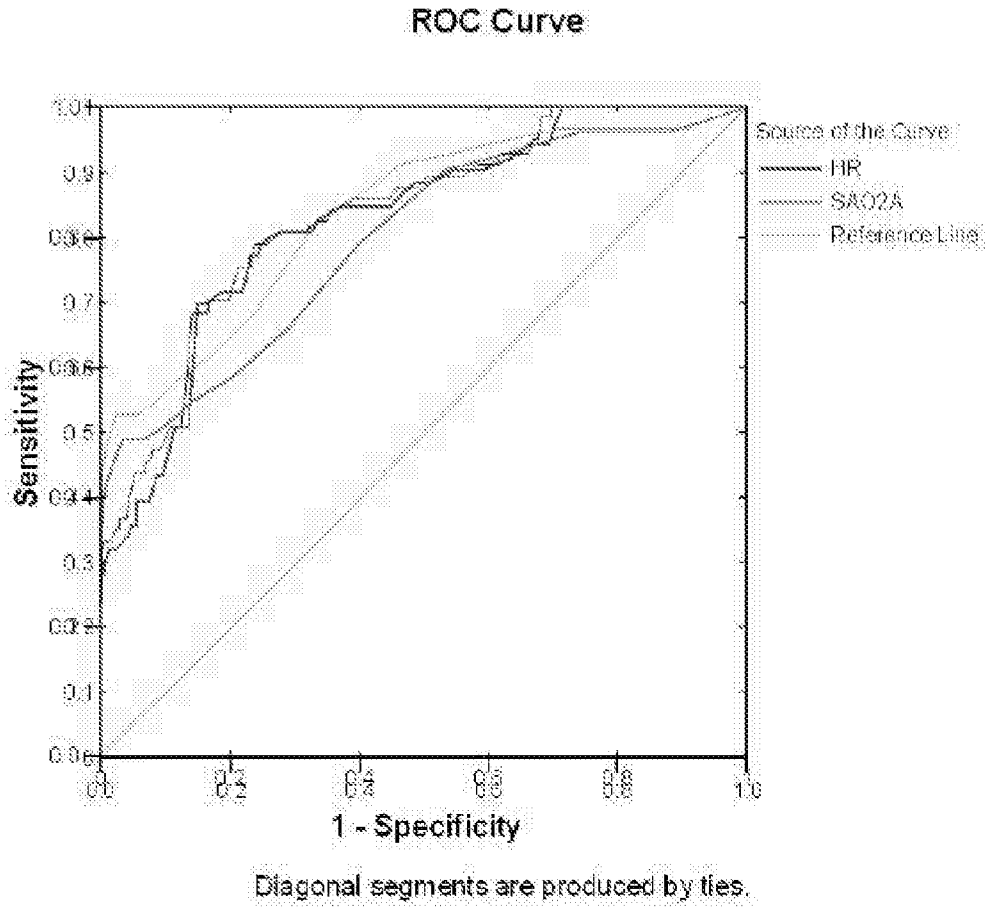

Figure 18

True positive	False positive
43	188
False negative	True negative
14	780
Sensitivity	Specificity
0.807	0.792

Figure 19a

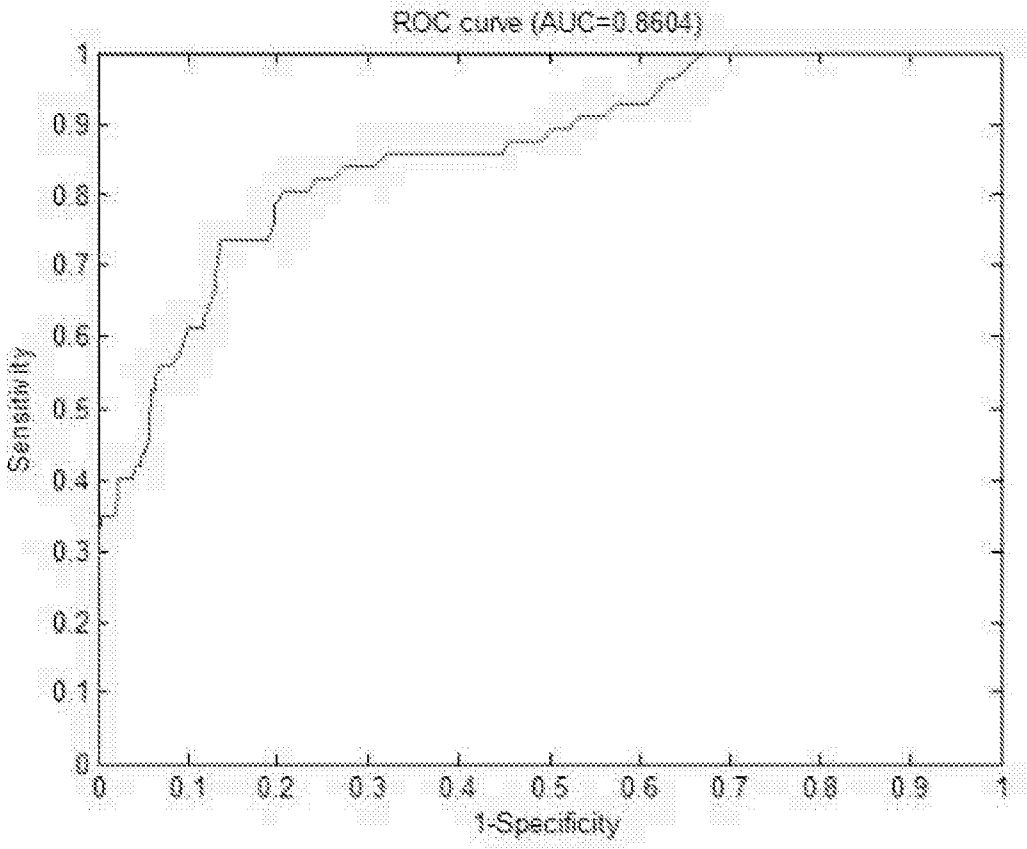

Figure 19b

True positive	False positive
48	108
False negative	True negative
9	860
Sensitivity	Specificity
0.842	0.888

Figure 20a

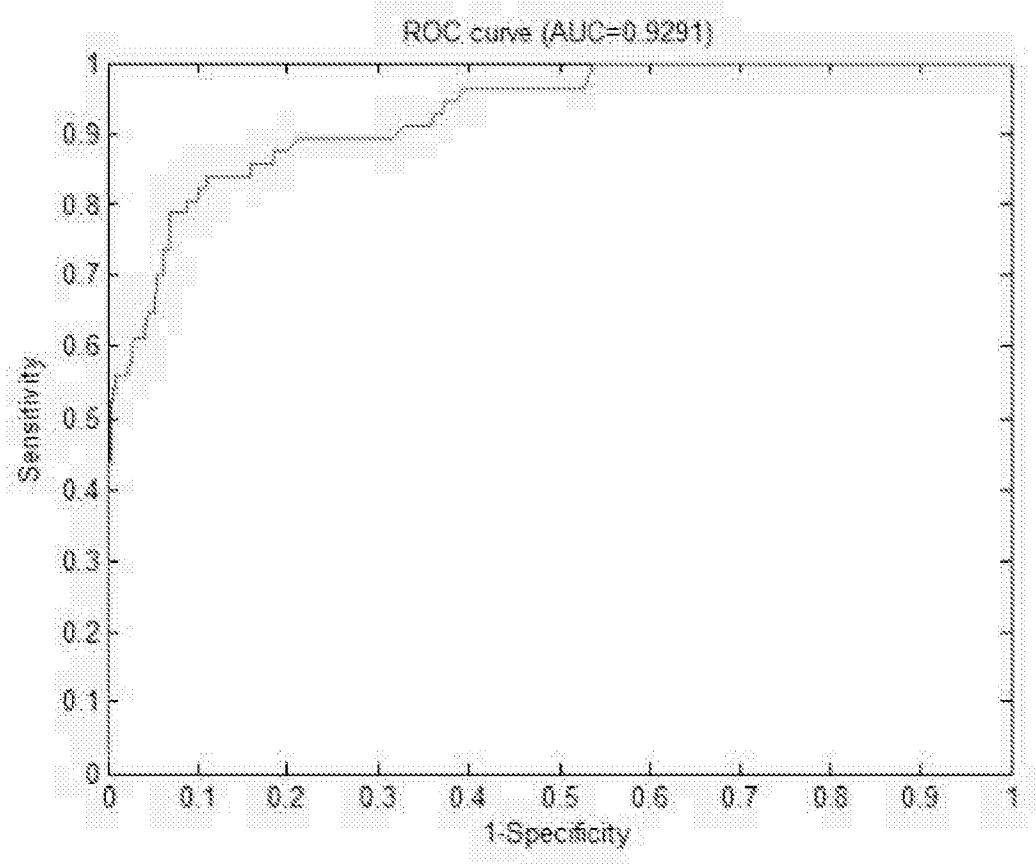

Figure 20b

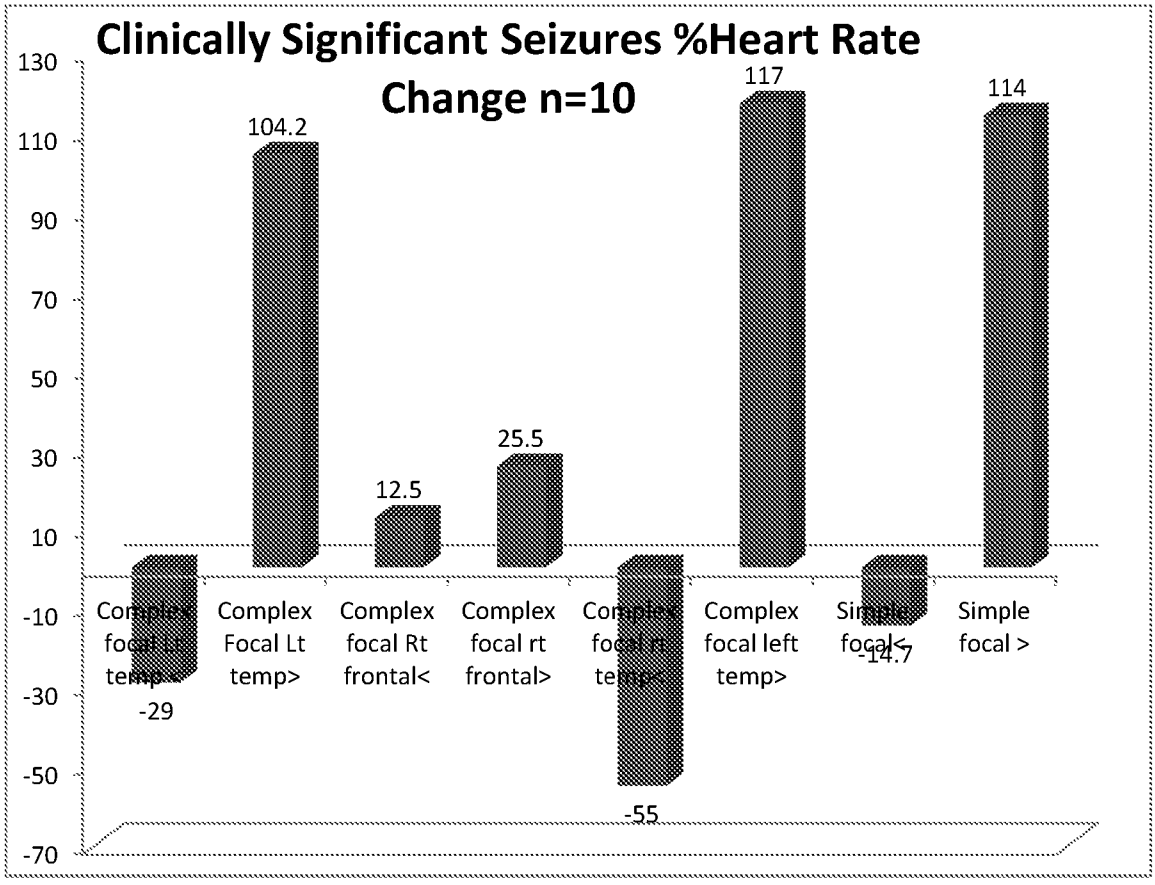

Figure 21

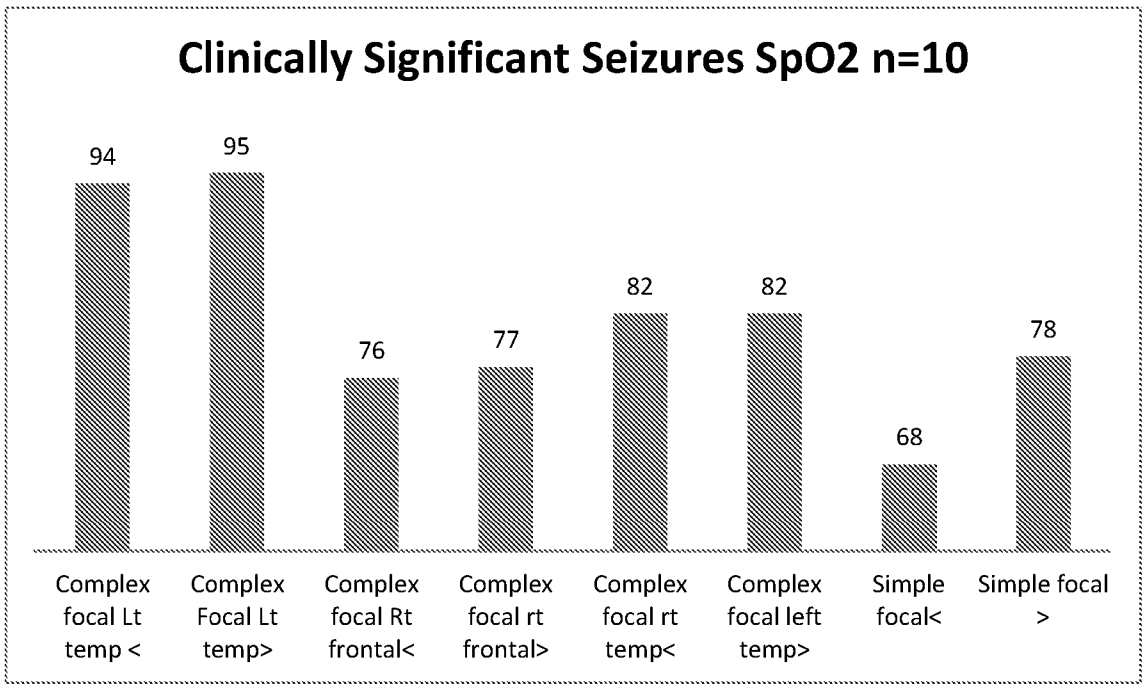

Figure 22

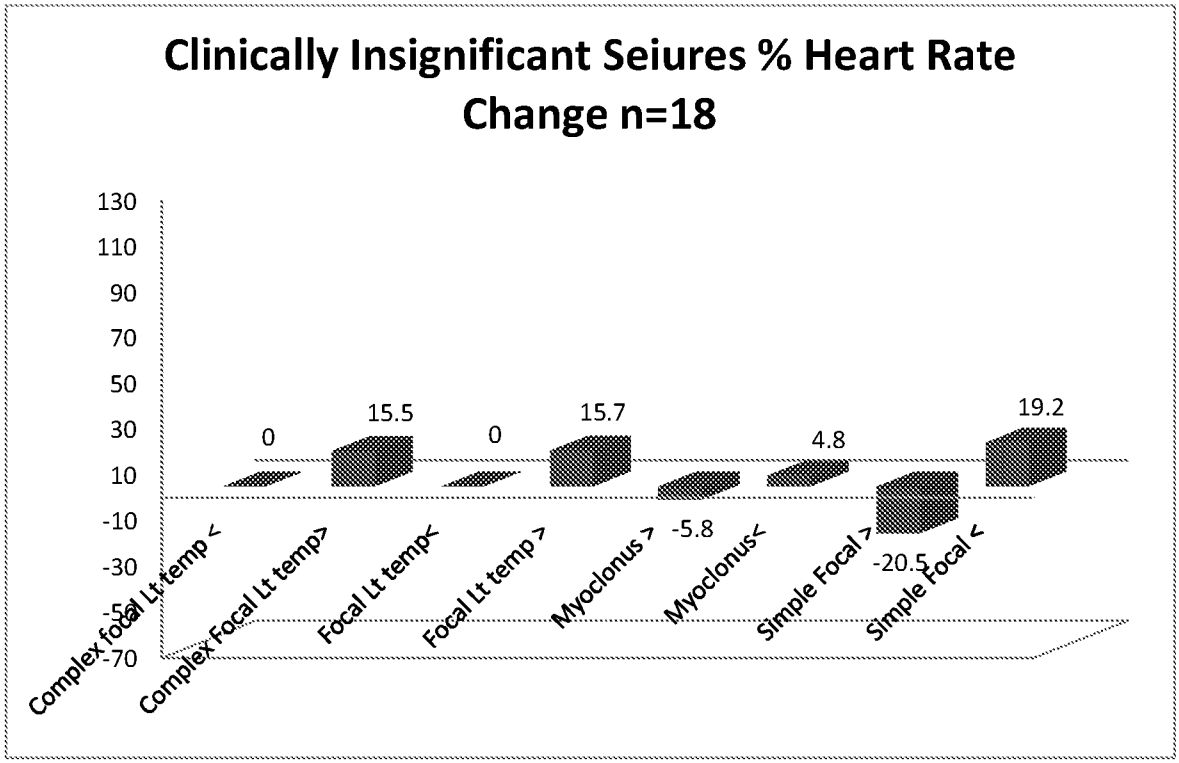

Figure 23

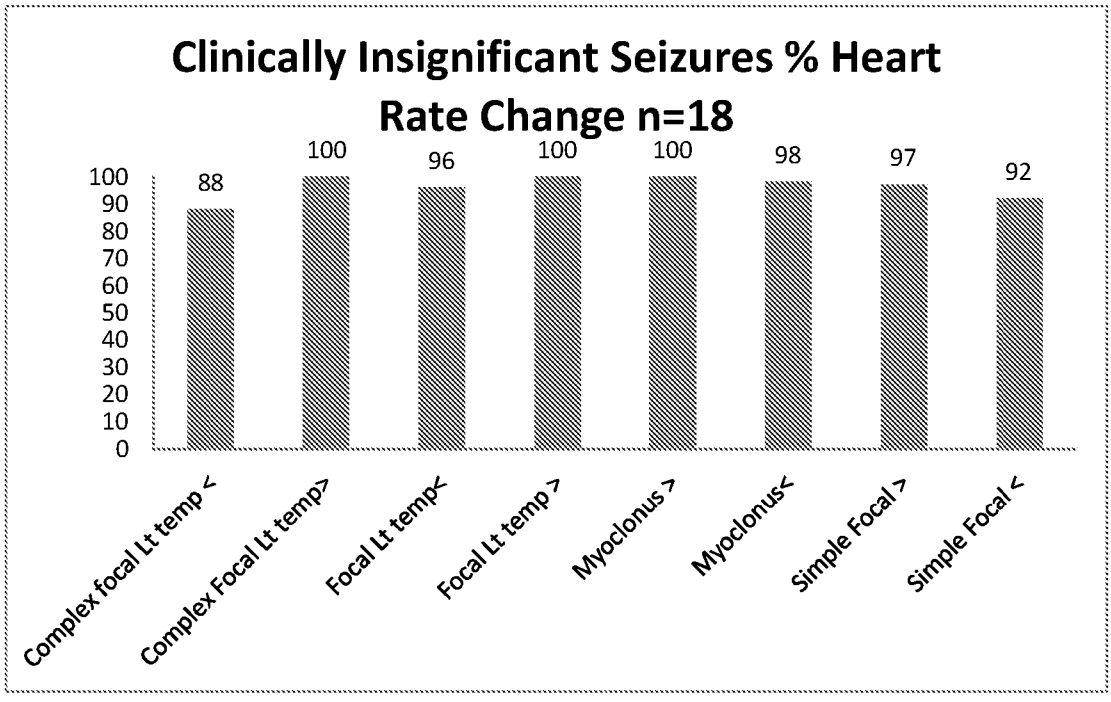

Figure 24

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2015/051783

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61B5/00 A61B5/0205 A61B5/1455
ADD. A61B5/08 A61B5/053 A61B5/0476 A61B5/0488 A61B5/11

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

B. FIELDS SEARCHED

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

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2012/310050 A1 (OSORIO IVAN [US]) 6 December 2012 (2012-12-06) paragraphs [0009], [0016], [0045], [0047], [0062], [0081], [0105], [0112], [0141], [0142] -----	35-41, 43-56, 62-78
X	WO 2011/149565 A1 (RES TRIANGLE INST INTERNAT [US]; PITRUZZELLO ANN [US]; KRONER BARBARA) 1 December 2011 (2011-12-01) page 12, lines 16, 28 page 16, line 27 page 17, lines 2, 10, 11 page 20, line 20 page 22, lines 16, 24 page 28, line 28 figures 1, 3 -----	35-41, 43-78

-/--

[X] Further documents are listed in the continuation of Box C.

[X] 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
24 August 2015	31/08/2015

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	Meyer, Wolfgang

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.
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INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2015/051783

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2011/137235 A1 (CYBERONICS INC [US]; OSORIO IVAN [US]; FREI MARK [US]) 3 November 2011 (2011-11-03) the whole document	35-78
A	WO 2007/142523 A1 (HOBO HEEZE B V [NL]; ARENDS JOHANNES BERNARDUS ALBE [NL]; GRIEP PAULUS) 13 December 2007 (2007-12-13) the whole document	35-78
A	US 2012/271181 A1 (LIAO WANGCAI [US]) 25 October 2012 (2012-10-25) the whole document	35-78

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB2015/051783

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.: 1-34(completely); 68-78(partially)
because they relate to subject matter not required to be searched by this Authority, namely:

Claims do not comply with Rule 39.1 PCT

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.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/GB2015/051783

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