A PORTABLE PULSEOXYMETER FOR A DIRECT AND IMMEDIATE AUTOMATED EVALUATION OF THE CARDIAC RHYTHM (REGULARITY) AND RELATED METHOD

Recording of the pulseoximetric waveform at the finger

Estimation of the time-occurrence of each beat, by adaptive thresholding and parabolic interpolation

Beat validation: evaluation of the ascendant and descendent tracts of any detected beat

Construction of the beat-to-beat interval series

Estimation of quantitative indexes:
- Coefficient of variation of dPP intervals
- Shannon entropy of PP intervals

Classification of the heart rhythm by the estimation of the Mahalanobis distance from population with sinus rhythm and with AF.

FIG. 1

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A PORTABLE PULSEOXIMETER FOR A DIRECT AND IMMEDIATE AUTOMATED EVALUATION OF THE CARDIAC RHYTHM (REGULARITY) AND RELATED METHOD

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The present invention relates to the field of patient monitoring. More particularly the invention relates to a system that performs short term acquisition of the plethysmographic waveform of a patient from a portable blood oxygenation level monitoring device and establishes whether the patient has an episode of Atrial Fibrillation (AF) or has a Normal Sinus Rhythm (NSR) or any other not-specific rhythm irregularity. Such classification is implemented directly in the device, suitable for at home use, and the result of the classification is displayed automatically using a three-state, traffic-light indicator.

BACKGROUND OF THE INVENTION

Atrial Fibrillation epidemiology

Atrial fibrillation is the most common sustained cardiac arrhythmia and affects more than 2 million individuals in the USA. Prevalence is expected to rise substantially over the next few decades because of the ageing population, improved cardiovascular treatments, and lengthened survival of individuals with heart disease. This condition is associated with strikingly increased morbidity and mortality. The most life-threatening consequences of atrial fibrillation are tromboembolic events and heart failure.

Importance of AF diagnosis

Early identification of individuals who are at
risk in the community would allow prevention and targeted intervention, and could decrease health-care costs. Also, once diagnosed, the arrhythmia can recur even under drug therapy, and the detection of arrhythmia recurrences can help in optimizing therapy. The results from AFFIRM study demonstrated a higher incidence of stroke (57%) in the "rhythm control" group after anticoagulation discontinuation despite the detection of sinus rhythm in an ambulatory ECG [1]. This result underlines how critical is the choice of a therapy for paroxysmal AF and how difficult the choice becomes when the feedback about the patient status is based on symptoms and/or sporadic ECG.

Methods for Atrial fibrillation diagnosis

Many patients with AF are identified once they are symptomatic or, fortuitously, when they go to the clinician for an unrelated complaint, and, in the course of the office visit, they have their ECG recorded.

Common methods of atrial arrhythmia monitoring include intermittent 24-hour Holter monitoring, infrequent periods of long-term monitoring (e.g., 7-day or 30-day recordings), and the transient use of event monitors when symptoms are present. However, many studies demonstrated the unreliability of AF diagnosis based on symptoms, because of many reasons including the change of symptom perception after ablation procedures and the influence of drug therapy independently of the heart rate. Indeed, AF is not always accompanied by clear symptoms and symptoms suggestive of AF may not correspond to a genuine AF
episode. Previous studies have underscored the unreliability of AF diagnosis based on symptoms in patients. Furthermore, symptom perception may change after procedures such as AF ablation. During AF episodes, symptoms may be correlated to the heart rate (HR) and its irregularity, but drug therapy may also influence symptom perception independently of the HR.

Each diagnosis method presents significant limitations for the diagnosis and quantification of atrial arrhythmias. The ability of Holter monitoring to diagnose and quantify AF is highly dependent on whether or not the day(s) selected for monitoring coincides with a cluster of AF episodes. External recorders now are capable of recording for up to 30 days and have been shown to increase the yield for arrhythmia detection compared with a single 24-hour Holter monitor. However, these external devices often are bulky and interfere with showering and other daily activities. In addition, the patch electrodes can cause skin irritation over such prolonged usage. As a result, patient compliance with such systems often is relatively low.

Daily transmission of short segments of ECG is also available (tele-ECG), but it requires the use of a few number of electrodes, together with a certain degree of patient skill and compliance. Data suggest that the vast majority of AF episodes are asymptomatic and that most symptoms attributed to AF actually are not associated with the arrhythmia. Therefore, monitoring of AF episodes based on only symptomatic events will adversely affect the reliability of
identifying patients with AF. Finally, although chronic monitoring with implantable devices has been demonstrated to have both high sensitivity and specificity, this monitoring requires an invasive implant procedure.

**Necessity of AF daily monitoring**

The intermittent nature of AT/AF episodes is diagnostically challenging and inevitably limits the usefulness of the snapshots provided by sporadic ECG monitoring. In addition, delayed information (by 7-day or 30-day Holter) about the onset of atrial fibrillation does not allow an immediate reaction with any therapy: indeed, prompt detection of the onset of AF provides an opportunity for therapy during the first 48 hours when expensive antithrombolic treatments may not be necessary because the formation of blood clots has not yet occurred in the atria. Finally, the longer patients are in AF, the more likely they are to remain in AF, making early detection desirable.

In an exhaustive review analyzing noninvasive methods of continuous cardiac monitoring to detect atrial fibrillation/flutter [2], it has been stated that increased duration of monitoring appears to be associated with increased rates of detection of AT/AF. However, the review was unable to determine the optimal duration of monitoring and the best time to initiate cardiac monitoring, since there are no systematic data on early monitoring (within 48 hours) of AT/AF events. The development of an accurate and specific (sensitive) AT/AF monitoring has become a necessity. Cardiac event recorders or event loop recorders are external devices
to be worn for long periods (up to 30-day) and often interfere with some daily activities, besides providing a sporadic monitoring.

From the analysis of the accuracy of several follow-up strategies after AF ablation conducted by Arya et al, [3] it emerges that the method with a degree of accuracy closer to the theoretic gold standard - or to the implantable device - is the daily ECG. Such a strategy can be easily developed by modern technology. In addition, daily ECG detection accuracy could gain benefit by optimizing the time moment of the ECG recording, that is performing a temporally-optimized ECG recording. Such a new concept of monitoring could improve the strategies to follow-up patient even at home and to optimize the therapy.

Home-daily monitoring and AF detection

The possibility of home monitoring of AF episodes relies on two main factors: the feasibility of self recordings of a suitable physiological signal (i.e. a signal containing the information related to the heart rhythm), the availability of a reliable algorithm to analyze such signal.

Automatic detection of AF is achieved by analysis of the electrocardiographic signal. The absence of the P-waves is the main criterium for AF detection. Alternative methods have been proposed. These methods are based on the measure of the irregularity of the ventricular rhythm. Various measures of such irregularity are known [4-10]. These measures quantify the variability of the RR intervals obtained from ECG signals, using combinations of various features:
standard deviations and probability density function \[4\], wavelet transform \[5\] entropy, Lorenz plots \[6\], probability density function of an embedded time series \[7\], Turning point ratio, standard deviation and entropy \[8\], Markov modeling in combination with P-wave analysis \[9\], Poincare plots \[10\].

It is known that ventricular rhythm can be extracted also from pulseoxymetric waveforms, during normal sinus rhythm \[11\] \[12\]. The reliability of ventricular rhythm during AF is not known.

It is known that the detection of AF from pulseoxymeter signals can be done by processing the combined information contained in the waveform amplitude and in the inter-beat intervals (US Patent 2007/0255146), using contextual analysis and hidden Markov model. The feasibility of AF detection using only the information carried on by the ventricular rhythm extracted by the pulseoxymetric signal has not been proved.

**SUMMARY OF THE INVENTION**

The invention consists of a system that performs short term acquisition of the plethysmographic waveform of a patient from a blood oxygenation level monitoring device and establishes whether the patient has an episode of Atrial Fibrillation (AF), or has a Normal Sinus Rhythm (NSR) or any other not-specific rhythm irregularity. Such classification is implemented in a software application that can be executed directly in the device, and the result of the classification is displayed using a three-state, traffic-light indicator.

The plethysmographic waveform is taken from the
patient's finger and is processed so that to obtain the pulse interval series.

Artifacts are rejected using a parametric modeling of the pulse waveform contour. Each detected beat is segmented into three sections. The similarity of the first section to a linear segment and the similarity of the third segment to an exponential decay are used to discriminate proper beats from artifacts. Similarity is assessed using the goodness of fit with linear and exponential interpolating functions.

An inter-beat series is obtained calculating the time delay between adjacent beats. Time delays shorter than 0.3 s or longer than 1.5 s are discharged from the further analysis.

This beat-to-beat series (PP intervals) is analyzed and two indexes are extracted, namely the coefficient of variation (CV) and the Shannon entropy (EN).

The combination of these two indexes is used to establish if the patient is in AF or not, by using a measure of the distance of the patient parameters from a reference population. Such distance is calculated using the Mahalanobis formula.

Coefficients and thresholds used for the classification are obtained from reference populations, and are embedded in the system.

The entire algorithm is implemented on an embedded system, preferably directly connected to the pulse oxymeter sensor.

**DETAILED DESCRIPTION OF THE INVENTION**

The method for the detection of AF episode is
based on the estimation of the heart rhythm irregularity, specifically on two indexes extracted from the beat-to-beat interval series obtained from pulsoximetric waveform.

The method foresees the following steps:

• Acquisition of the pulseoximetric signal/waveform from the finger.
• Estimation of the time-occurrence of each beat from the pulseoximetric waveform.
• Construction of the beat-to-beat series.
• Beat validation to reduce artifacts
  o Characterization of pulseoximetric waveform, by morphological analysis of the ascendent and descendent tracts of a single pulse
  o Removal of beat intervals with values lower than 0.3 s and longer than 1.5 s
• Estimation of quantitative indexes
  o Coefficient of variation of the first differences of beat-to-beat interval series
  o Shannon entropy of the beat-to-beat interval series
• Classification of the heart rhythm:
  o Estimation of the Mahalanobis distance from population with sinus rhythm and with AF.

With reference to fig. 1, the device according to the present invention substantially carries out a process comprising the following steps:

1. Recording of the pulseoxymetric waveform at the finger;
2. Estimation of the time-occurrence of each beat, by adaptive thresholding and parabolic interpolation;
3. Beat validation: evaluation of the ascendant and
descendent tracts of any detected beat;
4. Construction of the beat-to-beat interval series
5. Estimation of quantitative indexes:
   • Coefficient of variation of dPP intervals
   • Shannon entropy of PP intervals
6. Classification of the heart rhythm by the
   estimation of the Mahalanobis distance from
   population with sinus rhythm and with AF.

**Details on beat validation**

Artifacts are rejected using a parametric modeling
of the pulse waveform contour. Each detected beat is
segmented into three sections. The similarity of the
first section to a linear segment and the similarity of
the third segment to an exponential decay are used to
discriminate proper beats from artifacts. Similarity is
assessed using the goodness of fit (R-squared) with
linear and exponential interpolating functions. If the
R-squared of the linear and exponential tracts are
lower than a reference level, the beat is categorized
as artifact and neglected.

**Beat validation: evaluation of the ascendant and
descendent tracts of any detected beat**

Referring to figures 2 and 3, showing a sketch of
pulse contours, respectively with the interpolating
linear function (fig. 2) and exponential function (fig.
3), it is useful to point out the following validation
steps.

Step 1. Each detected beat is segmented into three
sections.
Step 2. The similarity of the first section to a
linear segment is evaluated using linear fitting. Similarity is quantified using the goodness of fit (R-squared) with a linear function (fig. 2).

Step 3. The similarity of the third segment to an exponential decay is evaluated using and exponential fitting. Similarity is quantified using the goodness of fit (R-squared) with an exponential interpolating function (fig. 3).

Step 4. If the R-squared of the linear and exponential tracts are both lower than a reference level, the beat is categorized as artifact.

Rational for parameter choice

Known parameters based on the morphological analysis of the ECG signal were excluded (e.g. P-wave detection). It is known that there are several parameters aimed to detect AF by analyzing the irregularity of the heart rhythm. Some of these parameters does not suit a short-term detection since they requires a relatively large number of beats, others require significant computational effort / memory occupation. Such methods have been excluded. Among the other known parameters a novel combination of two of them has been adopted, by empirical testing. Such peculiar combination has not been used previously. The performances of the proposed method have been verified on a population of 61 patients (43 with NSR, 14 with AF and 4 with other arrhythmias).

Details on indexes computation

Coefficient of variation is the ratio between the
standard deviation for the series of the first derivatives of the beat-to-beat interval series ($\sigma_{\Delta PP}$) and the mean value of the beat-to-beat interval series ($\mu_{PP}$):

$$\frac{PP}{\mu_{PP}}$$

where:

$$\mu_{PP} = \frac{1}{N} \sum_{i=1}^{N} PP_i : \text{mean value of the beat-to-beat interval series}$$

$$(PP = \sqrt{\left( (1)/N \sum_{i=1}^{N} \sigma_{\Delta PP} \right)^2 \left( [\mu_{PP}]^2 - 1 \right) \mu_{\Delta PP}^2})$$

standard deviation of the series of the first derivatives of the beat-to-beat interval series

$$\mu_{\Delta PP} = (1)/(N - 1) \sum_{i=1}^{N} (N - 1) \sum_{i=1}^{N} \sigma_{\Delta PP}^2 \mu_{\Delta PP}^2$$

mean of the series of the first derivative of the beat-to-beat interval series

$$(\mu_{PP})_{i} = PP_{i}(i + 1) - PP_{i}$$

series of the first derivatives of the beat-to-beat interval series

$${PP}_i : \text{Interval between two consecutive beats}$$

$$N : \text{Number of (consecutive) available beats}$$

Conventionally, CV of a temporal series is computed as the ratio between its standard deviation and its mean value. In this case, since the mean value of the first derivatives of the beat-to-beat interval series ($\Delta PP$) is close to zero, the computation is made dividing for the mean value of the beat-to-beat interval series ($PP$).

The entropy is computed from the Shannon formula, that implies the estimation of the probability density function of the beat-to-beat interval series (by construction of the histogram).
\[ E_{NPp} = - \sum_{k=1}^{M} p_k \ln(p_k) \]

where:
M = is the number of bins used to construct histogram

\[ p_k \] = is the probability of occurrence of a beat-to-beat interval, estimated as the ratio \( n_k/N \), with \( n_k \) representing the number of beat-to-beat intervals within the \( k^{th} \) bin.

The bin amplitude have to be chosen sufficiently higher than the time resolution of the PP series, to obtain a reliable estimate of the histogram density, but not too large to avoid disruption of relevant information for the rhythm discrimination. The bin amplitude has been set to 16.6 ms.

**Algorithm for rhythm classification**

Rhythm classification is based on the measure of the distance of the couple of values CV and EN for a patient respect to the values characterizing a population of patients in atrial fibrillation and of subjects in sinus rhythm. Instead of the Euclidean distance, the Mahalanobis distance is used since it takes into account the parameters' dispersion within the population and their mutual correlation. Classification in NSR, AF or other arrhythmia is achieved by the following criteria:

If the Mahalanobis distance from the AF is lower than a properly selected value, rhythm is classified as AF, else
if the Mahalanobis distance from NSR is lower than a properly selected value, rhythm is classified as Normal, else rhythm is classified as "Other Arrhythmia"

The properly selected values of the Mahalanobis distances have been chosen on the basis of the result from the clinical validation of the method.

From a set of values representative of a given population, the Mahalanobis distance is computed as

\[ D^2(x) = (x - \mu)^T S^{-1}(x - \mu) \]

Where:
- \( x \) = set of parameters of the patient to be classified (CV and EN)
- \( \mu \) = set of the mean value of the parameters in the reference population (sinus rhythm or atrial fibrillation) \([\mu_{CV} \mu_{EN}]\).
- \( S \) = Covariance matrix, estimated on the parameters obtained from the reference population.

The formula becomes:

\[
D^2_S(i) = [CV_i - \mu_{CV_S}, EN_i - \mu_{EN_S}] [S_{1,1} \quad S_{1,2} \quad S_{2,1} \quad S_{2,2}] [CV_i - \mu_{CV_S}, EN_i - \mu_{EN_S}]
\]

\[
D^2_{AF}(i) = [CV_i - \mu_{CV_{AF}}, EN_i - \mu_{EN_{AF}}] [a_{f1,1} \quad a_{f1,2} \quad a_{f2,1} \quad a_{f2,2}] [CV_i - \mu_{CV_{AF}}, EN_i - \mu_{EN_{AF}}]
\]

where:
- \( D_S(i) \) = distance of the patient \( i \) respect to the population in sinus rhythm
- \( D_{AF}(i) \) = distance of the patient \( i \) respect to the population in atrial fibrillation
- \( \mu_{CV_S} \) = mean of parameter CV for the population of patients in sinus rhythm
- \( \mu_{EN_S} \) = mean of parameter EN for the population of patients in sinus rhythm
\( \mu_{CV_{AF}} \) = mean of parameter CV for the population of patients in atrial fibrillation

\( \mu_{EN_{AF}} \) = mean of parameter EN for the population of patients in atrial fibrillation

\[
\begin{pmatrix}
S_{11} & S_{12} \\
S_{21} & S_{22}
\end{pmatrix}
\] coefficients of the inverse of covariance matrix, for the population in sinus rhythm

\[
\begin{pmatrix}
a_{f11} & a_{f12} \\
a_{f21} & a_{f22}
\end{pmatrix}
\] coefficients of the inverse of covariance matrix, for the population in atrial fibrillation

**Scientific evidence / clinical validation**

The performances of the proposed method have been verified on a population of 61 patients with an history/suspect of AF. Heart Rhythm diagnosis was performed by an expert cardiologist, before each signal collection. 43 patients had NSR, 14 AF and 4 other arrhythmias.

A short -term pulseoximetric signal was collected at the finger, using a commercial pulseoximeter, which may have a connection with a laptop PC for signal storage and further analysis.

Beat validation showed high sensitive and specificity (>95%) in discriminating proper beats from artifacts.

The method classified correctly 43 out of 43 patient with Sinus Rhythm, 14 out of 14 patient with AF, 3 out of 4 patients with other arrhythmias. One patient with a supraventricular tachycardia was classified as normal sinus rhythm.
In terms of Sensitivity (Se) and Specificity (Sp) of AF detection, the method shows a Sp = 100% and Se = 100%. The accuracy was 98.4%.

References


Claims

1) Method for the detection of AF episode based on the estimation of the heart rhythm irregularity characterized in that it comprises the following steps:
   a) processing the plethysmographic waveform of a patient taken from a blood oxygenation device so that to obtain a threshold pulse interval (PP) series;
   b) analyzing said pulse interval series and extracting two indexes, namely the Coefficient of Variation (CV) of dPP interval and the Shannon entropy (EN) of PP interval,
   c) classification of the heart rhythm by the estimation of the Mahalanobis distance of the patient parameters from a reference population of patients in atrial fibrillation and of subjects in sinus rhythm, using the combination of the two indexes.

2) Method according to claim 1 wherein the step a) comprises:
   I) estimation of the time-occurrence of each beat from the pulseoximetric waveform:
   II) construction of the beat-to-beat series;
   III) Beat-validation to reduce artifacts through morphological analysis of the ascendent and descendent tracts of a single pulse using a parametric modelling of the pulse waveform contour;
   IV) removal of beat intervals with values lower than 0.3 s and longer than 1.5 s.

3) A method according to claim 1 wherein in the step b), the Coefficient of variation is the ratio between the standard deviation for the series of the
first derivatives of the beat-to-beat interval series (\(\sigma \Delta P_P\)) and the mean value of the beat-to-beat interval series

\[
\frac{P_P}{\mu_{PP}}
\]

where:

\[
\mu_{PP} = \frac{1}{N} \sum_{i=1}^{N} P_{P_i} \quad \text{: mean value of the beat-to-beat interval series;}
\]

\[
\sigma_{\Delta P_P} = \sqrt{\left( \frac{1}{N} \sum_{i=1}^{N} (P_{P_i} - \mu_{PP})^2 \right)^2} \quad \text{: standard deviation of the series of the first derivatives of the beat-to-beat interval series}
\]

\[
\mu(P_P) = \frac{(1/N - 1) \sum_{i=1}^{N} (P_{P_i})}{(N - 1)^2} \quad \text{: mean of the series of the first derivative of the beat-to-beat interval series}
\]

\[
[(P_P)_{i+1} = P_{P_{i+1}} - P_{P_i}] \quad \text{: series of the first derivatives of the beat-to-beat interval series,}
\]

\(P_{P_{i+1}}\): Interval between two consecutive beats,

\(N\): Number of (consecutive) available beats,

while

the entropy is computed from the Shannon formula, that implies the estimation of the probability density function of the beat-to-beat interval series (by construction of the histogram),

\[
E_{NN} = - \sum_{k=1}^{M} p_k \ln(p_k)
\]

where:

\(M\) is the number of bins used to construct histogram , and

\(p_k\) is the probability of occurrence of a beat-to-beat interval, estimated as the ratio \(n_k/N\), with \(n_k\)
representing the number of beat-to-beat intervals within the kth bin.

4) A system for the detection of AF episodes based on the estimation of the heart rhythm irregularity characterized in that it comprises:
- a portable blood oxygenation monitoring device able to acquiring also at home a plethysmographic waveform of a patient over a period of time,
- means to storage in said device a computer program for processing said plethysmographic waveform according to method of claim 1;
- a CPU configured to receive the plethysmographic waveform and further configured to execute said computer program,

wherein, when the computer program is executed,
a) the plethysmographic waveform is processed so that to obtain the pulse interval series;
b) said pulse interval series are analyzed and two indexes are extracted, namely the Coefficient of Variation (CV) of dPP interval and the Shannon entropy (EN) of PP interval, and
c) the heart rhythm is classified by the estimation of the Mahalanobis distance of the patient parameters from a reference population of patients in atrial fibrillation and of subjects in sinus rhythm, using a combination of the two indexes, and
d) the result of the classification is displayed using a a three-state, traffic-light indicator of the monitoring device.
5) A system according to preceding claim wherein the monitoring device is a pulse oximeter sensor.
Recording of the pulseoxymetric waveform at the finger

Estimation of the time-occurrence of each beat, by adaptive thresholding and parabolic interpolation

Beat validation: evaluation of the ascendant and descendent tracts of any detected beat

Construction of the beat-to-beat interval series

Estimation of quantitative indexes:
- Coefficient of variation of dPP intervals
- Shannon entropy of PP intervals

Classification of the heart rhythm by the estimation of the Mahalanobis distance from population with sinus rhythm and with AF.

FIG. 1
A. CLASSIFICATION OF SUBJECT MATTER
INV. A61B5/024
ADD.

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

B. FIELDS SEARCHED

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

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category*</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
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Further documents are listed in the continuation of Box C. See patent family annex.

* Special categories of cited documents:
  "A" document defining the general state of the art which is not considered to be of particular relevance
  "E" earlier document 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
  "N" document member of the same patent family

Date of the actual completion of the international search: 21 March 2011

Date of mailing of the international search report: 28/03/2011

Name and mailing address of the ISA:
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NL-2280 HV Rijswijk
Tel. (+31-70) 340-3040,
Fax: (+31-70) 340-3016

Authorized officer: Vanderperren, Yves
<table>
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<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
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*abstract cited in the application on page 665
INTERNATIONAL SEARCH REPORT

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

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

1. ☒ Claims Nos.: 1-3 because they relate to subject matter not required to be searched by this Authority, namely:

   see FURTHER INFORMATION sheet PCT/ISA/210

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

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

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

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

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

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

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

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

Remark on Protest

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

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

☐ No protest accompanied the payment of additional search fees.
Continuation of Box II.I

Claims Nos.: 1-3

Claims 1-3 relate to subject-matter considered by this Author to be covered by the provisions of Rule 39.1(iv)/67.1(iv) PCT. A meaningful search is not possible on the basis of claims 1-3 because they are directed to a diagnostic method practiced on the human or animal body (Rule 39.1(iv) PCT). It is pointed out that the claims comprise - the step of collecting data (Claim 1: "processing the plethysmographic waveform of a patient taken from a blood oxygenation device"; data is taken from a pulse oximeter); - the step of comparing these with standard values (Claim 1: "analyzing said pulse interval series and extracting two indexes", "classification of the heart rhythm (...) from a reference population of patients") - the step of finding a significant deviation on respect to a reference is detected such that the result can be assigned to a certain category; this deviation is found in claim 1 by means of the Mahalanobis distance), and - the step of attributing the deviation to a particular clinical picture, i.e., the deductive medical or veterinary diagnostic phase (Claim 1: "method for the detection of atrial fibrillation on episode", "reference population in atrial fibrillation on and subjects in [normal] sinus rhythm"; the classification of the result in the category corresponding to atrial fibrillation on constites a step of attributing the deviation to a particular clinical picture).
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