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[Continued on next page]

(54) **Title**: METHOD FOR CONTROLLING AN ELECTROPORATION DEVICE

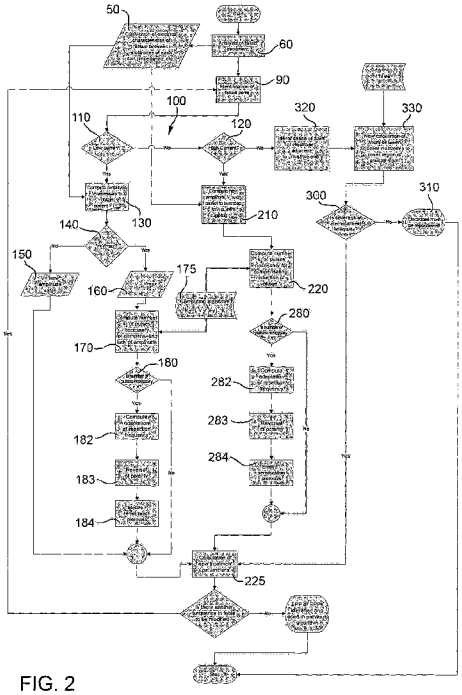


FIG. 2

(57) **Abstract**: A method for controlling an electroporation device configured for supplying an electrical power signal to a plurality of pairs of electrodes (5a, 5b) coupled to a portion of the human body (7), wherein the following steps are performed: detecting, in the course of an electroporation treatment, a condition of malfunctioning or fail for the pairs of electrodes for which at least one electrical parameter of the power signal supplied to the electrodes themselves has an anomalous value; storing an indicator (90) of the pairs of electrodes in the fail condition; and selecting (90) the pairs of electrodes in the fail condition and re-computing new parameters (225) in order to implement a subsequent electroporation process.

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— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

"METHOD FOR CONTROLLING AN ELECTROPORATION DEVICE"

TECHNICAL FIELD

The present invention relates to a method for controlling an electroporation device.

BACKGROUND ART

As is known, electroporation treatments are carried out using electronic devices designed to supply at output a pulsating a.c. signal to a plurality of electrodes applied to a tissue for creating currents induced in the tissue and modify the permeability of the cell membrane of the cells present in the tissue itself. The modification of the permeability of the cell membrane is normally used for carrying drugs, organic compounds, or generically molecules within the cell.

The parameters of the a.c. signal, for example the waveform, frequency, voltage, duty-cycle, and application time, are normally defined in an off-line mode, i.e., before starting the treatment, according to the effect that it is desired to obtain on the cells. Said definition includes the use of tables based upon experimental data, i.e., data that have been collected and refined by monitoring the results of a plurality of electroporation treatments performed previously.

Not always does the use of said experimental data enable execution of an electroporation treatment that obtains the desired effects. In the case of partial or total failure of the electroporation method, it is consequently difficult to determine what further actions to perform.

DISCLOSURE OF INVENTION

The aim of the present invention is to provide a method for controlling an electroporation device that, in the case of failure, will enable automatic modification of the parameters of the treatment previously performed by computing and implementing new parameters.

The above aim is achieved by the present invention in so far as this relates to a method for controlling an electroporation device configured for supplying an electrical power signal to a plurality of pairs of electrodes coupled to a portion of the human body, the method comprising the steps of: detecting, in the course of an electroporation treatment, a condition of malfunctioning or fail for the pairs of electrodes for which at least one electrical parameter of the power signal supplied to the electrodes themselves has an anomalous value; storing an indicator of the pairs of electrodes in the fail condition; selecting the pairs of electrodes in the fail condition and re-computing for them new parameters for implementing a subsequent electroporation process.

BRIEF DESCRIPTION OF THE DRAWINGS

The invention will now be described with reference to the attached drawings, which illustrate an example of embodiment thereof and in which:

- Figure 1 illustrates, in a schematic way, an electroporation device operating according to the method according to the present invention; and
- Figure 2 illustrates by means of a block diagram the method according to the present invention.

BEST MODE FOR CARRYING OUT THE INVENTION

In Figure 1, designated as a whole by 1 and illustrated schematically is an electroporation device which comprises a hardware structure of a known type, in which a signal generator 3 of an adjustable type produces at output a pulsating signal that is supplied at input to a power amplifier 4, which in turn supplies a power signal to a set of electrodes 5 (for example, to a plurality of needle-shaped electrodes arranged according to an orderly array structure).

The electrodes 5 are designed to be applied to a portion of human body 7 for generating electrical fields designed to modify the permeability of the cell membrane of the cells comprised in the portion 7 and impinged upon by the electrical

field. Typically, the power signal is supplied in sequence to different pairs of electrodes 5a, 5b so that the electrical field will impinge upon the entire portion 7 in which the electrodes 5 are arranged.

A control unit 10 of the signal generator 3 enables regulation of a plurality of parameters, amongst which:
- the waveform of the power signal (for example, square-wave, sawtooth, sinusoidal, triangular, exponential, etc.);
- the frequency of the power signal;
- the duty-cycle of the power signal;
- the application time of the power signal;
- the temporal spacing between groups of consecutive pulses; and
- other electrical parameters of the power signal.

The device 1 is provided with a plurality of sensors that monitor continuously the electrical quantities of the electroporation process in progress; in particular, sensors 12, 13, 14 are provided, designed to measure the instantaneous value of the current Ie supplied to each pair of electrodes 5a, 5b, the voltage value Ve applied to said pair of electrodes, and the impedance $Z(\omega)$ present between said pair of electrodes.

According to the present invention, the microprocessor unit of the control unit 10 implements a plurality of instructions that implement a control method, as described hereinafter with reference to Figure 2.

In use, on the basis of the type of electroporation treatment to be carried out, by means of a calculation procedure of an off-line type, the distance between the electrodes 5 and their arrangement are set, and the characteristics of the power signal and the duration of the electroporation treatment are also defined. Typically, the setting is made with a set of

maps (not illustrated) that take into account experimental data obtained from treatments performed previously.

The electroporation treatment starts. During said treatment the instantaneous values of the voltage Ve and of the current Ie are monitored continuously.

In the case where, for a given pair of electrodes, the value of current Ie departs from a range of acceptability (and, namely, is too high or too low) a situation of malfunctioning or fail is detected, for that pair of electrodes.

In the presence of an indication of fail the value of impedance $Z(\omega)$ present between the pair of electrodes considered is measured (said operation is indicated by block 50 in Figure 2) and an indicator (tag) is stored, which identifies the pairs of electrodes 5 that have given rise to a fail.

The control method according to the present invention performs, for the pairs of electrodes for which a fail has been detected and a tag has been stored, a further analysis (said operations are indicated by the respective block 90 and 60 in Figure 2) described hereinafter with reference to Figure 2.

With particular reference to Figure 2, the method comprises a block 100 (subsequent to block 90), which, since parameters of the electroporation process have been detected outside an interval of acceptability for a pair of electrodes selected (block 90 - Identification of failed pairs), performs an analysis for defining the type of corrective action for said pair of electrodes. The pair of electrodes in question is again supplied with the power signal for verifying the value of the electrical quantities associated thereto.

In this connection, block 100 comprises a block 110 that verifies whether the current that has been supplied to the electrodes I_E is lower than a minimum threshold value I_{LOW}; if it is not (i.e., if the current I_E is higher than the threshold value I_{LOW}) the current is recognized as acceptable, and block 110 is followed by a block 120; otherwise (i.e., if the current I_E is lower than the threshold value I_{LOW}), an anomalous current is recognized, which is an index of an electroporation process that has not yet started, and from block 110 control passes to block 130.

Block 130 computes (in a known way by applying Ohm's law once the impedance $Z(\omega)$ is known) the value of the voltage that can be applied to the electrodes necessary to obtain an increase of the current and bring the electroporation current to a target value (for example, at least 1.5 A). The calculation made in block 130 is possible in so far as the impedance of the tissue is known precisely.

Processing of block 130 continues until a current is calculated having a target value I_{TARGET} corresponding to which is a voltage V_T necessary to obtain said value of current.

Next, a check is made (block 140 subsequent to block 130) to verify whether the voltage V_T thus obtained is lower than (or equal to) the maximum voltage V_{Max} that can be supplied by the electroporation device 1; if so (i.e., in the case where the voltage calculated can be supplied by the device that implements the electroporation method, i.e., $V_T < V_{Max}$) block 140 is followed by a block 150 that stores the voltage equal to V_T to be applied for the pair of electrodes considered. The parameters of the electroporation process are thus redefined (block 225), and the verification process continues for each other pair of electrodes for which a fail condition has been detected (consequently control returns to block 90).

In the case where the voltage V_T thus obtained is higher than the maximum voltage V_{Max} that can be supplied, block 140 is followed by a block 160, which detects said physical limit in the voltage that can be supplied to implement a series of solutions aimed at obtaining in any case electroporation of the tissue. In this connection, block 160 is followed by a block 170 that calculates the number of pulses per unit time (for example, the treatment time) necessary to obtain electroporation of the tissues having available the voltage V_{Max}; in particular, the number of pulses supplied per unit time is increased bringing the current number of pulses N_{PULSE} to a higher number K_{PULSE} (with $K_{PULSE} > N_{PULSE}$); the number of pulses per unit time is thus increased. The calculation of the number of pulses K_{PULSE} necessary is carried out by a block 175 on the basis of an algorithm.

The algorithm of block 175 envisages calculation of the equivalent dose **EqD** absorbed by the means, according to the formula

$$\mathbf{EqD}=\sigma\ \mathbf{E}^2\ \mathbf{t}\ \mathbf{k}^{-1/2}\ \rho^{-1} \qquad [1]$$

where σ is the conductivity of the tissue, E the electrical field supplied, t the time duration of each pulse, k the number of pulses supplied, and ρ the density of the material.

Said equivalent dose is calculated first for the standard condition, i.e., the one that is determined by the protocol previously applied with parameters of the signal (for example, waveform, frequency, voltage, duty-cycle, application time) defined in an off-line mode and that has given rise to the fail condition.

In the present case, since the intensity $\mathbf{E}^2$ of the electrical field is no longer modifiable (block 160, the voltage reached is the limit voltage), it is alternatively possible to modify the number of pulses $\mathbf{k}^{-1/2}$ so as to maintain the equivalent dose **EqD** constant and equal to the one obtained in the

calculation executed for the standard condition.

Consequently, the number **k** of the pulses is given by

$$\mathbf{EqD=\sigma\ E2\ t\ k^{-1/2}\ \rho^{-1}} \qquad (1)$$

For completeness, given that it is one and the same tissue, Equation 1 can be simplified as follows

$$\mathbf{E_1^2\ k_1^{-1/2} = E_2^2\ k_2^{-1/2}}$$

Since E=V/d, if we assume maintaining the same geometry of the electrodes, it can be further simplified as follows

$$\mathbf{V_1^2\ k_1^{-1/2} = V_2^2\ k_2^{-1/2}}$$

$$k_{PULSE}=(V_2/V_1)^4\ k_1$$

In the case where the number of pulses necessary K_{PULSE} is lower than a threshold value X (said control is performed by a block 180 subsequent to block 170 that carries out the operation $K_{PULSE} < X$), stored as electroporation parameter is the value K_{PULSE} of pulses having a voltage equal to the maximum value that can be supplied by the machine (block 225), and the verification process continues for another pair of electrodes for which a fail condition has been detected.

In the case where the number of pulses necessary K_{PULSE} is higher than X, stored as electroporation parameter is the value X (block 182) of pulses having a voltage equal to the maximum value that can be supplied by the machine, and the verification process continues for another pair of electrodes for which a fail condition has been detected.

In the case where the maximum value of pulses X is detected, also a request for reversal of polarity of the power signal can be stored (block 183). Alternatively, the reversal of polarity can be carried out in any case irrespective of whether X is exceeded.

If necessary, other electro-sensitization techniques (block 184) can also be applied, i.e., techniques that increase the sensitivity of the tissues to the electroporation phenomenon, for example by dividing the number of pulses thus calculated into a number of applications separated by intervals in which no pulse is supplied (for example, 30 seconds - 30 minutes) .

All the parameters modified are stored, and the verification process continues for another pair of electrodes for which a fail condition has been detected.

Block 120 verifies whether the electroporation current I_E exceeds a maximum value I_{HIGH} beyond which the electroporation device cannot operate in safety conditions.

In the case where the current I_E exceeds the maximum value I_{HIGH}, the process continues with a block 210 subsequent to block 120 that calculates a reduced voltage value V_{min} that enables a reduction in the current such that the value of current I_E drops below the maximum value I_{HIGH} according to Ohm's law given that the impedance of the tissue is known.

Block 210 is followed by a block 220 that calculates the increase in the numbers of pulses necessary per unit time (for example, treatment time) in order to compensate for the reduction in voltage performed in block 210.

A value K_{COMP} of pulses is calculated with procedures (block 222) altogether similar to those of block 175 and consequently, for simplicity, not described in detail.

In the case where the number of pulses necessary K_{COMP} is lower than a threshold value X (said control is performed by a block 280 subsequent to block 270 that carries out the operation $K_{PULSE} < X$) stored as electroporation parameter is the value K_{PULSE} of pulses having a reduced voltage V_{min} equal to the one

calculated by block 210, and the verification process continues for another pair of electrodes for which a fail condition has been detected (block 225).

In the case where the necessary number of pulses K_{COMP} is higher than X, the maximum value X of pulses having a voltage corresponding to the reduced voltage V_{min} is stored (block 282) equal to the one calculated by block 210, and the verification process continues for another pair of electrodes for which a fail condition has been detected after a series of corrective actions have been attempted.

In fact, in the case where the maximum value of pulses X is detected, it is possible to store also a request for reversal of polarity (block 283) of the power signal. Alternatively, the reversal of polarity can be carried out in any case irrespective of whether X has been exceeded.

If necessary, it is also possible to apply other electro-sensitization techniques (block 284), i.e., techniques that increase the sensitivity of the tissues to the electroporation phenomenon, for example by dividing the number of pulses thus calculated into a number of applications separated by intervals in which no pulse is supplied (for example, 30 seconds - 30 minutes) .

All the parameters modified are stored (block 225), and the verification process continues for another pair of electrodes for which a fail condition has been detected.

The condition whereby the current does not exceed the threshold (output NO from block 120) is considered a non-realizable condition in so far as - in the case of presence of a current that is in any case acceptable - the fail condition would not arise.

A different output from block 120 is only possible when the post-pulse analysis detects a condition of overcurrent due to short circuit between the electrodes of a pair and not to a low-impedance load (transition from block 120 to block 210). It is possible to establish a minimum impedance below which this condition arises.

In the above case of short circuit, it is possible to resort to identification (block 320 subsequent to block 120) of a pair of electrodes different from the short-circuited one. From block 320 control then passes to a block 330 where the parameters of the pair identified are modified to increase the coverage of the electrical field so as to compensate for the absence of the short-circuited pair. In the case where the activity of compensation is not effective, from block 330 control goes to a block 300, which, in second instance, identifies all the pairs adjacent to the short-circuited one so as to modify the parameters of said pairs and increase the coverage of the electrical field in order to compensate for the absence of the short-circuited pair.

In the case where this procedure were to prove impracticable, a warning may be issued to signal the need to reposition the electrodes (block 310).

CLAIMS

1.- A method for controlling an electroporation device configured for supplying an electrical power signal to a plurality of pairs of electrodes (5a, 5b) coupled to a portion of the human body (7), the method comprising the steps of:
- detecting, in the course of an electroporation treatment, a condition of malfunctioning or fail for the pairs of electrodes for which at least one electrical parameter of the power signal supplied to the electrodes themselves has an anomalous value;
- storing an indicator (90) of the pairs of electrodes in the fail condition; and
- selecting (90) the pairs of electrodes in the fail condition and re-computing for them new parameters (225) for implementing a subsequent electroporation process.

2.- The method according to Claim 1, wherein said step of detecting, in the course of an electroporation treatment, a condition of malfunctioning or fail comprises the step of detecting whether the current Ie supplied to the electrodes departs from a range of acceptability.

3.- The method according to Claim 1 or Claim 2, wherein the step of re-computing new parameters comprises the step of:
- detecting the impedance existing between the electrodes (50) for which a condition of fail has been detected; and
- re-computing the parameters of the subsequent electroporation process on the basis of said impedance.

4.- The method according to any one of the preceding claims, wherein the step of re-computing new parameters comprises the step of:
- re-applying said power signal to said pair of electrodes in the fail condition;
- verifying the value of the current thus supplied to the

electrodes;
- in the case where said current is lower than a given threshold (110) performing the step of calculating a voltage value (130) configured for enabling an increase of the current such as to bring the current to a target value; and
- storing (225) said voltage value as new electroporation parameter.

5.- The method according to Claim 4, wherein the step of comparing (140) said voltage with a threshold value is performed; in the case where the voltage is lower than the threshold said voltage is stored (150) as new electroporation parameter; otherwise, corrective actions are adopted.

6.- The method according to Claim 5, wherein said corrective actions comprise at least one of the following actions:
- increase of the number of pulses (170) contained in the power signal;
- reversal of polarity (183) of the power signal; and
- application of electro-sensitization techniques (184).

7.- The method according to any one of the preceding claims, wherein the step of re-computing new parameters comprises the step of:
- re-applying said power signal to said pair of electrodes in the fail condition;
- verifying the value of the current thus supplied to the electrodes;
- in the case where said current is higher than a given threshold (120), performing the step of computing (210) a voltage value configured for enabling a reduction of the current such as to bring the current to a value equal to or lower than a target value; and
- storing (225) said voltage value as new electroporation parameter.

8.- The method according to Claim 7, wherein corrective actions are adopted designed to compensate for the reduction in voltage.

9.- The method according to Claim 8, wherein said corrective actions comprise at least one of the following actions:
- increase in the number of pulses (220) contained in the power signal;
- reversal of polarity (283) of the power signal; and
- application of electro-sensitization techniques (284).

10.- An electroporation device, wherein an electronic control unit is provided, which implements the method according to any one of Claims 1 to 9.

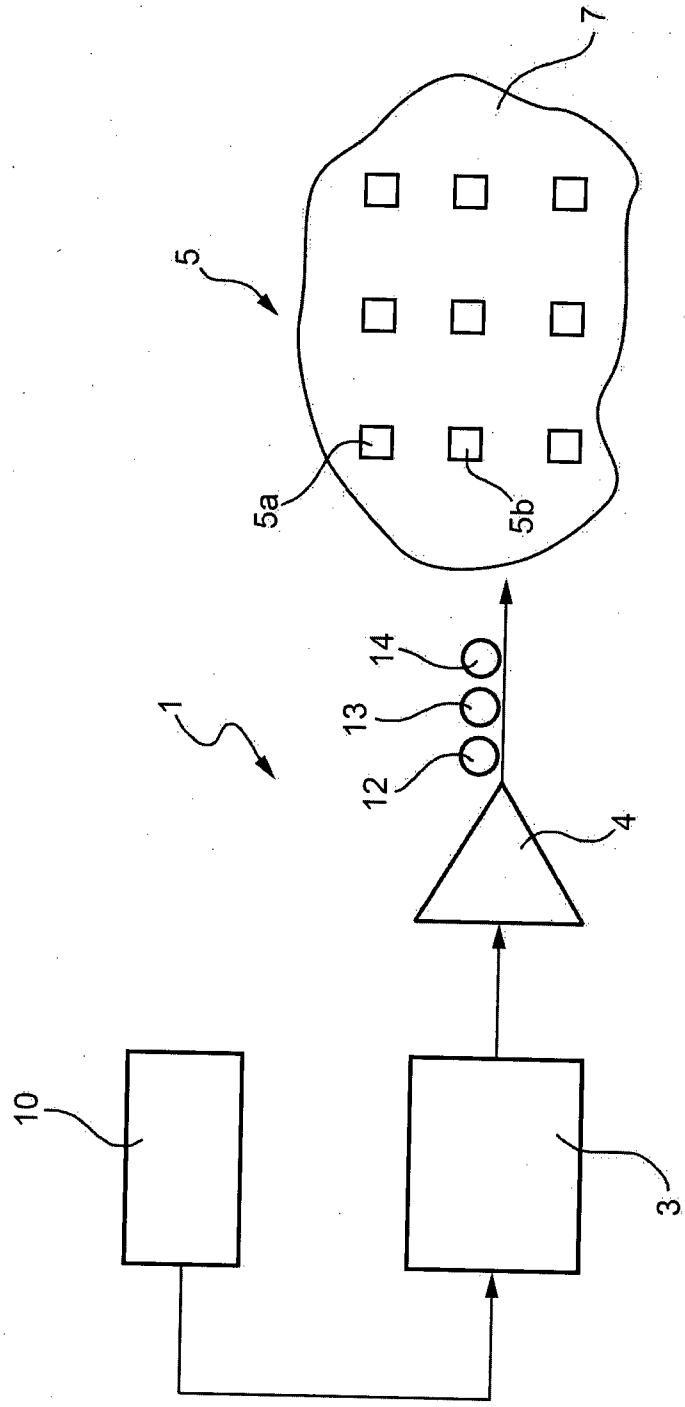


FIG. 1

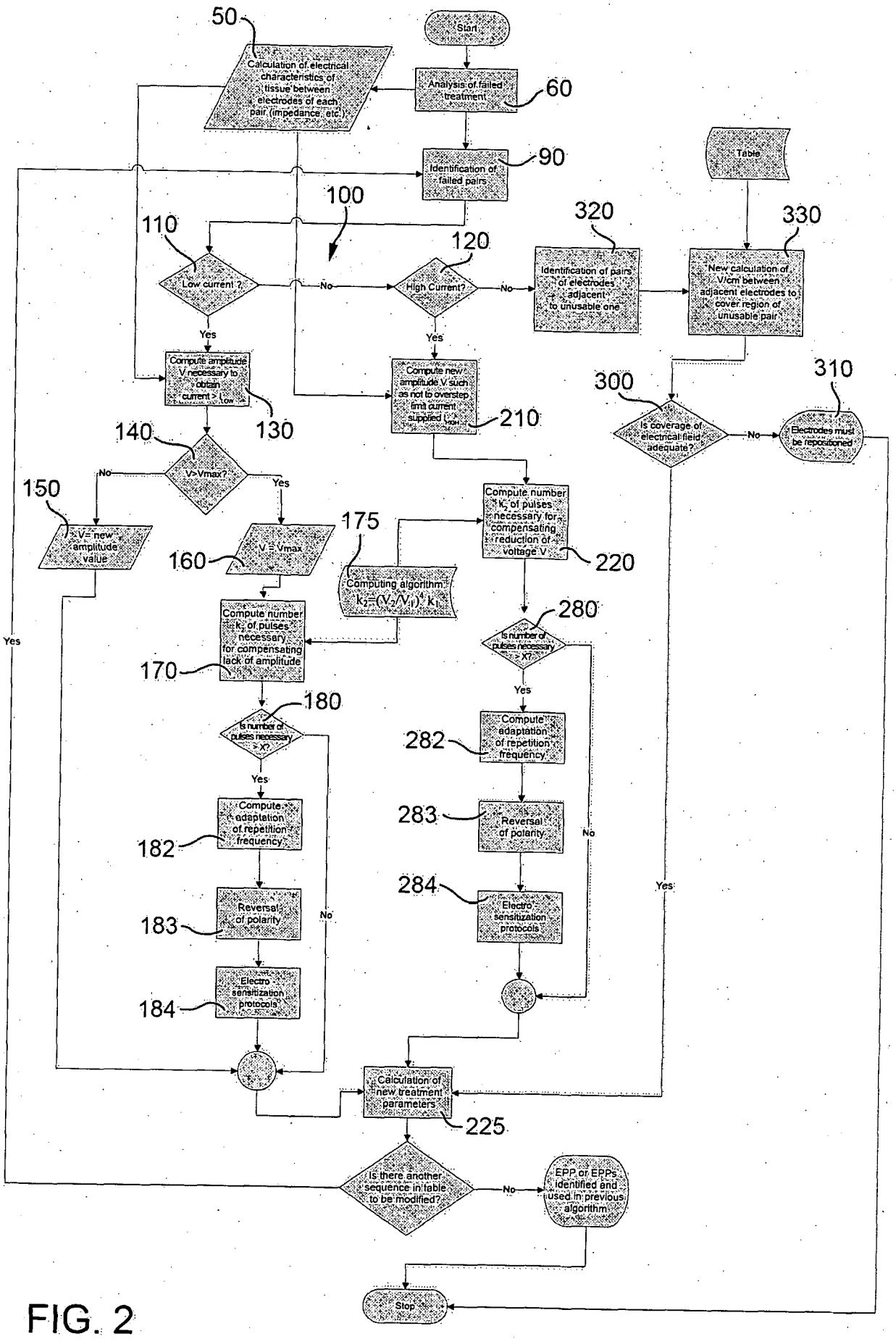

Start
50
Calculation of electrical characteristics of tissue between electrodes of each pair (impedance, etc.)
Analysis of failed treatment
60
Identification of failed pairs
90
Table
100
110
Low current ?
No
120
High Current?
No
320
Identification of pairs of electrodes adjacent to unusable one
330
New calculation of V/cm between adjacent electrodes to cover region of unusable pair
Yes
Yes
Compute amplitude V necessary to obtain current > Low
130
Compute new amplitude V such as not to overstep limit current supplied
210
300
Is coverage of electrical field adequate?
No
310
Electrodes must be repositioned
140
V>Vmax?
No
Yes
150
V= new amplitude value
160
V = Vmax
175
Computing algorithm $k_2=(V_2/V_1)^4 k_1$
Compute number k_1 of pulses necessary for compensating reduction of voltage V
220
Yes
Compute number k_2 of pulses necessary for compensating lack of amplitude
170
Is number of pulses necessary > X?
180
Yes
Compute adaptation of repetition frequency
182
Reversal of polarity
183
Electro sensitization protocols
184
No
Is number of pulses necessary > X?
280
Yes
Compute adaptation of repetition frequency
282
Reversal of polarity
283
Electro sensitization protocols
284
No
Yes
Calculation of new treatment parameters
225
Is there another sequence in table to be modified?
No
EPP or EPPs identified and used in previous algorithm
Stop

FIG. 2

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2012/052159

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61N1/32 A61N1/30
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)
A61N

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	WO 00/62857 A1 (JOHNSON & JOHNSON CONSUMER [US]) 26 October 2000 (2000-10-26) figure 6 page 3, line 27 - page 4, line 27 page 25, line 11 - page 26, line 3 page 26, lines 4-11	10
A	US 2008/208107 A1 (MCRAE STUART [US] ET AL) 28 August 2008 (2008-08-28) the whole document	10
A	EP 0 904 801 A2 (BECTON DICKINSON CO [US]) 31 March 1999 (1999-03-31) paragraphs [0017], [0022]	10

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
10 August 2012	20/08/2012

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	Gentil, Cédric

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2012/052159

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.: 1-9
because they relate to subject matter not required to be searched by this Authority, namely:

see FURTHER INFORMATION sheet PCT/ISA/210

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

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

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

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

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

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

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

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

Remark on Protest

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

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

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

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.1

Claims Nos.: 1-9

Rule 39.1(iv) PCT - Method of treatment of the human or animal being by therapy The control method for an electroporation device, as defined in claims 1-9, relates to the curing of diseases or malfunctions of the body in order to restore or maintain health; reference is also made to the description, Pars. [0002]-[0003]. It is accordingly considered that claims 1-9 define a method of treatment of the human or animal body by therapy, for which no international search needs to be carried out; Rule 39.1(iv) PCT.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2012/052159

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