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[Continued on next page]

(54) Title: HEART RATE VARIABILITY AS AN INDICATOR OF EXERCISE CAPACITY



(57) Abstract: Based upon patient studies, a high degree of correlation was found between HRV and VO_{2max} , i.e., the patient's exercise capacity. A pacing therapy optimization protocol for treating patients with CHF has been devised which involves first pacing the patient's heart with a pacemaker programmed to operate in a first mode for a predetermined time period and collecting data from which a HRV index is derived. The mode is then changed and the steps repeated until all possible modes have been utilized. The pacemaker is then programmed to function in that mode associated with the largest HRV index. Alternatively, the method of the present invention can be applied to changes in drug therapy instead of or in combination with pacing therapy. By the plotting the HRV index computed in the manner described, the efficacy of a change in therapy on a patient exercise capacity can be assessed.



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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

**HEART RATE VARIABILITY AS AN
INDICATOR OF EXERCISE CAPACITY**

Background of the Invention

CROSS REFERENCE TO RELATED APPLICATIONS

5 This application is a continuation-in-part of application serial no. 09/093,118, filed June 8, 1998.

 I. Field of the Invention: This invention relates generally to a method and apparatus for assessing patient well-being, and more particularly to a method and apparatus
10 for indirectly determining a patient's peak oxygen uptake (VO_{2MAX}) by measuring his/her heart rate variability (HRV).

 II. Discussion of the Prior Art: It is known in the art that HRV, i.e., the beat-to-beat variance in sinus cycle length over a period of time, is a predictor of
15 mortality and morbidity. Patients exhibiting low HRV show a significantly increased risk of sudden cardiac death. See "Heart Rate Variability" by Zsolt Ori, et al., Cardiology Clinics, Vol. 10, No. 3, August 1992, pp. 499-537 and "Depressed Heart Rate Variability As An Independent
20 Predictor of Death in Chronic Congestive Heart Failure Secondary to Ischemic or Idiopathic Dilated Cardiomyopathy" by Piotr Ponikowski, et al., The American Journal of Cardiology, Vol. 79, June 15, 1997, pp. 1645-1650. See also "Correlations Among Time and Frequency Domain Measures
25 of Heart Period Variability Two Weeks After Acute Myocardial Infarction" by J. Thomas Bigger et al., The American Journal of Cardiology, Vol. 69, April 1, 1992. In addition, the Spinelli et al. U.S. Patent 5,466,245 provides a very detailed method for automatically
30 determining AV delay based on evaluating a frequency domain measure of heart rate variability (HRV).

 In the Heemels et al. U.S. Patent 5,603,331, assigned to applicant's assignee, a method and apparatus is described for efficiently processing, logging and
35 disseminating essential features relating to HRV accumulated from a continuous, long-term monitoring of cardiac activity. As pointed out in that patent, the

method sufficiently conserves data memory, program memory and power consumption that it may be incorporated within an implantable pacemaker or defibrillator to log a 24-hour period of cardiac activity accumulated for subsequent
5 telemetry to an external monitor. The patent further describes a method of processing and displaying HRV data in a manner that is readily understandable by clinicians which provides an improved graphical contrast between normal and abnormal HRV patterns.

10 Further studies which we have recently conducted on several patients has revealed a high correlation between HRV and a patient's exercise capacity as measured by VO_{2MAX} . Based upon this realization, a method has been established for indirectly assessing a patient's maximum oxygen uptake
15 by computing the standard deviation of five minute mean RR intervals, i.e., the SDANN Index. In an alternative approach, a two-dimensional histogram array is plotted with RR intervals along one axis and the absolute value of the time difference between successive RR intervals plotted
20 along the second axis. By measuring the area on the plot occupied by the two-dimensional histogram, VO_{2MAX} can be estimated.

SUMMARY OF THE INVENTION

In accordance with a first aspect of the invention, an
25 estimation of a patient's maximum oxygen uptake can be derived by the following method:

First, a patient's ECG waveform is sensed and recorded over a 24-hour period. In a pacemaker implementation, the whole 24-hour recording is not possible. Instead, the R-R
30 interval is calculated in real time (on the fly). The recording is then analyzed and a determination is made as to the average length of normal RR intervals in 288 five-minute intervals. When the standard deviation of the 288 averages is computed, it yields an index exhibiting a high
35 correlation with the patient's peak oxygen consumption.

In an alternative method, rather than computing the SDANN Index, the length of RR intervals in the recorded ECG

waveform during a plurality of time segments of a predetermined length are measured and the absolute value of the time difference between successive RR intervals is determined. By plotting this data as a two-dimensional histogram and then measuring the area on the plot occupied by the two-dimensional histogram, the patient's peak oxygen uptake can be inferred. That is to say, studies have shown that there is a high correlation between the area or "footprint" of the histogram and the patient's peak oxygen uptake.

Irrespective of which of the above methods is employed, the information arrived at can be utilized in assessing the efficacy of a given mode of drug therapy or electrical cardiac stimulation on a patient's exercise capacity. By plotting the HRV Index computed over predetermined time intervals in accordance with the first method or the footprint area determined in accordance with the alternative method, trends in a patient's peak oxygen uptake resulting from a predetermined therapy regimen can be determined and used in adjusting the regimen. This is achieved without the need for conducting a breath-by-breath analysis of ventilatory flow and subjecting the patient to a treadmill test or the like.

DESCRIPTION OF THE DRAWINGS

Figure 1 is a graphical representation of a patient data collection schedule for ECG waveforms and $VO_{2\max}$ measurements;

Figure 2 is a plot of $VO_{2\max}$ and the computed SDANN index plotted on the same time axis and showing the correlation of each as the pacing protocol is changed;

Figure 3 is a pseudo three-dimensional histogram plot of RR interval vs. the absolute value of the difference in RR interval between successive heart beats;

Figure 4 is a two-dimensional histogram plot taken prior to pacemaker implant where frequency of occurrence of predetermined HRV values are represented by a gray scale;

Figure 5 is a plot like that of Figure 4 but representing HRV data taken following four weeks of pacing therapy;

Figure 6 is a plot showing the correlation between
5 histogram of footprint size and $VO_{2\max}$ for the data collection schedule of Figure 1;

Figure 7 is a flow chart of the algorithm for determining an optimum pacing mode based upon the relationship of HRV to peak oxygen uptake;

10 Figure 8(a) is a plot of average heart rate, with maximum and minimum vales indicated, over a 52-week period;

Figure 8(b) is a plot of average weekly histogram footprint size (area) over the same 52-week period; and

Figure 8(c) is a plot average week SDANN index over
15 the same 52-week period.

DESCRIPTION OF THE PREFERRED EMBODIMENT

Referring to Figure 1, there is graphically illustrated the data collection approach used in establishing the relationship between heart rate
20 variability and $VO_{2\max}$. Twenty-four hour surface ECG data was collected on seven CHF patients at four time points during a period of twelve weeks. Specifically, the data was collected just prior to the implant of a cardiac pacemaker, then again at the end of four weeks of pacing,
25 at the end of four weeks of no pacing (eight weeks), and at the end of four weeks of pacing (twelve weeks). The pacing mode was randomized between best univentricular pacing and biventricular pacing, during the two four-week periods during which pacing took place. ECG data was sampled at
30 500 Hz and recorded on a modified 16-bit solid state digital holter recorder. At each of the four time points, the patients also performed symptom-limited maximal exercise tests. $VO_{2\max}$, $VO_{2\max}$ at the anaerobic threshold, maximum power attained and total exercise duration were
35 some of the exercise parameters collected.

The surface ECG data was filtered to remove any premature ventricular contractions and other ectopic beats,

to obtain normal RR intervals. Various HRV parameters were calculated from the measured and filtered RR intervals. The well-known SDANN index, which is the standard deviation of five-minute intervals averaged over 288 five-minute
5 intervals in a 24-hour period, was computed for the four 24-hour sampling periods illustrated in Figure 1. The SDANN indices for these four sampling periods are plotted as curve 2 in Figure 2 and also plotted on the same graph as curve 4 are the values of VO_{2max} measured at the same
10 time. The change in SDANN index correlated well with the change in VO_{2max} . Also apparent is the fact that the pacing therapy proved effective in improving these patient's exercise capacity.

The HRV data collected in accordance with the protocol
15 of Figure 1 was also plotted as a two-dimensional histogram where the RR intervals and absolute value of the difference between successive RR intervals are quantized into a plurality of bins and then plotted against one another as shown in Figure 3. Through logarithmic compression, as
20 described fully in U.S. Patent 5,603,331, and which is hereby incorporated by reference, the frequency value to be plotted on the Z axis can be limited to a number of levels compatible with the amount of memory available.

In the graphs of Figures 4 and 5, the histogram is
25 plotted with a gray scale utilized to identify the frequency parameter. As in the case of Figure 3, the RR interval number is plotted against the absolute value of the difference between successive RR intervals and rather than having the distance along a Z axis as a measure of the frequency value, a gray scale color is used instead. Thus,
30 the plots of Figures 4 and 5 can be considered as contour maps of the pseudo three-dimensional histogram with different shades of gray representing various heights of the Z axis found in the pseudo three-dimensional plot. We
35 have found the area subtended by the plot, i.e., its footprint, to be an indicator of VO_{2max} with changes in footprint area due to pacing also tracking changes in VO_{2max} .

Comparing Figures 4 and 5, it is readily apparent that pacing the patient suffering CHF had the effect of increasing that patient's maximum exercise capacity. Footprint area is determined by counting the number of non-zero pixels in the two-dimensional plot.

Figure 7 is a software flow diagram for optimizing the pacing mode of an implantable programmable cardiac pacer based upon observed improvements in a patient's exercise capacity and which does not require cardiopulmonary exercise monitoring equipment in carrying out the method. This flow diagram is in sufficient detail such that a programmer of ordinary skill can write software code for allowing a microprocessor to carry out the indicated functions. Such microprocessor program may be implemented in the implantable pacemaker device itself or, alternatively, may comprise equipment external to the patient.

It is contemplated that the implantable pacemaker is of the type that allows its mode to be reprogrammed via a transcutaneous telemetry link. Most present-day pacemakers incorporate this capability. The first step in carrying out the process is to initialize a pacing mode table, a therapy time table and an evaluation period table as represented by block 20 in Figure 7. The implanted pacemaker is capable of operating in a plurality of modes M_k , $k=0, 1, \dots N$. For example, a first mode may be VDD with a first AV interval and a second mode may be VDD with a second, different AV interval. A mode change may also be based upon the pacing site (or sites in the case of a biventricular pacemaker). In fact, any change in the pacing regimen may be assigned as a mode in the pacing mode table.

The therapy time T_k determines the time that a mode change takes place and will typically be measured in terms of days, weeks or months. The evaluation period ΔT_k establishes the length of time over which heart rate

variability data is collected and will typically be measured in terms of hours.

Once the initialization steps reflected in block 20 have been programmed, the pacemaker will be set to the first mode M_0 (block 22) and the patient will continue to be paced in accordance with that first mode until the therapy time T_k has elapsed (block 24). At this time, the evaluation period timer ΔT_k is initialized to a starting point. With the evaluation period timer running, each RR interval (RR_i) is extracted from the ECG waveform (block 28) and repetitive calculations are made to measure heart rate variability as the absolute value of the difference between two successive RR intervals $|RR_i - RR_{i-1}|$. This is represented by block 30 in Figure 7. Each time a new HRV value is computed, it is stored in an appropriate bin of a histogram memory (block 32). A test is then made at decision block 34 to determine whether the evaluation period ΔT_k has expired. If not, control loops back via path 36 to the input of block 28 so that steps 28, 30 and 32 are repeated iteratively until the time interval ΔT_k has expired.

At that point, the histogram is effectively plotted (block 36). Next, either the 2D histogram footprint area or some other feature of the 2D histogram is calculated as a measure of HRV_k , i.e., the heart rate variability measure for the particular mode involved. While the 2D histogram footprint area has been determined to be a measure of $VO2_{max}$, other features of the 2D histogram may also be indicative of $VO2_{max}$. For example, the slope of the diagonal that is tangent to the base of the 2D plot is believed to be an indicator of HRV as well.

Irrespective of the approach used in deriving HRV_k , as represented by block 40, the next step in the algorithm is to compare the current HRV measure with that earlier derived relating to the immediately previous mode to determine whether HRV_k is greater than HRV_{k-1} . If it is, then the current mode is shown to have provided improved $VO2_{max}$ and the previous mode is discarded as an option.

However, had the current heart rate variability index been less than the index derived for the previous mode, then the current mode would be disregarded.

As indicated by decision block 42, a test is made to
5 determine whether all of the possible modes in the pacing mode table have been considered and, if not, the mode index is incremented (block 44) and control loops back over path 46 to the input of block 22 whereby the routine is repeated until all modes have been exercised.

10 We have determined, based upon patients' studies, that change in $VO_{2\max}$ correlates directly with change in heart rate variability and that information concerning the patient's exercise capacity can be derived from ECG signals. Moreover, the patient's exercise capacity can be
15 inferred from the SDANN index or, alternatively, from the area of the footprint of a two-dimensional histogram where heart rate variability is plotted against RR interval over a predetermined time interval.

The present invention allows the plotting of HRV
20 measures on a desired time scale and the resulting plot is deemed useful in assessing whether pacing therapy or drug therapy adjustments are beneficial. In Figure 8(a), there is shown a plot of the average weekly heart rate of a patient over a 52-week period with the vertical lines
25 passing through the average values indicating the range between the highest rate and the lowest rate for the week involved. Aligned with the plot of Figure 8(a) are the plots of Figures 8(b) and 8(c). Figure 8(b) shows a corresponding plot of heart rate variability as measured by the footprint area method. Figure 8(c) is a corresponding
30 plot of heart rate variability for the same patient as measured by the SDANN index.

The rise in heart rate variability between January and April indicates that the therapy then being applied
35 resulted in a beneficial increase in heart rate variability and, accordingly, an increase in peak VO_2 consumption. An apparent change in therapy in May had a negative result as

reflected by a decrease in HRV. Thus, it is apparent from the trending data plotted in Figures 8(b) or 8(c) that the efficacy of a particular therapy can be evaluated with periodic adjustments being made so as to optimize peak VO₂ consumption and, therefore, the patient's exercise capacity.

In a practical system implementing the present invention, the plots of Figures 8(a) through 8(c) may be displayed on a computer monitor or, alternatively, may be printed out as hard copy from a printer.

This invention has been described herein in considerable detail in order to comply with the patent statutes and to provide those skilled in the art with the information needed to apply the novel principles and to construct and use such specialized components as are required. However, it is to be understood that the invention can be carried out by specifically different equipment and devices, and that various modifications, both as to the equipment and operating procedures, can be accomplished without departing from the scope of the invention itself. For example, while the present invention has been described and illustrated in connection with patient therapy being carried out by electrical stimulation from an implantable pacemaker, it is also contemplated that the different therapy modes can be based on the administration of various drugs where such drugs have an influence on cardiac performance. Thus, the mode table can include a series of different drugs or the same drug but with differing dosages. Periodically, and in accordance with the entries in the therapy time table and the evaluation period table, the drug therapy mode would be changed and the effect on HRV, as measured by SDANN or a feature of the 2D histogram used to assess the efficacy of each mode.

What is claimed is:

CLAIMS

1. A method of indirectly assessing a patient's maximum oxygen uptake (VO_{2MAX}) comprising the steps of:

(a) sensing and recording RR intervals from ECG waveform of a patient over a 24-hour period;

(b) determining from the recording the average length of R-to-R intervals in 288 five-minute intervals; and

(c) computing the standard deviation of the 288 averages determined in step (b) to create a HRV index correlating with VO_{2MAX} for the patient.

2. A method of assessing the efficacy of a given mode of cardiac therapy on a patient's exercise capacity, comprising the steps of:

(a) applying cardiac therapy to the patient's heart in accordance with said given mode;

(b) recording ECG waveforms from the patient over a first predetermined time period;

(c) measuring the average length of R-to-R intervals in said waveforms during a plurality of predetermined segments of the first predetermined time period;

(d) computing the standard deviation of the plurality of said segment averages to create a HRV index;

(e) repeating steps (b)-(d) at a time subsequent to said first predetermined time; and

(f) comparing the HRV index computed in step (d) associated with ECG waveforms recorded at said first predetermined time with the HRV index computed in step (d) associated with the ECG waveforms recorded at said subsequent time to determine whether the given mode of therapy improves or degrades the patient's exercise capacity.

3. The method of Claim 2 and further including the step of:

(g) changing the mode of cardiac therapy so as to cause an increase in the HRV index computed in step (d)

associated with the ECG waveforms recorded at said subsequent time over the HRV index computed in step (d) associated with the ECG waveforms recorded at said first time.

5 4. The method as in any one of Claims 1-3 wherein the mode of cardiac therapy comprises a mode of electrical cardiac stimulation.

10 5. The method as in any one of Claims 1-3 wherein the mode of cardiac therapy comprises a mode of drug applications.

6. The method as in any one of Claims 1-3 and further including the step of creating a plot of the HRV index at fixed predetermined time intervals.

15 7. A method of optimizing a mode of therapy applied to a patient, comprising the steps of:

(a) measuring and recording ECG waveforms over a predetermined time interval at a first point in time;

20 (b) computing from said ECG waveforms the absolute value of the difference in the length of successive RR intervals;

(c) plotting a two-dimensional histogram of the values computed in step (b) vs. RR intervals;

(d) measuring the area subtended by the plot of step (c) as an indicator of a patient's exercise capacity;

25 (e) subsequently changing the mode of therapy applied to the patient;

(f) repeating steps (a) through (d) at a later time;

30 (g) plotting a value of the area measured in step (d) at the first point in time and at the later time to display trends in the patient's exercise capacity.

(h) comparing the area measured in step (d) at the first point in time to the area measured in step (d) at the later time to assess which area is the greater; and

35 (i) adjusting the mode of therapy to increase the patient's exercise capacity.

AMENDED CLAIMS

[received by the International Bureau on 19 February 2001 (19.02.01);
original claims 1-7 replaced by new claims 1-6 (2 pages)]

1. A method of indirectly assessing a patient's maximum oxygen uptake (VO_{2MAX}) comprising the steps of:
 - (a) sensing and recording RR intervals from ECG waveform of a patient over a 24-hour period;
 - (b) determining from the recording the average length of R-to-R intervals in 288 five-minute intervals; and
 - (c) computing the standard deviation of the 288 averages determined in step (b) to create a HRV index correlating with VO_{2MAX} for the patient.
2. A method of assessing the efficacy of a given mode of cardiac therapy on a patient's exercise capacity, comprising the steps of:
 - (a) recording ECG waveforms from the patient over a first predetermined time period during which a first mode of therapy is involved;
 - (b) measuring the average length of R-to-R intervals in said waveforms during a plurality of predetermined segments of the first predetermined time period;
 - (c) computing the standard deviation of the plurality of said segment averages to create a HRV index;
 - (d) repeating steps (b)-(d) at a time subsequent to said first predetermined time; and
 - (e) comparing the HRV index computed in step (d) associated with ECG waveforms recorded at said first predetermined time with the HRV index computed in step (d) associated with the ECG waveforms recorded at said subsequent time to determine whether the first mode of therapy improves or degrades the patient's exercise capacity.
3. The method as in Claim 2 wherein the mode of cardiac therapy comprises a mode of electrical cardiac stimulation.
4. The method as in Claim 2 wherein the mode of cardiac therapy comprises a mode of drug applications.
5. The method as in Claims 1 or 2 and further including the step of creating a plot of the HRV index at fixed predetermined time intervals.

6. A method of indirectly assessing a patient's maximum oxygen uptake (VO_{2MAX}) comprising the steps of:
- (a) sensing and recording RR intervals from an ECG waveform of a patient;
 - (b) recording said RR intervals over a predetermined time period;
- and
- (c) calculating a value relating RR intervals to VO_{2MAX} .

STATEMENT UNDER ARTICLE 19(1)

The replacement pages 10 and 11 containing claims 1-6 are intended to replace the originally submitted pages 10 and 11 containing claims 1-7. The claims contain modifications intended to clarify and more concisely describe the invention, including differences from references cited. These claims are consistent with the claims of the application to which this application claims priority.

The newly presented amended claims and new claim 6 are believed to be within the scope of the invention described in the specification and, in addition to capturing the inventive concept more concisely, the amended claims enhance the definition over the reference cited in category "X" in the International Search Report.

The International Search Authority found claims 2-7 unsearchable under Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy. Claims 1, 2, 4-6 have been amended and claims 3 and 7 have been cancelled. New claim 6 has been added. These changes are believed to obviate the objection based on Rule 39.1(iv). These claims are no longer directed to a method of treating a human by surgery or therapy, but instead to a method of assessing the outcome of a change in therapy.

Claim 1 has been amended at line 2, by changing "update" to -- uptake -- to correct a typographical error. Claims 4-6 have been amended to claim their dependency.

PATIENT DATA COLLECTION SCHEDULE FOR 24 HOUR HRV

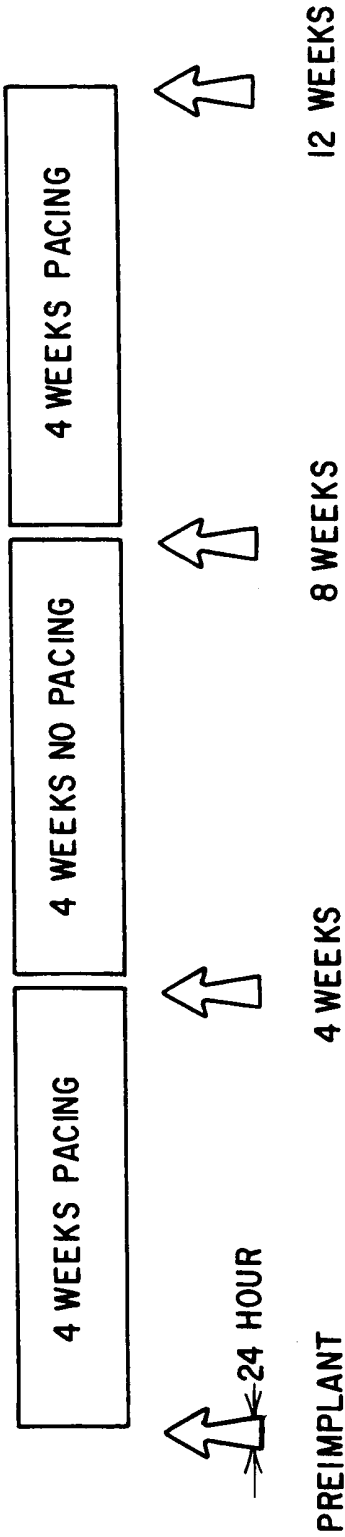


FIG. 1

SDANN INDEX AND PEAK VO₂ TEND TO INCREASE WITH PACING THERAPY

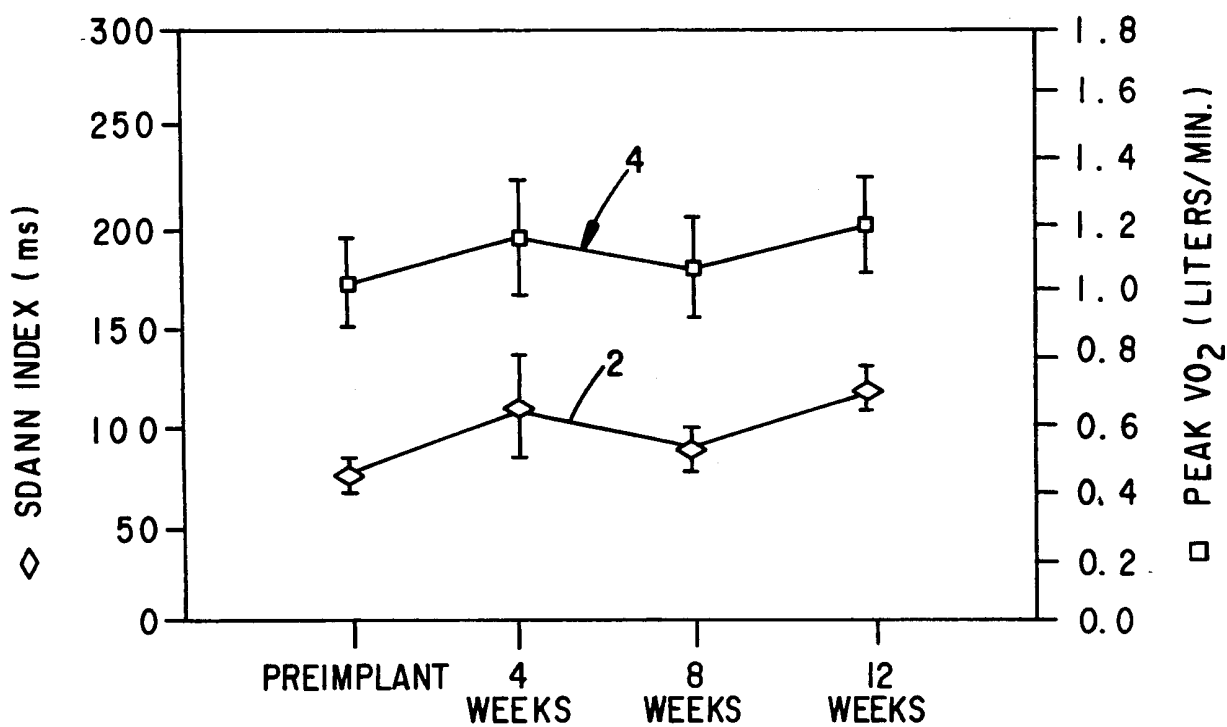


FIG. 2

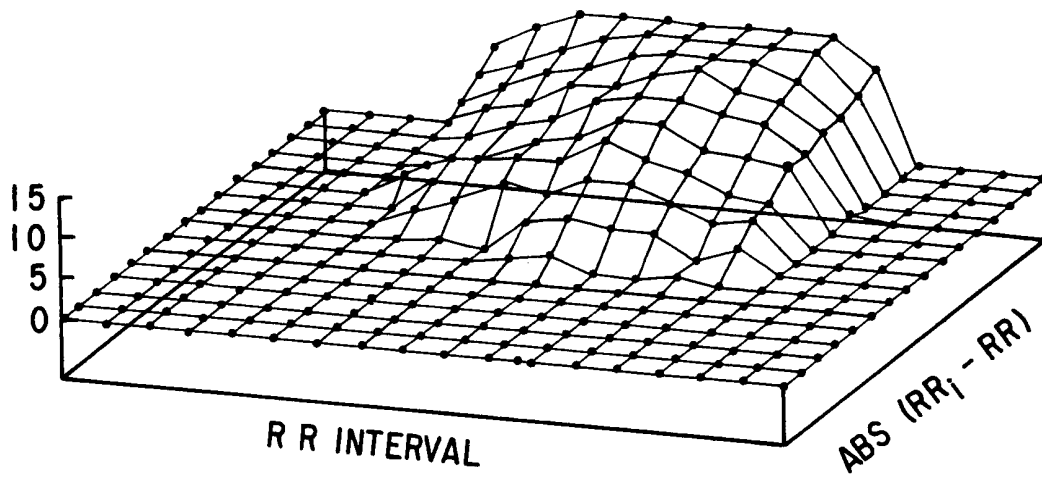


FIG. 3

THE HEART RATE VARIABILITY FOOTPRINT

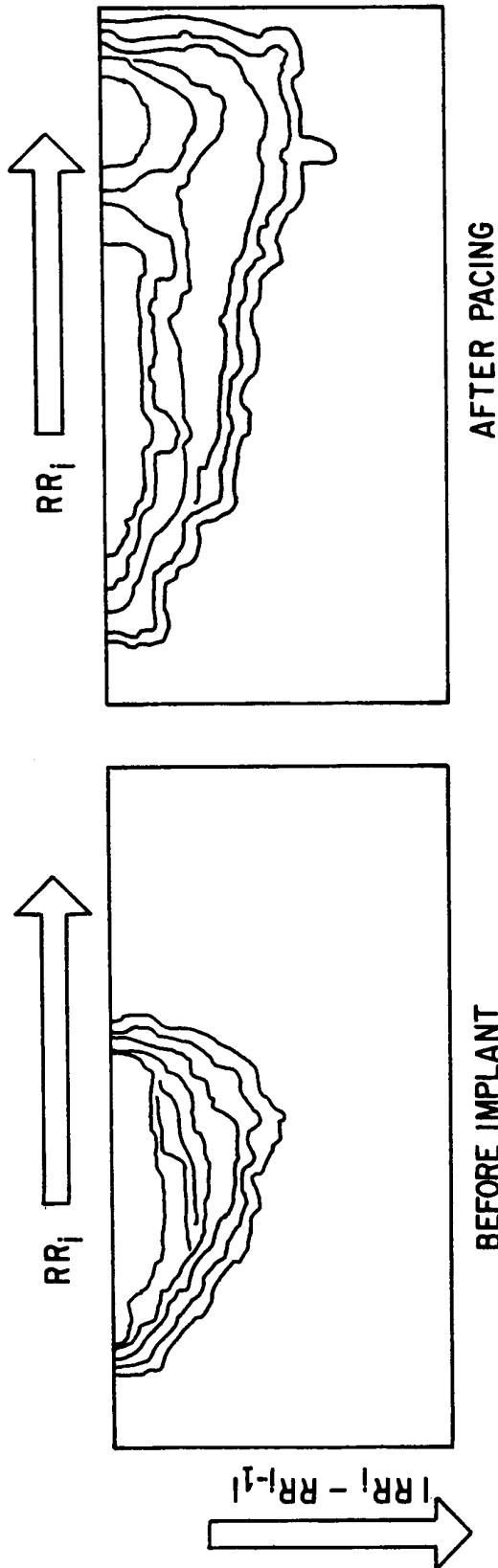


FIG. 5

FIG. 4

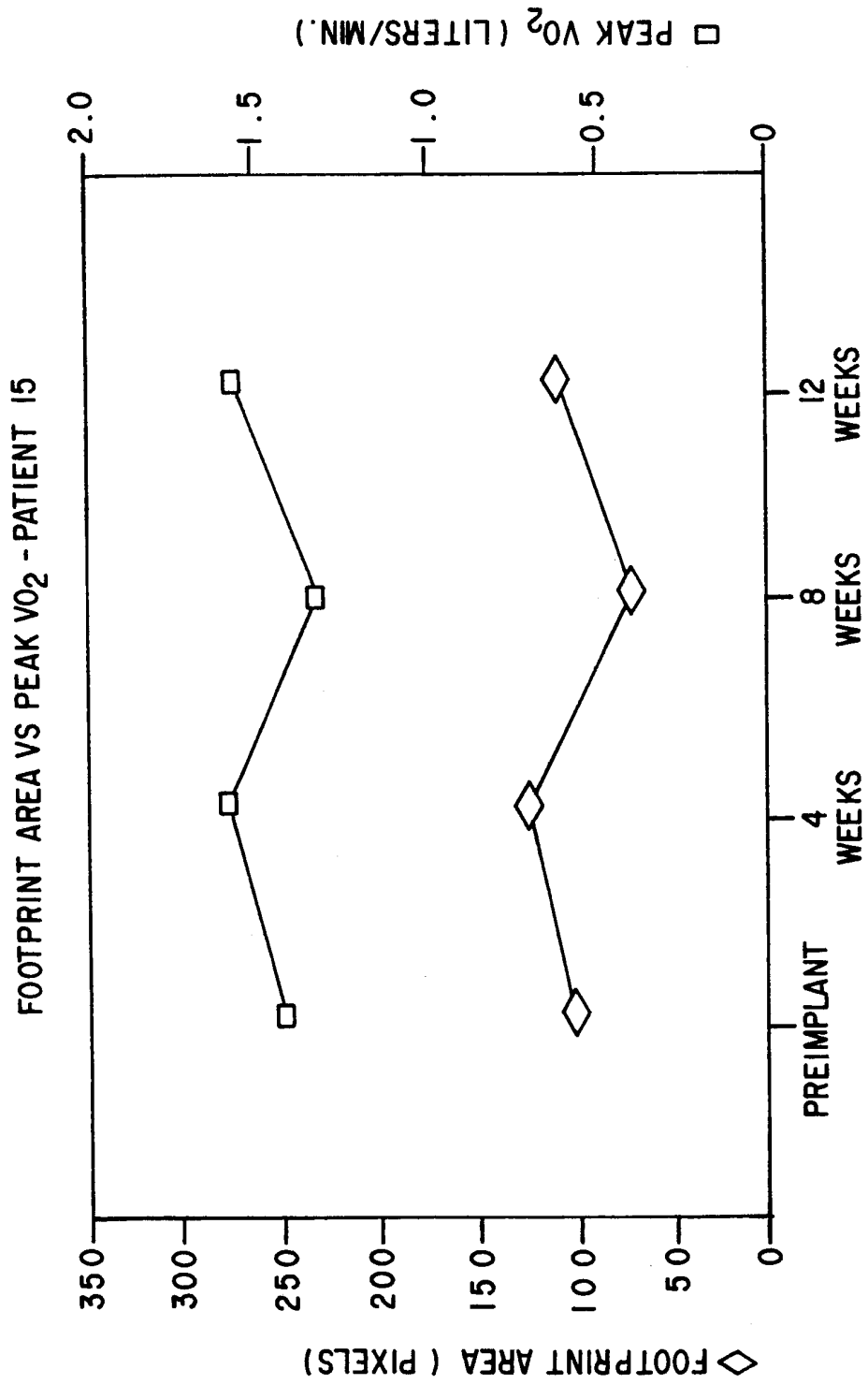


FIG. 6

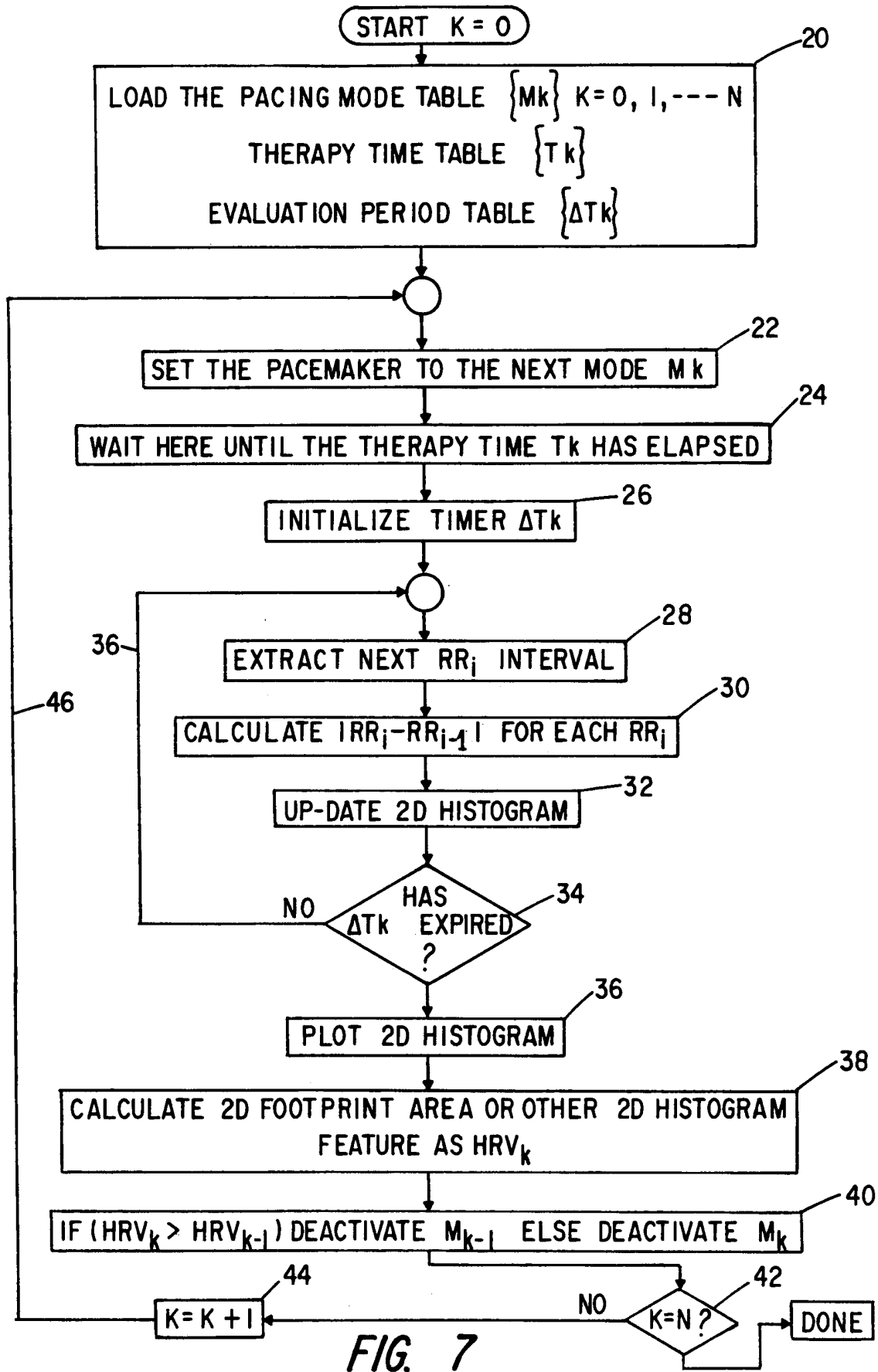


FIG. 7

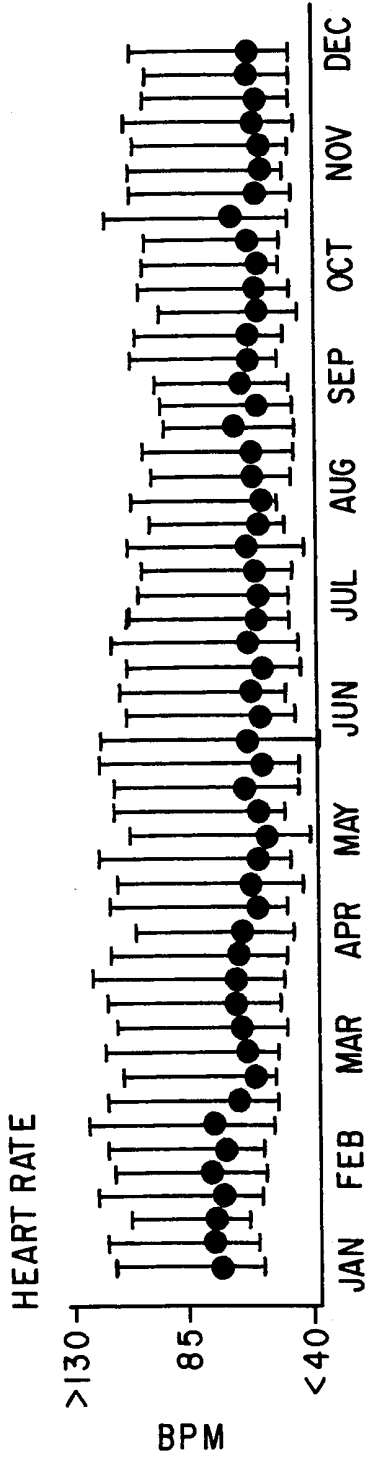


FIG. 8(a)

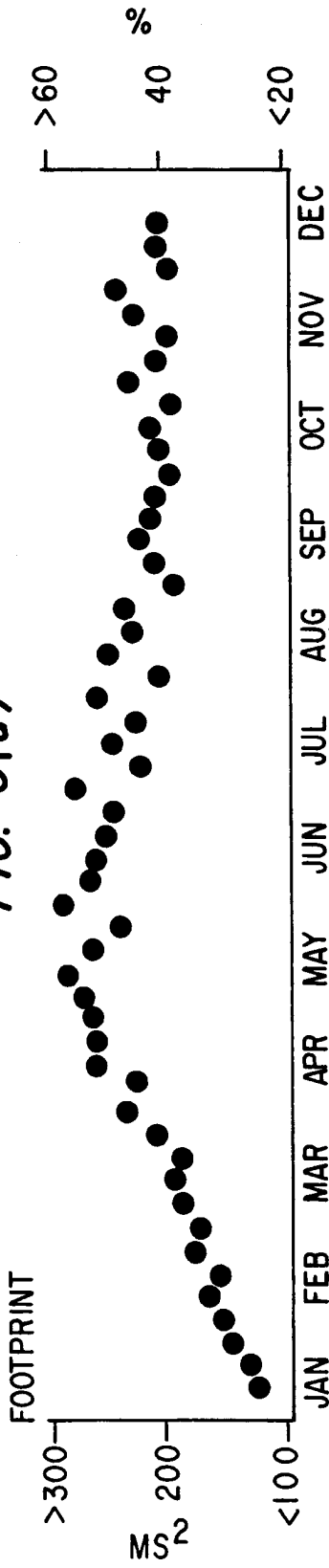


FIG. 8(b)

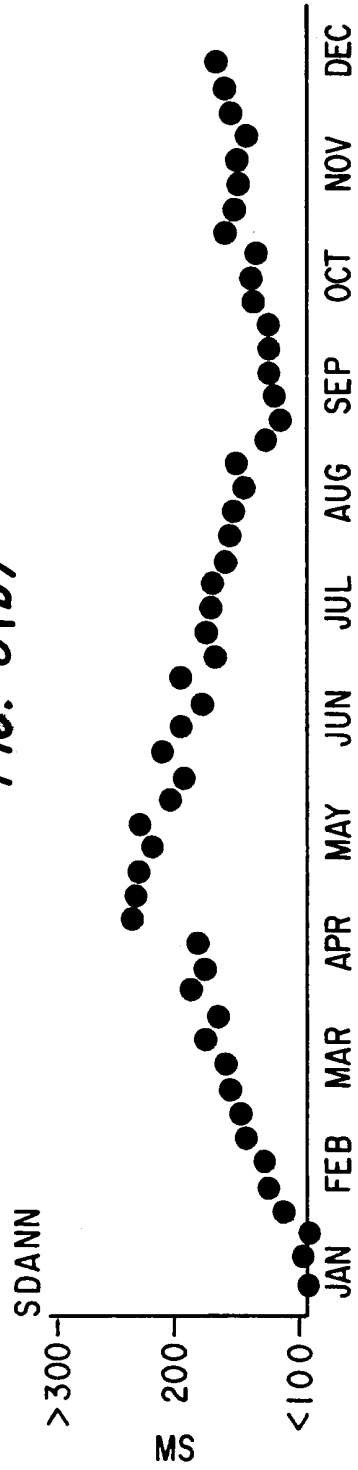


FIG. 8(c)

INTERNATIONAL SEARCH REPORT

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| International Application No PCT/US 00/26334 |
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A. CLASSIFICATION OF SUBJECT MATTER
 IPC 7 A61B5/22 A61N1/37 A61N1/372

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)
 IPC 7 A61N 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, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|--|-----------------------|
| P, X | WO 99 64108 A (CARDIAC PACEMAKERS, INC) 16 December 1999 (1999-12-16) the whole document --- | 1 |
| Y | US 5 603 331 A (J. P. HEEMELS ET AL) 18 February 1997 (1997-02-18) cited in the application the whole document --- | 1 |
| Y | EP 0 829 226 A (SEIKO EPSON CORPORATION) 18 March 1998 (1998-03-18) page 3, line 41 -page 7, line 16 --- | 1 |
| A | US 5 749 900 A (E. A. SCHROEPEL ET AL) 12 May 1998 (1998-05-12) column 1, line 56 -column 7, line 16 --- -/-- | 1 |

Further documents are listed in the continuation of box C. Patent family members are listed in annex.

° Special categories of cited documents :

| | |
|--|--|
| <p>*A* document defining the general state of the art which is not considered to be of particular relevance</p> <p>*E* earlier document but published on or after the international filing date</p> <p>*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)</p> <p>*O* document referring to an oral disclosure, use, exhibition or other means</p> <p>*P* document published prior to the international filing date but later than the priority date claimed</p> | <p>*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</p> <p>*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</p> <p>*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.</p> <p>*&* document member of the same patent family</p> |
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| Date of the actual completion of the international search 12 January 2001 | Date of mailing of the international search report 30/01/2001 |
| Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016 | Authorized officer Geffen, N |

INTERNATIONAL SEARCH REPORT

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| International Application No PCT/US 00/26334 |
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| 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 96 02185 A (B. GOLOSARSKY ET AL) 1 February 1996 (1996-02-01) page 2, line 1 - line 22 page 5, line 1 -page 14, line 10 ----- | 1 |
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Information on patent family members

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|---|

| Patent document cited in search report | A | Publication date | Patent family member(s) | Publication date |
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| | | | | |
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