Applicant: CORVENTIS INC.
IN Application No.: 2845/CHENP/2010 **Amended Claims (Markup Copy)**

~~WHAT IS CLAIMED IS:~~

WE CLAIM:

~~1. A method of detecting an impending cardiac decompensation of a patient, the method comprising:~~

~~measuring at least two of an electrocardiogram signal of the patient, a hydration signal of the patient, a respiration signal of the patient or an activity signal of the patient; and~~

~~combining the at least two of the electrocardiogram signal, the hydration signal, the respiration signal or the activity signal to detect the impending cardiac decompensation.~~

~~2. The method of claim 1 wherein the at least two comprise at least three of the electrocardiogram signal, the hydration signal, the respiration signal or the activity signal and the at least three are measured and combined to detect the impending cardiac decompensation.~~

~~3. The method of claim 2 wherein the at least three comprise at least four of the electrocardiogram signal, the hydration signal, the respiration signal or the activity signal and the at least four are measured and combined to detect the impending cardiac decompensation.~~

~~4. The method of claim 1 wherein the at least two of the electrocardiogram signal, the hydration signal, the respiration signal or the activity signal are used simultaneously to determine impending cardiac decompensation.~~

~~5. The method of claim 1 wherein combining comprises using the at least two of the electrocardiogram signal, the hydration signal, the respiration signal or the activity signal to look up a value in a previously existing array.~~

~~6. The method of claim 1 wherein combining comprises at least one of adding, subtracting, multiplying, scaling or dividing the at least two of the electrocardiogram signal, the hydration signal, the respiration signal or the activity signal.~~

~~7. The method of claim 1 wherein the at least two of the electrocardiogram signal, the hydration signal, the respiration signal or the activity signal are combined with at least one of a weighted combination, a tiered combination or a logic gated combination, a time weighted combination or a rate of change.~~

~~8. The method of claim I wherein a flag status is determined in response to the at least two of the electrocardiogram signal, the hydration signal, the respiration signal or the activity signal.~~

~~9. The method of claim 8 wherein the flag status is determined in response to a change in the at least two of the electrocardiogram signal, the hydration signal, the respiration signal or the activity signal.~~

~~10. The method of claim 8 wherein additional signal measurements of the patient are made in response to the flag status.~~

~~11. The method of claim 1 wherein the at least two of the electrocardiogram signal, the hydration signal, the respiration signal or the activity signal are combined in response to a time of day.~~

~~12. The method of claim I wherein the at least two of the electrocardiogram signal, the hydration signal, the respiration signal or the activity signal comprise at least one of a derived signal, a time averaged signal, a filtered signal or a raw signal.~~

~~13. The method of claim 1 further comprising determining baseline values of the patient for the at least two of the electrocardiogram signal, the hydration signal, the respiration signal or the activity signal and wherein the at least two of the electrocardiogram signal, the hydration signal, the respiration signal or the activity signal signals comprise changes from the baseline values.~~

~~14. The method of claim 1 wherein the at least two of the electrocardiogram signal, the hydration signal, the respiration signal or the activity signal comprise differences from baseline values of a patient population and wherein the impending decompensation is detected in response to the differences from the baseline value of the patient population.~~

~~15. The method of claim 1 wherein the hydration signal comprises an impedance signal and the activity signal comprise an accelerometer signal.~~

~~16. The method of claim 1 wherein the activity signal comprise an accelerometer signal to determine a posture of the patient.~~

~~17 The method of claim 16 wherein the accelerometer signal comprises a three dimensional inclination signal to determine a three dimensional orientation of the patient.~~

~~18. The method of claim 1 wherein a temperature signal is combined with the at least two of the electrocardiogram signal, the hydration signal, the respiration signal or the activity signal to detect the impending cardiac decompensation.~~

~~19. The method of claim 1 further comprising transmitting the at least two of the electrocardiogram signal, the hydration signal, the respiration signal or the activity signal to a remote site where the at least two of the electrocardiogram signal, the hydration signal, the respiration signal or the activity signal are combined to detect the impending cardiac decompensation.~~

~~20. The method of claim 1 further comprising transmitting instructions from a remote site to a processor supported with the patient, and wherein the at least two of the electrocardiogram signal, the hydration signal, the respiration signal or the activity signal are combined with the processor in response to the instructions to detect the impending cardiac decompensation.~~

~~2~~1. A system to detect impending cardiac decompensation of a patient, the system comprising:

circuitry (130, 134, 136, 138, 152) to measure ~~at least two of an electrocardiogram signal of the patient, a hydration signal of~~ an impedance associated with the patient~~, or an activity signal~~ and a temperature of a skin of the patient; and

a processor system (100, 102, 106, or 146) comprising a tangible medium in communication with the circuitry (130, 134, 136, 138, 152), the processor system (100, 102, 106, or 146) configured to ~~combine the at least two of the electrocardiogram signal,~~ calculate a hydration measurement based on the measured impedance and corrects the calculated hydration measurements based on the measured skin temperature of the patient, wherein the processor system utilizes the corrected hydration ~~signal, the respiration signal or the activity signal~~ measurement to detect the impending cardiac decompensation of the patient.

Commented [M1]: The Examiner, in FER under "**NON-PATENTABILITY"** has objected that the claims fall under section 3(i) of The Patents Act.
As per Indian Patent law, claims relating to "***any process for the medicinal, surgical, curative, prophylactic diagnostic, therapeutic or other treatment of human beings or any process for a similar treatment of animals to render them free of disease or to increase their economic value or that of their products."*** fall under Sections 3(i) are considered as non-patentable subject matter.

Therefore, to overcome this objection, we have to cancelled method claims 1-20.

Commented [M2]: Support can be found at least in paragraph [0064]

~~22~~2. The system ~~of claim 21~~as claimed in claim 1, wherein the processor system (100, 102, 106, or 146) comprises a least one processor a location remote from the patient configured to detect the decompensation.

~~23~~3. The system ~~of claim 21~~ as claimed in claim 1, wherein the processor system (100, 102, 106, or 146), supported with the patient, receives instructions transmitted from a remote site and ~~combines the at least two~~ calculates the hydration measurement in response to the instructions to detect the impending cardiac decompensation.

~~24~~4. The system ~~of claim 21~~ as claimed in claim 1, wherein the ~~at least two comprise at least three of the electrocardiogram signal, the hydration signal, the respiration signal or the activity signal and the at least three are measured and combined~~ circuity (130, 134, 136, 138, 152) measures one or more of an electrocardiogram signal of the patient, a respiration signal, and an activity signal and combines the one or more measured signals with the corrected hydration measurement to detect the impending cardiac decompensation.

~~25~~5. The system ~~of claim 24~~ as claimed in claim 4, wherein ~~the at least three comprise at least four~~ two or more of the electrocardiogram signal, the hydration signal, the respiration signal or the activity signal ~~and the at least four~~ are measured and combined with the corrected hydration measurement to detect the impending cardiac decompensation.

~~26~~6. The system ~~of claim 21~~ as claimed in claim 4, wherein the processor system (100, 102, 106, or 146) simultaneously uses the ~~at least two~~ one or more of the electrocardiogram signal, ~~the hydration signal,~~ the respiration signal or the activity signal in combination with the corrected hydration measurement to determine impending cardiac decompensation.

~~27. The system of claim 21 wherein combining comprises the processor system using the at least two of the electrocardiogram signal, the hydration signal, the respiration signal or the activity signal to look up a value in a previously existing array.~~

~~28. The system of claim 21 wherein combining comprises at least one of adding, subtracting, multiplying, scaling or dividing the at least two of the electrocardiogram signal, the hydration signal, the respiration signal or the activity signal.~~

~~29. The system of claim 21 wherein the processor system combines the at least two of the electrocardiogram signal, the hydration signal, the respiration signal or the activity signal with at least one of a weighted combination, a tiered combination or a logic gated combination, a time weighted combination or a rate of change.~~

~~30. The system of claim 21 wherein the processor system determines a flag status in response to the at least two of the electrocardiogram signal, the hydration signal, the respiration signal or the activity signal.~~

~~31. The system of claim 28 wherein the processor system determines the flag status in response to a change in the at least two of the electrocardiogram signal, the hydration signal, the respiration signal or the activity signal.~~

~~32. The system of claim 28 wherein the processor system affects the circuitry to make additional signal measurements of the patient in response to the flag status.~~

~~33~~7. The system ~~of claim 21~~ as claimed in claim 4, wherein the processor system (100, 102, 106, or 146) combines the ~~at least two~~ one or more of the electrocardiogram signal, ~~the hydration signal,~~ the respiration signal or the activity signal with the corrected hydration measurement in response to a time of day.

~~34. The system of claim 21 wherein the at least two of the electrocardiogram signal, the hydration signal, the respiration signal or the activity signal comprise at least one of a derived signal, a time averaged signal, a filtered signal or a raw signal.~~

~~35. The system of claim 21 wherein the processor determines baseline values of the patient for the at least two of the electrocardiogram signal, the hydration signal, the respiration signal or the activity signal and wherein the at least two of the electrocardiogram signal, the hydration signal, the respiration signal or the activity signal signals comprise changes from the baseline values.~~

~~36. The system of claim 21 wherein the at least two of the electrocardiogram signal, the hydration signal, the respiration signal or the activity signal comprise differences from baseline~~

~~values of a patient population and wherein the impending decompensation is detected in response to the differences from the baseline value of the patient population.~~

~~37. The system of claim 21 wherein the hydration signal comprises an impedance signal and the activity signal comprise an accelerometer signal.~~

~~38~~8. The system ~~of claim 21~~ as claimed in claim 4, wherein the activity signal comprises an accelerometer signal to determine a posture of the patient.

~~39~~ 9 The system ~~of claim 36~~ as claimed in claim 8, wherein the accelerometer signal comprises a three dimensional inclination signal to determine a three dimensional orientation of the patient.

~~40. The system of claim 21 wherein the processor system combines a temperature signal with the at least two of the electrocardiogram signal, the hydration signal, the respiration signal or the activity signal to detect the impending cardiac decompensation.~~

~~41~~10. The system ~~of claim 21~~ as claimed in claim 4, wherein the processor transmits the ~~at least two~~ one or more of the electrocardiogram signal, ~~the hydration signal,~~ the respiration signal or the activity signal to a remote site where the ~~at least two~~ one or more of the electrocardiogram signal, ~~the hydration signal,~~ the respiration signal or the activity signal are combined with the corrected hydration signal to detect the impending cardiac decompensation.

~~42~~11. The system ~~of claim 21~~ as claimed in claim 4, ~~further~~ comprising transmitting instructions from a remote site to a processor supported with the patient, and wherein the processor combines ~~at least two~~ the one or more of the electrocardiogram signal, the hydration signal, the respiration signal or the activity signal with the corrected hydration signal in response to the instructions to detect the impending cardiac decompensation.

12. The system as claimed in claim 1, wherein the circuitry (130, 134, 136, 138, 152) places a voltage and/or current at one or more of electrodes connected to the circuitry (130, 134, 136, 138, 152) having a frequency between 0.5 kHz and about 20 kHz such that the hydration measurement corresponds to the extracellular fluid of the patient.

Commented [M3]: Support can be found at least in paragraph [0070]

13.The system as claimed in claim 1, wherein the processor system (100, 102, 106, or 146) corrects the calculated hydration measurement by lowering the hydration measurement in response to an increase in measured skin temperature.

Commented [M4]: Support can be found at least in paragraph [0064]

14. The system as claimed in claim 1, wherein the processor system (100, 102, 106, or 146) corrects the calculated hydration measurement by increasing the hydration measurement in response to a decrease in the measured skin temperature.

Commented [M5]: Support can be found at least in paragraph [0064]

15. The system as claimed in claim 1, wherein the processor system (100, 102, 106, or 146) corrects the calculated hydration measurement such that the hydration measurement remains substantially unchanged when the measured impedance decreases and the skin temperature increases.

Commented [M6]: Support can be found at least in paragraph [0064]

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Via epoline

Date: 9 December 2014
Our ref: 226577 TOD/ABN

Appl./Reg.No.: 08830067.8
Applicant: Corventis, Inc.

Dear Sirs,

In response to the communication pursuant to Rules 70(2) and 70a(2) EPC dated 1 July 2014 with regard to the above referenced patent application, it is hereby indicated that the applicant wishes to proceed further with the European patent application.

With regard to the deficiencies noted in the European Search Report, the applicant wishes to present arguments and amended claims as specified below.

Amendments
The present set of claims is to be replaced by the attached amended set of claims.

In the amended set of claims, the method claims 1-7 have been deleted. The remaining claims have been renumbered and the claim referenced adapted thereto.

The amended system claim 1 (previous claim 8) has been amended by limiting to a circuitry to measure an electrocardiogram signal and a hydration signal of the patient. In the amended system claim 1 (previous claim 8), the processor system has accordingly been amended to be configured to combine the electrocardiogram signal and the hydration signal. The support for these amendments is found in previous claim 8 and in paragraphs [0085] and [0086]. The amended claim 1 (previous claim 8) has also been divided in a preamble and a characterising portion.

In amended claim 2 (previous claim 9), the formulation has been improved by amending to "a location".

Amended claims 3-8 (previous claims 10-15) have been amended to be consistent with the amendment of amended claim 1. The support for these amendments is found in the previous corresponding claims. In addition, the support for the amendment of claim 4 (previous claim 11) is also found in previous claim 8. In addition, the support for the amendment of claim 6 (previous claim 13) is also found in previous claim 4 and in paragraphs [0085], [0086] and [0092]. In addition, the support for the amendment of claim 8 (previous claim 15) is also found in [0092].

In the amended set of claims, reference numerals have been added to the claims.

The present page 2 of the description is to be replaced by the attached amended page 2 and the attached new page 2a is to be added between page 2 and 3. On page 2a a disclosure of the cited documents D1 and D2 has been added.

Novelty

D1 does not show measurement of a hydration signal associated with a patient. Consequently, the present invention as defined in amended claim 1 is novel in view of D1.

D2 does not show any combination of an electrocardiogram signal and a hydration signal. In paragraph [0108] of D2 it is discussed that a physiologic monitoring system as described in D2 may be employed in a long-term patient-administered method. In connection thereto it is mentioned that detected physiologic parameters may be derived from measured data and that "heart failure progression can be estimated using fluid load impedance". However, this is disclosed in isolation. Consequently, the present invention as defined in amended claim 1 is novel in view of D2.

In light of the above, the invention as defined in the independent claim 1 is novel.

Inventive step

The present invention is concerned with how to better detect impending cardiac decompensation in patients. As described in the background, electrocardiogram signals have previously been used to detect cardiac decompensation, but are not sufficiently reliable. The claimed invention improves the ability to reliable detect impending cardiac decompensations by combining electrocardiogram measurements with hydration measurements. For example, paragraph [0085] of the present application discloses a table that relates ECG heart rate values to hydration values. Amended claim 1 has been amended to recite a system that detects impending cardiac decompensation based on a combination of a measured electrocardiogram signal and a measured hydration signal. The combination of the electrocardiogram signal and hydration signal is utilized to better predict an impending cardiac decompensation.

Considering D1 as closest prior art, a difference between the present invention as defined in claim 1 and D1 is that an electrocardiogram signal and a hydration signal of a patient are combined to detect impending cardiac decompensation. As explained above an effect of combining an electrocardiogram signal and a hydration signal is better prediction of impending cardiac decompensation.

As described above, D1 does not disclose measurement of a hydration signal. Instead, D1 relies on nocturnal breathing habits in isolation to detect worsening heart failure. Thereby, a skilled person finds no guidance in D1 to combine an electrocardiogram signal and a hydration signal. To the contrary, a skilled person would be guided away from the solution of the present invention and instead use nocturnal breathing habits. Thus, a skilled person facing the problem of improve predictability of impending cardiac decompensation would not be able to be guided by D1 and arrive at the present invention. Consequently, the present invention as defined in claim 1 involves an inventive step in view of D1.

As also described above, D2 does not disclose combination of an electrocardiogram signal and a hydration signal. D2 discloses that "heart failure progression can be estimated using fluid load impedance" in isolation. D2 does not teach or suggest that predictability of impending cardiac decompensation can be improved by combining an electrocardiogram signal and a hydration signal. A skilled person facing the problem of improving predictability of impending cardiac decompensation would not be able to modify D1 guided by D2 and arrive at the present invention. Consequently, the present invention as defined in claim 1 involves an inventive step in view of the combination of D1 and D2.

Therefore, the invention as defined in the independent claim 1 involves an inventive step.

Objection under Art. 53(c)
Since previous claims 1-7 have been deleted, the objection related to Art. 53(c) EPC is no longer relevant.

Concluding remarks
Grant of a European Patent based on the amended claims is requested.

Merely as a precaution, in case the Examining Division should contemplate refusal of the application, oral proceedings pursuant to Art. 116 EPC are hereby requested.

If it is deemed that it might advance prosecution, the Examining Division is kindly invited to contact the undersigned representative by telephone.

Yours faithfully
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Encl. Amended claims (marked and clean)
Amended page 2
New page 2a

The examination is being carried out on the **following application documents**:

Description, Pages

1-23 as published

Claims, Numbers

1-15 filed with entry into the regional phase before the EPO

Drawings, Sheets

1/10-10/10 as published

1 Reference is made to **the following documents**; the numbering will be adhered to in the rest of the procedure.

D1 PINNA G D ET AL: "Nocturnal periodic breathing is an independent predictor of cardiac death and multiple hospital admissions in Heart failure", COMPUTERS IN CARDIOLOGY, 2006, IEEE, PISCATAWAY, NJ, USA, 17 September 2006 (2006-09-17), pages 837-840, XP031249101, ISBN: 978-1-4244-2532-7

D2 WO 2007/103835 A2 (PHYSIOWAVE INC [US]; KOVACS GREGORY T A [US]) 13 September 2007 (2007-09-13)

Exceptions to Patentability (Article 53 EPC)

2 The present application does not meet the requirements of Article 52(1) EPC because the subject-matter of **independent method claim 1** is excluded from patentability according to Article 53(c) EPC.

The subject-matter of **claim 1** comprises a diagnostic method, which is excluded from patentability according to Article 53(c) EPC.

According to the Guidelines G-II. 4.2.1.3 it must be established, if a claim consists of method steps relating to four necessary phases in order to be a diagnostic method (see also decision G 1/04), whereby the first three phases must be performed on a human body, only if they correspond to technical steps which are not purely intellectual:

(i) **Measurement:** Measuring certain signals of a patient is a technical step performed on a human body.

(ii) **Comparing:** In order to "detect impending cardiac decompensation" by "combining" signals the step of comparing a final result of that combination with a standard outcome is an implicit method step of claim 1. It is non-technical and needs not to be checked for performance on a human body.

(iii) **Deviation:** A "cardiac decompensation" may only be detected, if there is a difference between the final result and a standard outcome, rendering this non-technical method step implicit to claim 1.

(iv) **Diagnosis:** The act of detecting "impending cardiac decompensation" is a diagnosis "in stricto sensu" (see Guidelines).

All four necessary phases are at least implicitly present in **claim 1** and they are performed on a human body as far as they are technical.

Novelty (Article 54(1) and (2) EPC)

3 Furthermore, notwithstanding the above-mentioned objection, the subject-matter of **claims 1-3, 5, 8, 11, 12 and 13** is not new within the meaning of Article 54(1) and (2) EPC, and the requirements of Article 52(1) EPC are therefore not met.

3.1 With respect to **independent method claim 1** document **D1** discloses:

A method (abstract) of detecting an impending cardiac decompensation of a patient (p. 840, left col., l. 17-22: "HF...early detection"), the method comprising:
measuring (p. 837, right col., l. 24: "cardiorespiratory recording"), using external patches (p. 837, right col., l. 30: "ECG electrodes"), at least two of an electrocardiogram signal (p. 837, right col., l. 31: "ECG signal") of the patient, a hydration signal of the patient, a respiration signal (p. 837, right col., l. 31-32: "respiratory signal") of the patient or an activity signal (p. 837, right col., l. 33: "body movement and position sensors") of the patient; and
combining (p. 838, left col., l. 33-34: "as indicated by the body position

signal"; p. 838, right col., l. 2: "adjusting factors") the at least two of the electrocardiogram signal (p. 838, right col., l. 1: "heart rate"), the hydration signal, the respiration signal (p. 838, left col., l. 28-29: "indexes of...breathing disorders") or the activity signal (tab. 2: "resting heart rate") to detect the impending cardiac decompensation (p. 840, left col., l. 17-22: "HF...early detection").

3.2 **Independent system claim 8** relates to similar subject-matter as independent method claim 1 with the additional features of "circuitry" and "a processor system". In addition to the features of claim 1, as discussed above (see paragraph 4.1), document **D1** discloses the "circuitry...to measure" (p. 837, right col., l. 26-27: "Holter-style 24-hour solid-state portable device") and a "processor system" (p. 838, left col., l. 3: "dedicated software package"; fig. 1: "printout...signal analysis module"; directly and unambiguously derivable from "software" and "signal analysis") for performing the corresponding methods is implied. Hence, the **independent system claim 8** is not new.

3.3 The additional subject-matter of **dependent claims 2, 3, 5, 11, 12 and 13** is also disclosed in **D1**:

claims 2, 3, 5, 11, 12, 13: p. 838, left col., l. 33-34: "as indicated by the body position signal"; p. 838, right col., l. 1-2: "heart rate...adjusting factors"; p. 840, left col., l. 17-22: "HF...early detection"

Inventive Step (Article 56 EPC)

4 Furthermore, notwithstanding the above-mentioned objection, the subject-matter of **dependent claims 4, 6, 7, 9, 10, 14 and 15** does not involve an inventive step within the meaning of Article 56 EPC, and the requirements of Article 52(1) EPC are therefore not met.

4.1 Comparing calculated parameters with previously stored values is a straightforward step in any kind of automatized decision process, rendering the subject-matter of **claim 4** not inventive.

4.2 Updating a "flag status" (**claims 6, 14**) and comparing measurements to "baseline values" (**claim 7**) are obvious steps the skilled person would perform without involving an inventive step, see document **D2** (par. 86: "condition indicators...condition-detection flag"; par. 109: "comparing such measured parameters to pretreatment baseline data") for "Physiologic Monitoring Systems And Methods" (title) implementing both features.

4.3 Receiving and analyzing "remote" data (**claim 9**), and sending "instructions" to a personal monitoring device (**claim 10**) are straightforward options, see also document **D2** using an "initialization console 260" for "the initialization and physiologic data download steps" (par. 69) and "Physiologic Monitor...Configuration" (fig. 6-B).

4.4 With respect to **dependent system claim 15** document **D1** implies the calculation of differences between measured signals and a larger number of data sets (p. 840, left col., l. 10: "large sample of HF patients") recorded from patients with well-known outcome in order to create classifiers (figs. 2, 3) by combining the signals for regression analysis (tabs. 2-5). The regression result for new signals appears to be a specific type of "difference from the baseline values" as is also suggested by pars. 80 and 86 of the description ("a patient population") of the present application. Moreover, also document **D2** discloses the comparison of signals to "predetermined ranges" (par. 58). In summary **claim 15** results from an obvious combination of features in **D1** and **D2**.

Further remarks

5 To meet the requirements of Rule 42(1)(b) EPC, documents **D1 and D2** should be identified in the description and the relevant background art disclosed therein should be briefly discussed.

6 It is not at present apparent which part of the application could serve as a basis for a new, allowable claim. Should the applicant nevertheless regard some particular matter as patentable an independent claim including such matter should be filed taking account of Rules 43(1) and 43(7) EPC.

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SUPPLEMENTARY EUROPEAN SEARCH REPORT

Application Number
EP 08 83 0067

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (IPC)
X	PINNA G D ET AL: "Nocturnal periodic breathing is an independent predictor of cardiac death and multiple hospital admissions in Heart failure", COMPUTERS IN CARDIOLOGY, 2006, IEEE, PISCATAWAY, NJ, USA, 17 September 2006 (2006-09-17), pages 837-840, XP031249101, ISBN: 978-1-4244-2532-7	1-5,8, 11-13	INV. A61B5/00 G06F19/00 A61B5/0205 A61B5/0408 A61B5/024 A61B5/0452 A61B5/053 A61B5/0404
Y	* page 837, right-hand column, lines 24, 26, 27, 30-33 * * page 838, left-hand column, lines 3, 28, 29, 33, 34 * * page 838, right-hand column, lines 1, 2 * * page 840, left-hand column, lines 10, 17-22 * * figures 1-3 * * tables 2-5 * * abstract *	6,7,9, 10,14,15	ADD. A61B5/08
Y	WO 2007/103835 A2 (PHYSIOWAVE INC [US]; KOVACS GREGORY T A [US]) 13 September 2007 (2007-09-13) * paragraphs [0058], [0069], [0086], [0109] * * figures 6-B * * title *	6,7,9, 10,14,15	TECHNICAL FIELDS SEARCHED (IPC) A61B G06F G01N

-/--

The supplementary search report has been based on the last set of claims valid and available at the start of the search.

Place of search	Date of completion of the search	Examiner
The Hague	6 June 2014	Meyer, Wolfgang

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

EPO FORM 1503 03.82 (P04C04)

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SUPPLEMENTARY EUROPEAN SEARCH REPORT

Application Number
EP 08 83 0067

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (IPC)
A	ELLERY S ET AL: "Predicting mortality and rehospitalization in heart failure patients with Home Monitoring-; The Home CARE pilot study", CLINICAL RESEARCH IN CARDIOLOGY, STEINKOPFF-VERLAG, DA, vol. 95, no. 3, 1 April 2006 (2006-04-01), pages iii29-iii35, XP019382870, ISSN: 1861-0692, DOI: 10.1007/S00392-006-1306-6 * the whole document *	1-15	
A	PINNA ET AL: "Home telemonitoring of vital signs and cardiorespiratory signals in heart failure patients: System architecture and feasibility of the HHH model", INTERNATIONAL JOURNAL OF CARDIOLOGY, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 120, no. 3, 19 July 2007 (2007-07-19) , pages 371-379, XP022157300, ISSN: 0167-5273, DOI: 10.1016/J.IJCARD.2006.10.029 * the whole document *	1-15	TECHNICAL FIELDS SEARCHED (IPC)
A	TEN-HMS INVESTIGATORS ET AL: "Noninvasive Home Telemonitoring for Patients With Heart Failure at High Risk of Recurrent Admission and Death", JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY, ELSEVIER, NEW YORK, NY, US, vol. 45, no. 10, 17 May 2005 (2005-05-17), pages 1654-1664, XP027719672, ISSN: 0735-1097 [retrieved on 2005-05-17] * the whole document *	1-15	

The supplementary search report has been based on the last set of claims valid and available at the start of the search.

Place of search	Date of completion of the search	Examiner
The Hague	6 June 2014	Meyer, Wolfgang

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

2

EPO FORM 1503 03.82 (P04C04)

ANNEX TO THE EUROPEAN SEARCH REPORT ON EUROPEAN PATENT APPLICATION NO. EP 08 83 0067

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report. The members are as contained in the European Patent Office EDP file on
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06-06-2014

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2007103835 A2	13-09-2007	EP 2001354 A2	17-12-2008
		EP 2540215 A2	02-01-2013
		JP 2009528909 A	13-08-2009
		WO 2007103835 A2	13-09-2007

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82

US008790257B2

(12) **United States Patent**
Libbus et al.

(10) **Patent No.: US 8,790,257 B2**
(45) **Date of Patent: Jul. 29, 2014**

(54) **MULTI-SENSOR PATIENT MONITOR TO DETECT IMPENDING CARDIAC DECOMPENSATION**

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None
See application file for complete search history.

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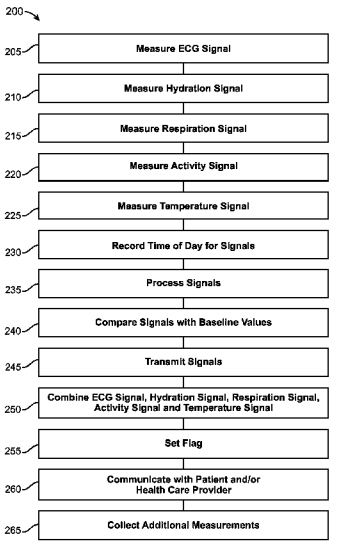
(57) **ABSTRACT**

Systems and methods of detecting an impending cardiac decompensation of a patient measure at least two of an electrocardiogram signal of the patient, a hydration signal of the patient, a respiration signal of the patient or an activity signal of the patient. The at least two of the electrocardiogram signal, the hydration signal, the respiration signal or the activity signal are combined with an algorithm to detect the impending cardiac decompensation.

31 Claims, 10 Drawing Sheets



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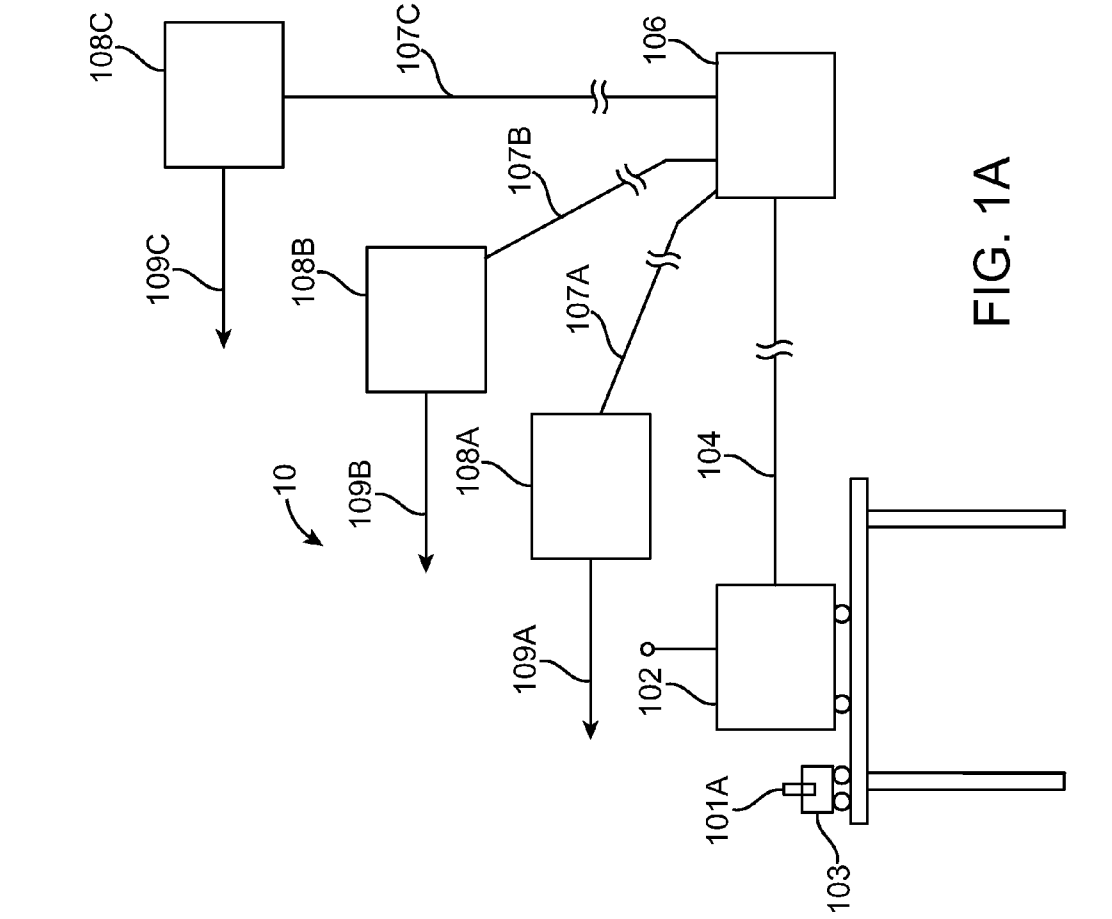
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101A
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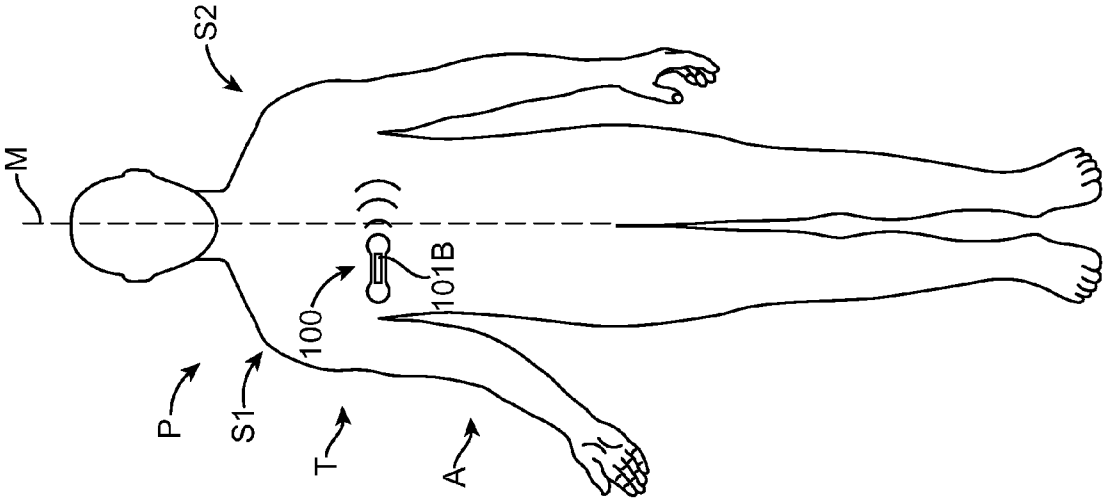
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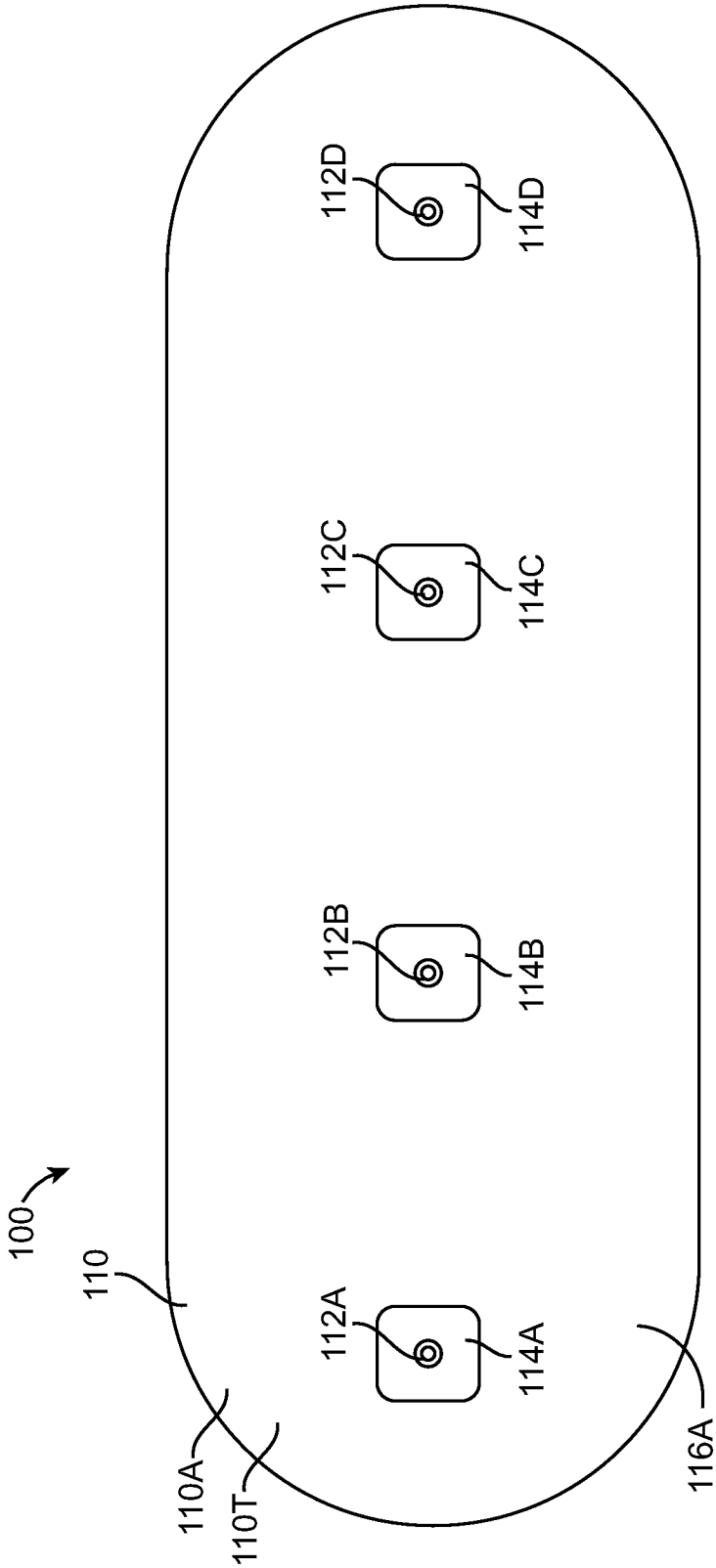
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116A

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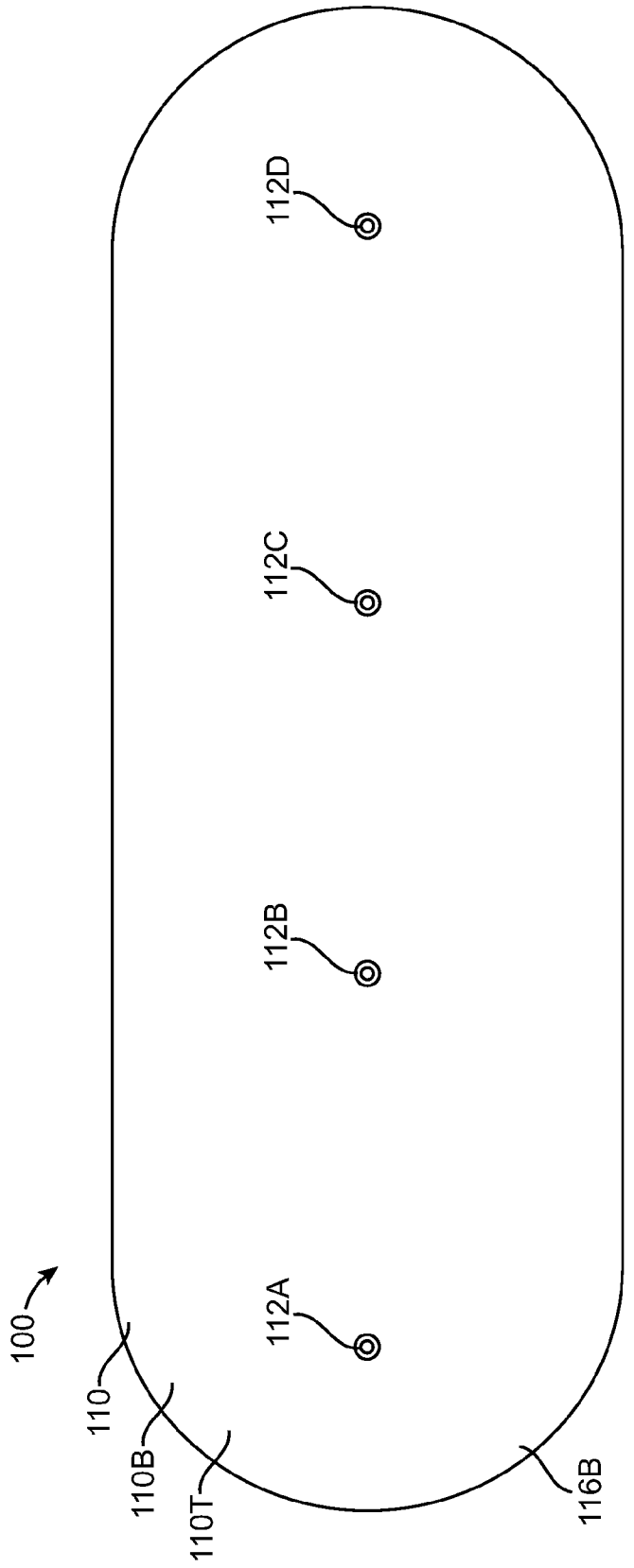

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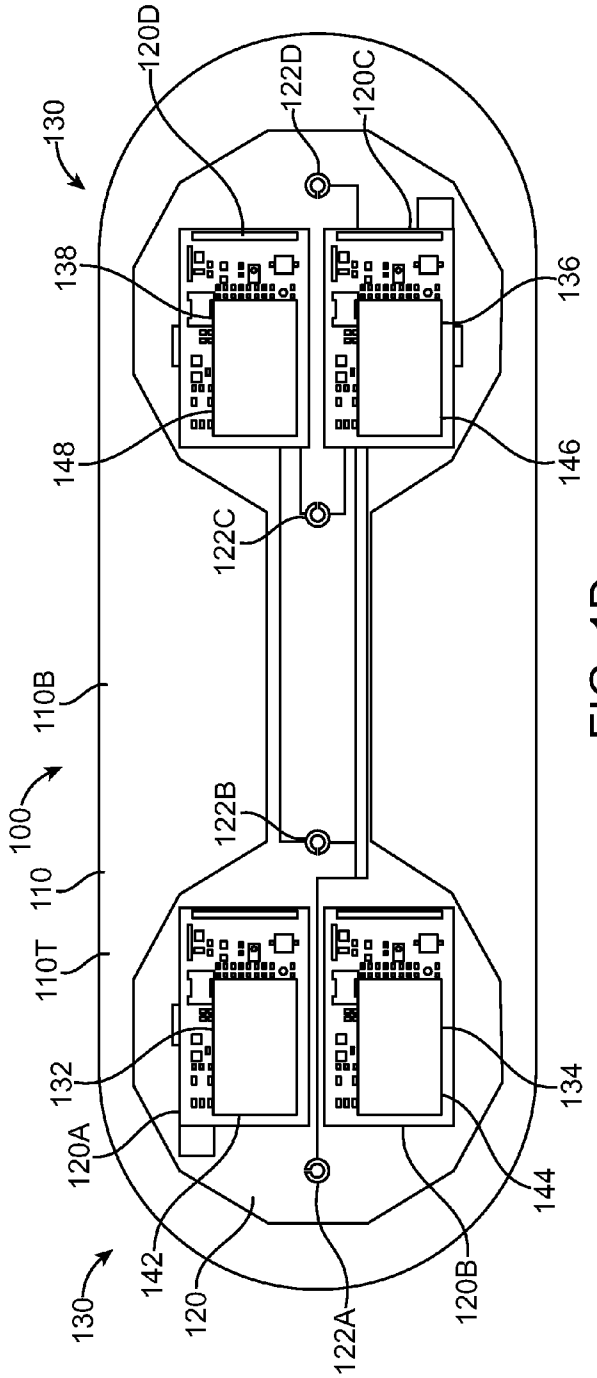

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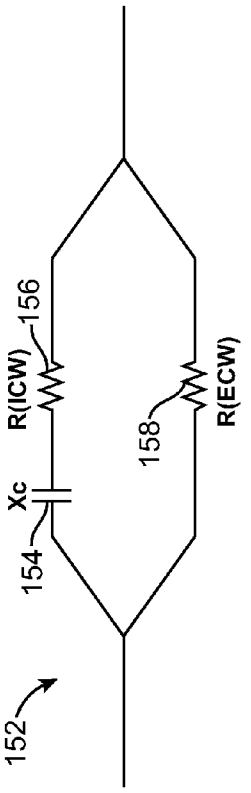

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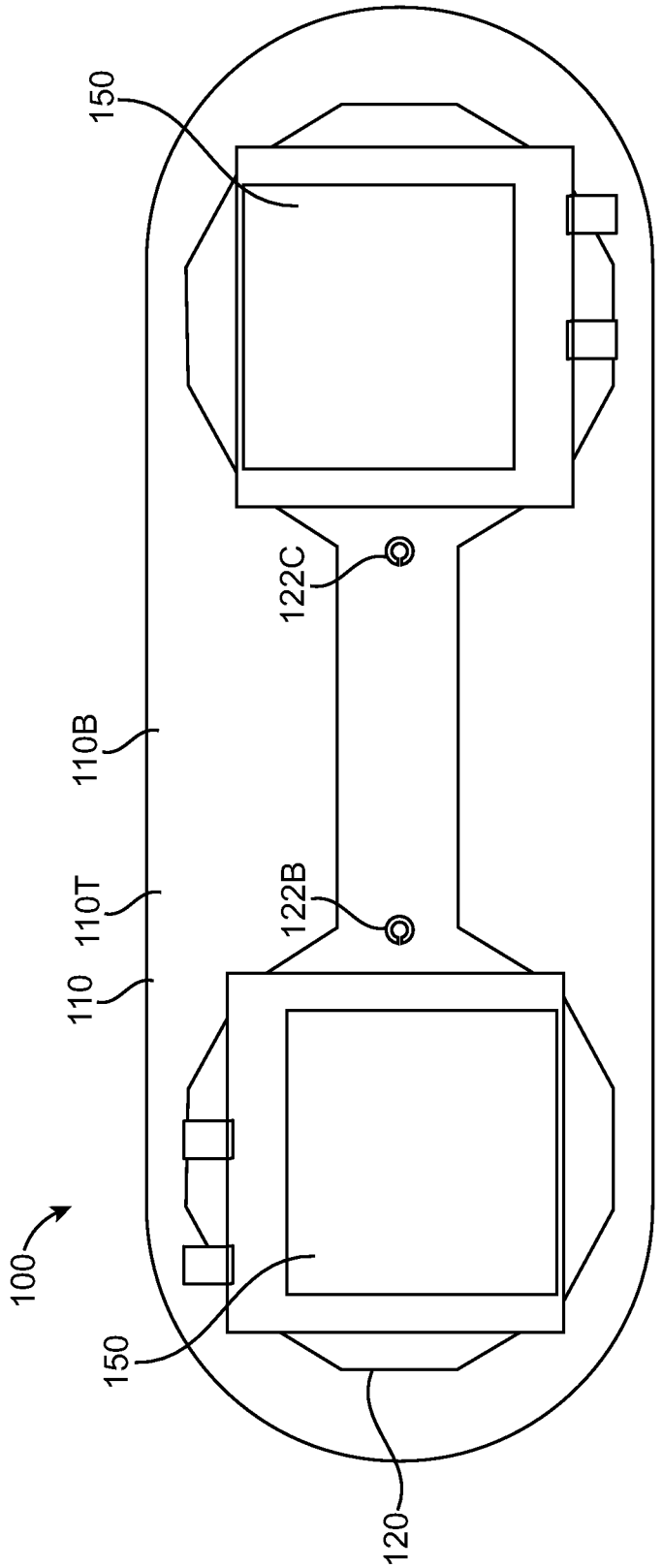

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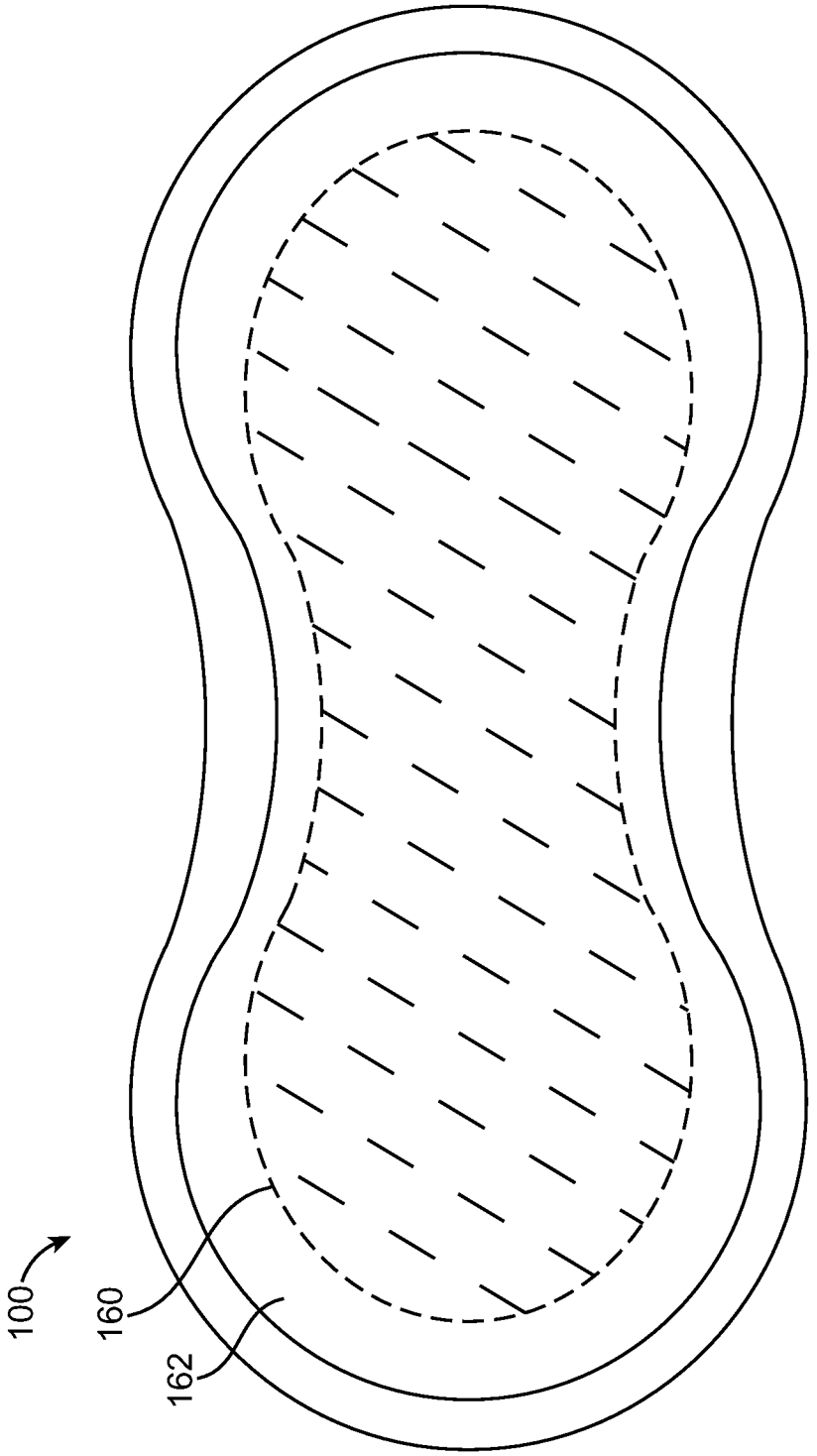

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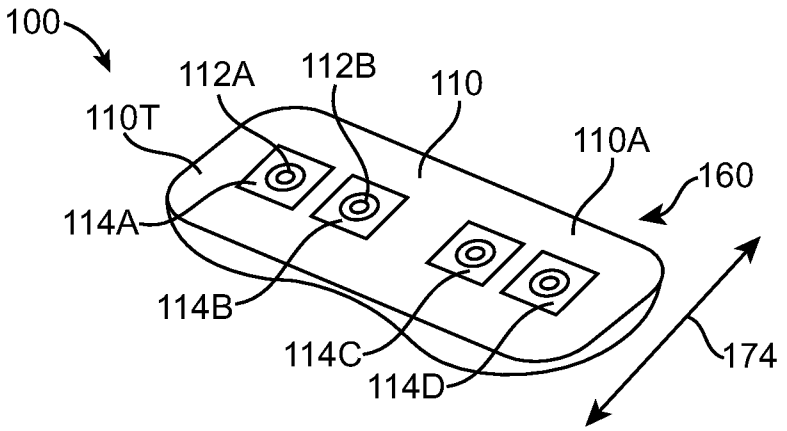
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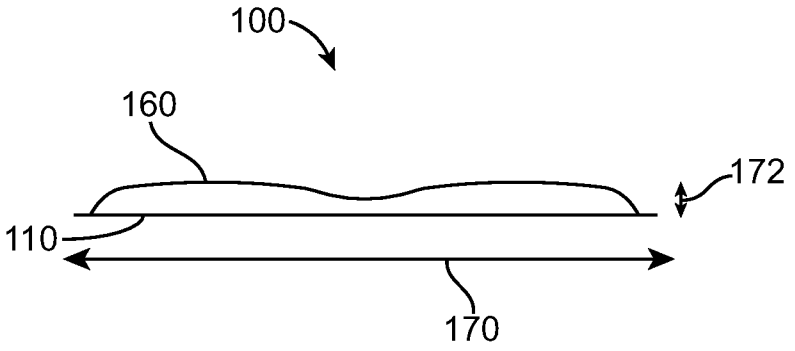
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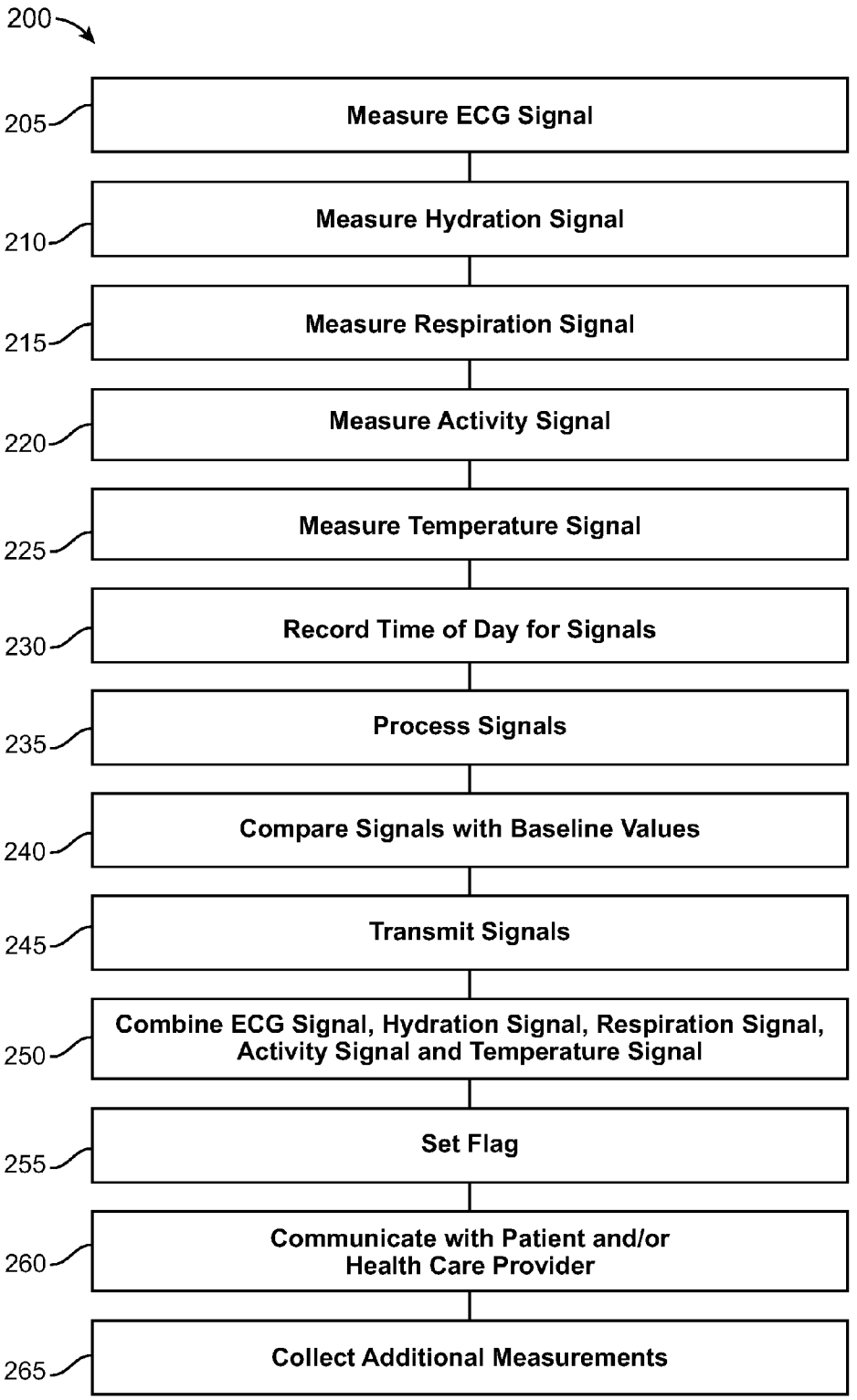
FIG. 1G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Measure Hydration Signal
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Measure Respiration Signal
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Measure Activity Signal
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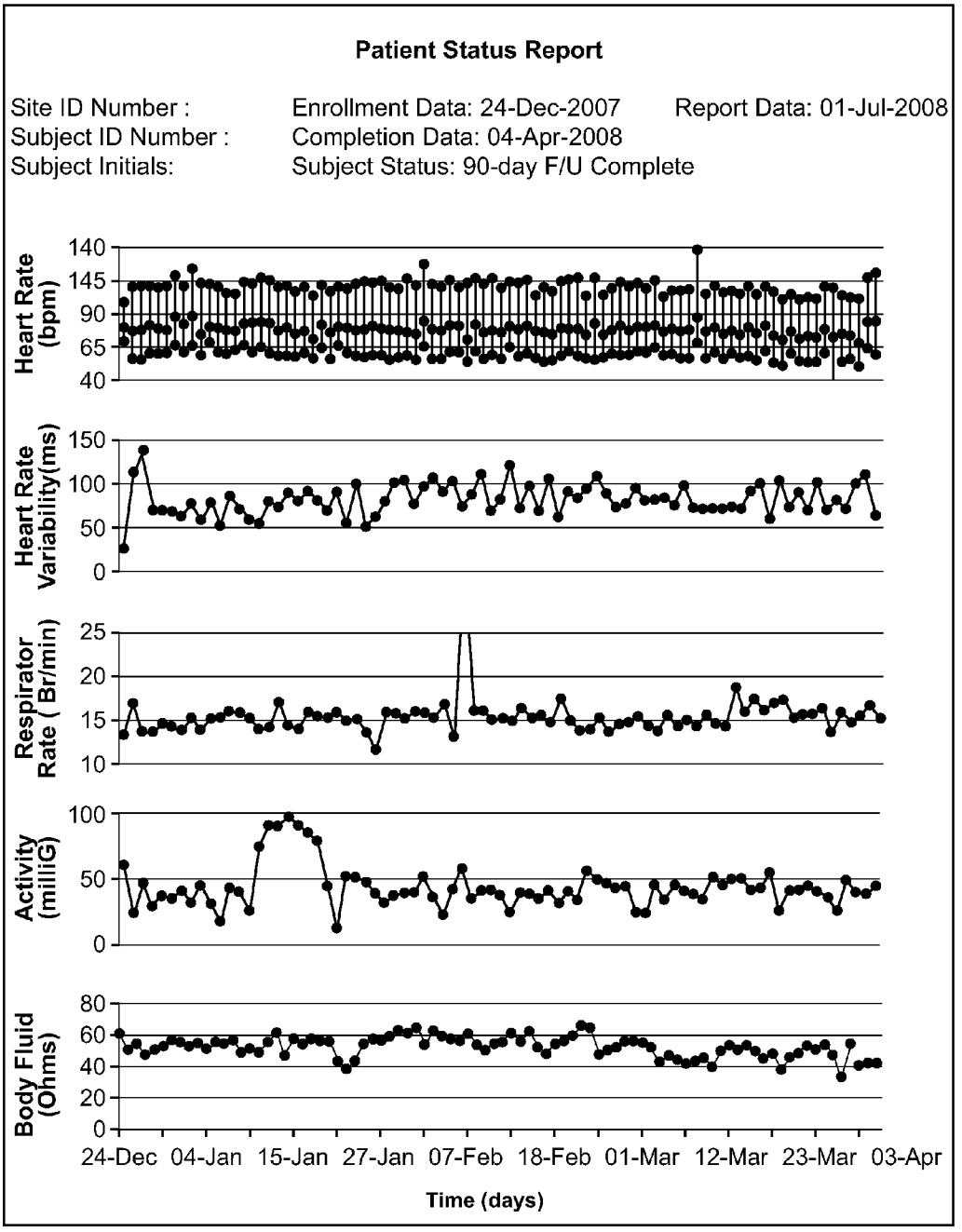
Measure Temperature Signal
230
Record Time of Day for Signals
235
Process Signals
240
Compare Signals with Baseline Values
245
Transmit Signals
250
Combine ECG Signal, Hydration Signal, Respiration Signal, Activity Signal and Temperature Signal
255
Set Flag
260
Communicate with Patient and/or Health Care Provider
265
Collect Additional Measurements

FIG. 2A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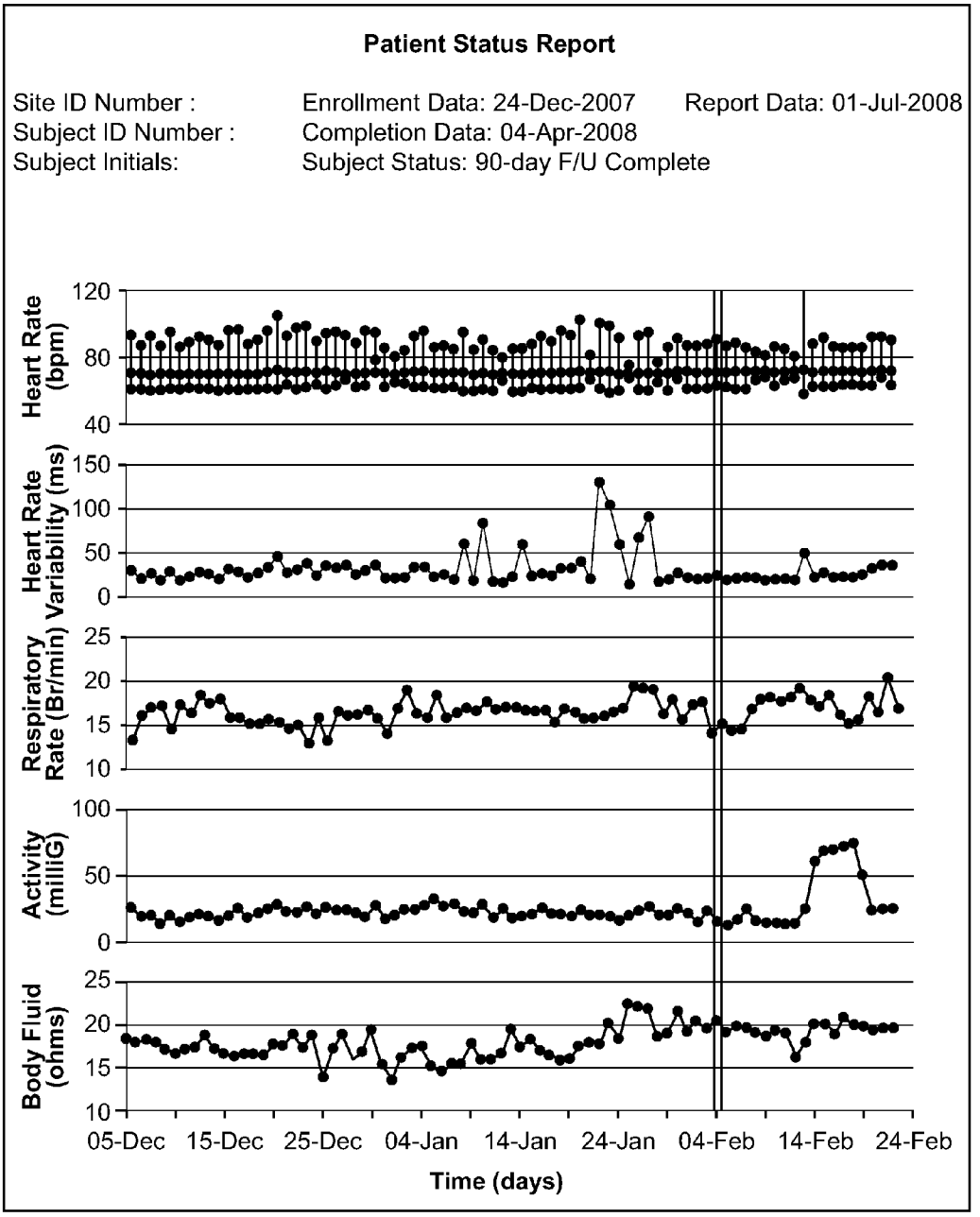
Completion Data: 04-Apr-2008
Subject Status: 90-day F/U Complete
Report Data: 01-Jul-2008
Heart Rate (bpm)
140
145
90
65
40
Heart Rate Variability(ms)
150
100
50
0
Respirator Rate (Br/min)
25
20
15
10
Activity (milliG)
100
50
0
Body Fluid (Ohms)
80
60
40
20
0
24-Dec 04-Jan 15-Jan 27-Jan 07-Feb 18-Feb 01-Mar 12-Mar 23-Mar 03-Apr
Time (days)

FIG. 3A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120
80
40
Heart Rate Variability (ms)
150
100
50
0
Respiratory Rate (Br/min)
25
20
15
10
Activity (milliG)
100
50
0
Body Fluid (ohms)
25
20
15
10
05-Dec
15-Dec
25-Dec
04-Jan
14-Jan
24-Jan
04-Feb
14-Feb
24-Feb
Time (days)

FIG. 3B

MULTI-SENSOR PATIENT MONITOR TO DETECT IMPENDING CARDIAC DECOMPENSATION

CROSS-REFERENCES TO RELATED APPLICATIONS

The present application claims the benefit under 35 USC 119(e) of U.S. Provisional Application Nos. 60/972,512 and 60/972,537 both filed Sep. 14, 2007, and 61/055,666 filed May 23, 2008; the full disclosures of which are incorporated herein by reference in their entirety.

The subject matter of the present application is related to the following applications: 60/972,329; 60/972,354; 60/972,616; 60/972,363; 60/972,343; 60/972,581; 60/972,629; 60/972,316; 60/972,333; 60/972,359; 60/972,336; 60/972,340 all of which were filed on Sep. 14, 2007; 61/046,196 filed Apr. 18, 2008; 61/047,875 filed Apr. 25, 2008; 61/055,645, 61/055,656, 61/055,662 all filed May 23, 2008; and 61/079,746 filed Jul. 10, 2008.

The following applications are being filed concurrently with the present application, on Sep. 12, 2008: application Ser. No. 12/209,288 entitled "Adherent Device with Multiple Physiological Sensors"; application Ser. No. 12/209,430 entitled "Injectable Device for Physiological Monitoring"; application Ser. No. 12/209,479 entitled "Delivery System for Injectable Physiological Monitoring System"; application Ser. No. 12/209,262 entitled "Adherent Device for Cardiac Rhythm Management"; application Ser. No. 12/209,268 entitled "Adherent Device for Respiratory Monitoring"; application Ser. No. 12/209,269 entitled "Adherent Athletic Monitor"; application Ser. No. 12/209,259 entitled "Adherent Emergency Monitor"; application Ser. No. 12/209,273 entitled "Adherent Device with Physiological Sensors"; application Ser. No. 12/209,276 entitled "Medical Device Automatic Start-up upon Contact to Patient Tissue"; application Ser. No. 12/210,078 entitled "System and Methods for Wireless Body Fluid Monitoring"; application Ser. No. 12/209,265 entitled "Adherent Cardiac Monitor with Advanced Sensing Capabilities"; application Ser. No. 12/209,292 entitled "Adherent Device for Sleep Disordered Breathing"; application Ser. No. 12/209,278 entitled "Dynamic Pairing of Patients to Data Collection Gateways"; application Ser. No. 12/209,508 entitled "Adherent Multi-Sensor Device with Implantable Device Communications Capabilities"; application Ser. No. 12/209,528 entitled "Data Collection in a Multi-Sensor Patient Monitor"; application Ser. No. 12/209,271 entitled "Adherent Multi-Sensor Device with Empathic Monitoring"; application Ser. No. 12/209,274 entitled "Energy Management for Adherent Patient Monitor"; and application Ser. No. 12/209,294 "Tracking and Security for Adherent Patient Monitor."

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates to patient monitoring, and more specifically to patient monitoring to detect and/or avoid impending cardiac decompensation. Although embodiments make specific reference to monitoring impedance and electrocardiogram signals with an adherent patch, the system methods and device described herein may be applicable to many applications in which physiological monitoring is used, for example wireless physiological monitoring with implantable devices for extended periods.

Patients are often treated for diseases and/or conditions associated with a compromised status of the patient, for example a compromised physiologic status such as heart disease. In some instances a patient may have suffered a heart attack and require care and/or monitoring after release from the hospital. While such long term care may be at least partially effective, many patients are not sufficiently monitored and eventually succumb to cardiac decompensation, or heart failure. One example of a device that may be used to monitor a patient is the Holter monitor, or ambulatory electrocardiography device. Although such a device may be effective in measuring electrocardiography, such measurements alone may not be sufficient to reliably detect and/or avoid an impending cardiac decompensation.

In addition to measuring heart signals with electrocardiograms, known physiologic measurements include impedance measurements. For example, transthoracic impedance measurements can be used to measure hydration and respiration. Although transthoracic measurements can be useful, such measurements may use electrodes that are positioned across the midline of the patient, and may be somewhat uncomfortable and/or cumbersome for the patient to wear.

Work in relation to embodiments of the present invention suggests that known methods and apparatus for long term monitoring of patients may be less than ideal to detect and/or avoid an impending cardiac decompensation. In at least some instances, cardiac decompensation can be difficult to detect, for example in the early stages. At least some of the known devices may not collect the right kinds of data to treat patients optimally. For example, although successful at detecting and storing electrocardiogram signals, devices such as the Holter monitor can be somewhat bulky and may not collect all of the kinds of data that would be ideal to diagnose and/or treat a patient, for example to detect decompensation. In at least some instances, devices that are worn by the patient may be somewhat uncomfortable, which may lead to patients not wearing the devices and not complying with direction from the health care provider, such that data collected may be less than ideal. Although implantable devices may be used in some instances, many of these devices can be invasive and/or costly, and may suffer at least some of the shortcomings of known wearable devices. As a result, at least some patient are not adequately monitored, and may go into cardiac decompensation, or even die. Work in relation to embodiments of the present invention suggests that improved monitoring may avoid patient trauma, save lives, and decrease health care costs.

Therefore, a need exists for improved patient monitoring. Ideally, such improved patient monitoring would avoid at least some of the short-comings of the present methods and devices.

2. Description of the Background Art

The following U.S. Patents and Publications may describe relevant background art: U.S. Pat. Nos. 4,121,573; 4,955,381; 4,981,139; 5,080,099; 5,353,793; 5,469,859; 5,511,553; 5,544,661; 5,558,638; 5,724,025; 5,772,586; 5,862,802; 6,047,203; 6,117,077; 6,129,744; 6,225,901; 6,308,094; 6,385,473; 6,416,471; 6,454,707; 6,454,708; 6,527,711; 6,527,729; 6,551,252; 6,595,927; 6,595,929; 6,605,038; 6,645,153; 6,821,249; 6,980,851; 7,020,508; 7,054,679; 7,153,262; 7,160,252; 2004/133079; 2004/152956; 2005/0113703; 2005/0131288; 2006/0010090; 2006/0031102; 2006/0089679; 2006/122474; 2006/0155183; 2006/0224051; 2006/0264730; 2007/0021678; 2007/0038038; 2005/256418; 2005/137626; and 2006/161459. The following PCT Publication(s) may also describe relevant background art: WO2006/111878.

BRIEF SUMMARY OF THE INVENTION

Embodiments of the present invention provide systems and methods for the detection of an impending cardiac decom-

pensation. In many embodiments, the impending decompensation can be detected early enough to avoid, or at least delay, the impending decompensation, such that patient trauma and/or expensive ICU care can be avoided. Although embodiments make specific reference to monitoring impedance and electrocardiogram signals with an adherent patch, the system methods and device described herein may be applicable to many applications in which physiological monitoring is used, for example wireless physiological monitoring with implanted sensors for extended periods.

In a first aspect, embodiments of the present invention provide a method of detecting an impending cardiac decompensation of a patient. At least two of an electrocardiogram signal of the patient, a hydration signal of the patient, a respiration signal of the patient or an activity signal of the patient are measured. The at least two of the electrocardiogram signal, the hydration signal, the respiration signal or the activity signal are combined to detect the impending cardiac decompensation. In many embodiments, the impending decompensation can be detected at least 24 hours before the decompensation occurs, for example 72 hours, and in many embodiments with a confidence level of at least 80%, for example 90%.

In many embodiments, the at least two comprise at least three of the electrocardiogram signal, the hydration signal, the respiration signal or the activity signal, and the at least three are measured and combined to detect the impending cardiac decompensation. In specific embodiments, the at least three comprise at least four of the electrocardiogram signal, the hydration signal, the respiration signal or the activity signal, and the at least four are measured and combined to detect the impending cardiac decompensation.

In specific embodiments, the electrocardiogram signal, the hydration signal, the respiration signal and the activity signal are measured combined to detect the impending cardiac decompensation.

In many embodiments, the at least two of the electrocardiogram signal, the hydration signal, the respiration signal or the activity signal can be used simultaneously to determine impending cardiac decompensation. The at least two signals can be used simultaneously in many ways.

In many embodiments, combining comprises using the at least two of the electrocardiogram signal, the hydration signal, the respiration signal or the activity signal to look up a value in a previously existing array. In some embodiments, combining may comprise at least one of adding, subtracting, multiplying, scaling or dividing the at least two of the electrocardiogram signal, the hydration signal, the respiration signal or the activity signal. In some embodiments, the at least two of the electrocardiogram signal, the hydration signal, the respiration signal or the activity signal can be combined with at least one of a weighted combination, a tiered combination or a logic gated combination, a time weighted combination or a rate of change.

In many embodiments, a flag status is determined in response to the at least two of the electrocardiogram signal, the hydration signal, the respiration signal or the activity signal. The flag status can be determined in response to a change in the at least two of the electrocardiogram signal, the hydration signal, the respiration signal or the activity signal. In some embodiments, additional signal measurements of the patient can be made in response to the flag status.

In many embodiments, the at least two of the electrocardiogram signal, the hydration signal, the respiration signal or the activity signal are combined in response to a time of day.

In many embodiments, the at least two of the electrocardiogram signal, the hydration signal, the respiration signal or the activity signal may comprise at least one of a derived signal, a time averaged signal, a filtered signal or a raw signal.

In many embodiments, baseline values of the patient for the at least two of the electrocardiogram signal, the hydration signal, the respiration signal or the activity signal are determined, and the at least two of the electrocardiogram signal, the hydration signal, the respiration signal or the activity signal signals comprise changes from the baseline values.

In many embodiments, the at least two of the electrocardiogram signal, the hydration signal, the respiration signal or the activity signal comprise differences from population baseline values, and the impending decompensation is detected in response to the differences from the baseline values of the patient population.

In many embodiments, the hydration signal comprises an impedance signal and the activity signal comprise an accelerometer signal.

In many embodiments, the activity signal may comprise an accelerometer signal to indicate a posture of the patient. In specific embodiments, the accelerometer signal may comprise a three dimensional inclination signal to determine a three dimensional orientation of the patient.

In many embodiments, a temperature signal is combined with the at least two of the electrocardiogram signal, the hydration signal, the respiration signal or the activity signal to detect the impending cardiac decompensation.

In many embodiments, the at least two of the electrocardiogram signal, the hydration signal, the respiration signal or the activity signal are transmitted to a remote site where the at least two of the electrocardiogram signal, the hydration signal, the respiration signal or the activity signal are combined to detect the impending cardiac decompensation.

In many embodiments, instructions are transmitted from a remote site to a processor supported with the patient, and the at least two of the electrocardiogram signal, the hydration signal, the respiration signal or the activity signal are combined with the processor in response to the instructions to detect the impending cardiac decompensation.

In another aspect, embodiments of the present invention provide a system to detect impending cardiac decompensation of a patient. The system comprises circuitry to measure at least two of an electrocardiogram signal of the patient, a hydration signal of the patient, or an activity signal of the patient. A processor system comprising a tangible medium in communication with the circuitry is configured to combine the at least two of the electrocardiogram signal, the hydration signal, the respiration signal or the activity signal to detect the impending cardiac decompensation.

In some embodiments, the processor system comprises a least one processor remote from the patient configured to combine the at least two to detect the decompensation.

In some embodiments, the processor system comprises a processor supported with the patient configured to receive instructions transmitted from a remote site and combine the at least two in response to the instructions to detect the impending cardiac decompensation.

In many embodiments, the at least two comprise at least three of the electrocardiogram signal, the hydration signal, the respiration signal or the activity signal and the at least three are measured and combined to detect the impending cardiac decompensation. In specific embodiments, the at least three comprise at least four of the electrocardiogram signal, the hydration signal, the respiration signal or the activity signal and the at least four are measured and combined to detect the impending cardiac decompensation.

In specific embodiments, the processor system simultaneously uses the at least two of the electrocardiogram signal,

the hydration signal, the respiration signal or the activity signal to determine impending cardiac decompensation. The at least two signals can be used simultaneously in many ways,

In many embodiments, combining comprises the processor system using the at least two of the electrocardiogram signal, the hydration signal, the respiration signal or the activity signal to look up a value in a previously existing array. In some embodiments, combining comprises at least one of adding, subtracting, multiplying, scaling or dividing the at least two of the electrocardiogram signal, the hydration signal, the respiration signal or the activity signal. In some embodiments, the at least two of the electrocardiogram signal, the hydration signal, the respiration signal, or the activity signal can be combined with at least one of a weighted combination, a tiered combination or a logic gated combination, a time weighted combination or a rate of change.

In many embodiments, the processor system determines a flag status in response to the at least two of the electrocardiogram signal, the hydration signal, the respiration signal or the activity signal. The processor system determines the flag status in response to a change in the at least two of the electrocardiogram signal, the hydration signal, the respiration signal or the activity signal. In some embodiments, the processor system affects the circuitry to make additional signal measurements of the patient in response to the flag status.

In many embodiments, the processor system combines the at least two of the electrocardiogram signal, the hydration signal, the respiration signal or the activity signal in response to a time of day.

In many embodiments, the at least two of the electrocardiogram signal, the hydration signal, the respiration signal or the activity signal comprise at least one of a derived signal, a time averaged signal, a filtered signal or a raw signal.

In many embodiments, the processor determines baseline values of the patient for the at least two of the electrocardiogram signal, the hydration signal, the respiration signal or the activity signal. The at least two of the electrocardiogram signal, the hydration signal, the respiration signal or the activity signal signals may comprise changes from the baseline values.

In many embodiments, the at least two of the electrocardiogram signal, the hydration signal, the respiration signal or the activity signal comprise differences from baseline values of a patient population. The impending decompensation is detected in response to the differences from the baseline value of the patient population.

In many embodiments, the hydration signal comprises an impedance signal and the activity signal comprise an accelerometer signal.

In many embodiments, the activity signal may comprise an accelerometer signal to determine a posture of the patient. In specific embodiments, the accelerometer signal may comprise a three dimensional inclination signal to determine a three dimensional orientation of the patient.

In many embodiments, the processor system combines a temperature signal with the at least two of the electrocardiogram signal, the hydration signal, the respiration signal or the activity signal to detect the impending cardiac decompensation.

In many embodiments, the processor transmits the at least two of the electrocardiogram signal, the hydration signal, the respiration signal or the activity signal to a remote site where the at least two of the electrocardiogram signal, the hydration signal, the respiration signal or the activity signal are combined to detect the impending cardiac decompensation.

In many embodiments, instructions are transmitted from a remote site to a processor supported with the patient. The processor combines at least two of the electrocardiogram signal, the hydration signal, the respiration signal or the activity signal in response to the instructions to detect the impending cardiac decompensation

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1**A shows a patient and a monitoring system comprising an adherent device, according to embodiments of the present invention;

FIG. **1**B shows a bottom view of the adherent device as in FIG. **1**A comprising an adherent patch;

FIG. **1**C shows a top view of the adherent patch, as in FIG. **1**B;

FIG. **1**D shows a printed circuit boards and electronic components over the adherent patch, as in FIG. **1**C;

FIG. **1**D-**1** shows an equivalent circuit that can be used to determine optimal frequencies for determining patient hydration, according to embodiments of the present invention;

FIG. **1**E shows batteries positioned over the printed circuit board and electronic components as in FIG. **1**D;

FIG. **1**F shows a top view of an electronics housing and a breathable cover over the batteries, electronic components and printed circuit board as in FIG. **1**E;

FIG. **1**G shows a side view of the adherent device as in FIGS. **1**A to **1**F;

FIG. **1**H shown a bottom isometric view of the adherent device as in FIGS. **1**A to **1**G;

FIG. **2**A shows a method of predicting an impending cardiac decompensation, according to embodiments of the present invention; and

FIGS. **3**A and **3**B show clinical data measured with an adherent patch device.

DETAILED DESCRIPTION OF THE INVENTION

Embodiments of the present invention provide systems and methods for the detection of an impending cardiac decompensation. In many embodiments, the impending decompensation can be detected early enough to avoid, or at least delay, the impending decompensation, such that patient trauma and/or expensive ICU care can be avoided. Although embodiments make specific reference to monitoring impedance and electrocardiogram signals with an adherent patch, the system methods and device described herein may be applicable to many applications in which physiological monitoring is used, for example wireless physiological monitoring with implanted sensors for extended periods. In some embodiments, implanted sensors may be used, for example as described in U.S. Pat. Nos. 6,208,894; 6,315,721; 6,185,452; and U.S. Application No. 60/972,329, entitled "Injectable Device for Physiological Monitoring" filed on Sep. 14, 2007, the same day as the present application with the same assignee, the full disclosures of which are incorporated by reference.

Decompensation is failure of the heart to maintain adequate blood circulation. Although the heart can maintain at least some pumping of blood, the quantity is inadequate to maintain healthy tissues. Several symptoms can result from decompensation including pulmonary congestion, breathlessness, faintness, cardiac palpitation, edema of the extremities, and enlargement of the liver. Cardiac decompensation can result in slow or sudden death. Sudden Cardiac Arrest (hereinafter "SCA"), also referred to as sudden cardiac death, is an abrupt loss of cardiac pumping function that can be caused by a ventricular arrhythmia, for example ventricular tachycardia and/or ventricular fibrillation. Although decom-

pensation and SCA can be related in that patients with decompensation are also at an increased risk for SCA, decompensation is primarily a mechanical dysfunction caused by inadequate blood flow, and SCA is primarily an electrical dysfunction caused by inadequate and/or inappropriate electrical signals of the heart.

FIG. **1**A shows a patient P and a monitoring system **10**. Patient P comprises a midline M, a first side S1, for example a right side, and a second side S2, for example a left side. Monitoring system **10** comprises an adherent device **100**. Adherent device **100** can be adhered to a patient P at many locations, for example thorax T of patient P. In many embodiments, the adherent device may adhere to one side of the patient, from which data from the one side can be collected. Work in relation with embodiments of the present invention suggests that location on a side of the patient can provide comfort for the patient while the device is adhered to the patient.

Monitoring system **10** includes components to transmit data to a remote center **106**. Adherent device **100** can communicate wirelessly to an intermediate device **102**, for example with a single wireless hop from the adherent device on the patient to the intermediate device. Intermediate device **102** can communicate with remote center **106** in many ways, for example with an internet connection. In many embodiments, monitoring system **10** comprises a distributed processing system with at least one processor on device **100**, at least one processor on intermediate device **102**, and at least one process at remote center **106**, each of which processors is in electronic communication with the other processors. Remote center **106** can be in communication with a health care provider **108**A with a communication system **107**A, such as the Internet, an intranet, phone lines, wireless and/or satellite phone. Health care provider **108**A, for example a family member, can be in communication with patient P with a communication, for example with a two way communication system, as indicated by arrow **109**A, for example by cell phone, email, landline. Remote center **106** can be in communication with a health care professional, for example a physician **108**B, with a communication system **107**B, such as the Internet, an intranet, phone lines, wireless and/or satellite phone. Physician **108**B can be in communication with patient P with a communication, for example with a two way communication system, as indicated by arrow **109**B, for example by cell phone, email, landline. Remote center **106** can be in communication with an emergency responder **108**C, for example a 911 operator and/or paramedic, with a communication system **107**C, such as the Internet, an intranet, phone lines, wireless and/or satellite phone. Emergency responder **108**C can travel to the patient as indicated by arrow **109**C. Thus, in many embodiments, monitoring system **10** comprises a closed loop system in which patient care can be monitored and implemented from the remote center in response to signals from the adherent device.

In many embodiments, the adherent device may continuously monitor physiological parameters, communicate wirelessly with a remote center, and provide alerts when necessary. The system may comprise an adherent patch, which attaches to the patient's thorax and contains sensing electrodes, battery, memory, logic, and wireless communication capabilities. In some embodiments, the patch can communicate with the remote center, via the intermediate device in the patient's home. In the many embodiments, the remote center receives the data and applies the prediction algorithm. When a flag is raised, the center may communicate with the patient, hospital, nurse, and/or physician to allow for therapeutic intervention to prevent decompensation.

The adherent device may be affixed and/or adhered to the body in many ways. For example, with at least one of the following an adhesive tape, a constant-force spring, suspenders around shoulders, a screw-in microneedle electrode, a pre-shaped electronics module to shape fabric to a thorax, a pinch onto roll of skin, or transcutaneous anchoring. Patch and/or device replacement may occur with a keyed patch (e.g. two-part patch), an outline or anatomical mark, a low-adhesive guide (place guide|remove old patch|place new patch|remove guide), or a keyed attachment for chatter reduction. The patch and/or device may comprise an adhesiveless embodiment (e.g. chest strap), and/or a low-irritation adhesive model for sensitive skin. The adherent patch and/or device can comprise many shapes, for example at least one of a dogbone, an hourglass, an oblong, a circular or an oval shape.

In many embodiments, the adherent device may comprise a reusable electronics module with replaceable patches (the module collects cumulative data for approximately 90 days) and/or the entire adherent component (electronics+patch) may be disposable. In a completely disposable embodiment, a "baton" mechanism may be used for data transfer and retention, for example baton transfer may include baseline information. In some embodiments, the device may have a rechargeable module, and may use dual battery and/or electronics modules, wherein one module **101**A can be recharged using a charging station **103** while the other module **101**B is placed on the adherent device. In some embodiments, the intermediate device **102** may comprise the charging module, data transfer, storage and/or transmission, such that one of the electronics modules can be placed in the intermediate device for charging and/or data transfer while the other electronics module is worn by the patient.

In many embodiments, the system can perform the following functions: initiation, programming, measuring, storing, analyzing, communicating, predicting, and displaying. The adherent device may contain a subset of the following physiological sensors: bioimpedance, respiration, respiration rate variability, heart rate (average, minimum, maximum), heart rhythm, HRV, HRT, heart sounds (e.g. S3), respiratory sounds, blood pressure, activity, posture, wake/sleep, orthopnea, temperature/heat flux, and weight. The activity sensor may be one of the following: ball switch, accelerometer, minute ventilation, HR, bioimpedance noise, skin temperature/heat flux, BP, muscle noise, posture.

In many embodiments, the patch wirelessly communicates with a remote center. In some embodiments, the communication may occur directly (via a cellular or Wi-Fi network), or indirectly through intermediate device **102**. Intermediate device **102** may consist of multiple devices which communicate wired or wirelessly to relay data to remote center **106**.

FIG. **1**B shows a bottom view of adherent device **100** as in FIG. **1**A comprising an adherent patch **110**. Adherent patch **110** comprises a first side, or a lower side **110**A, that is oriented toward the skin of the patient when placed on the patient. In many embodiments, adherent patch **110** comprises a tape **110**T which is a material, preferably breathable, with an adhesive **116**A. Patient side **110**A comprises adhesive **116**A to adhere the patch **110** and adherent device **100** to patient P. Electrodes **112**A, **112**B, **112**C and **112**D are affixed to adherent patch **110**. In many embodiments, at least four electrodes are attached to the patch, for example six electrodes. In some embodiments the patch comprises at least two electrodes, for example two electrodes to measure an electrocardiogram (ECG) of the patient. Gel **114**A, gel **114**B, gel **114**C and gel **114**D can each be positioned over electrodes **112**A, **112**B, **112**C and **112**D, respectively, to provide elec-

trical conductivity between the electrodes and the skin of the patient. In many embodiments, the electrodes can be affixed to the patch **110**, for example with known methods and structures such as rivets, adhesive, stitches, etc. In many embodiments, patch **110** comprises a breathable material to permit air and/or vapor to flow to and from the surface of the skin.

FIG. **1**C shows a top view of the adherent patch **100**, as in FIG. **1**B. Adherent patch **100** comprises a second side, or upper side **110**B. In many embodiments, electrodes **110**A, **110**B, **110**C and **110**D extend from lower side **110**A through the adherent patch to upper side **110**B. In some embodiments, an adhesive **116**B can be applied to upper side **110**B to adhere structures, for example, a cover, to the patch such that the patch can support the electronics and other structures when the patch is adhered to the patient. The printed circuit board (PCB) comprise completely flex PCB, rigid PCB combined flex PCB and/or rigid PCB boards connected by cable.

FIG. **1**D shows a printed circuit boards and electronic components over adherent patch **110**, as in FIG. **1**C. A printed circuit board (PCB), for example flex PCB **120**, can be positioned above **110**B of patch **110**. Flex PCB **120** can include traces that extends to connectors **122**A, **122**B, **122**C and **122**D on the flex PCB. Connectors **122**A, **122**B, **122**C and **122**D can be positioned on flex PCB **120** in alignment with electrodes **112**A, **112**B, **112**C and **112**D so as to electrically couple the flex PCB with the electrodes. In some embodiments, connectors **122**A, **122**B, **122**C and **122**D may comprise insulated wires or a flex circuit that provide strain relief between the PCB and the electrodes. In some embodiments, additional PCB's for example PCB **120**A, **120**B, **120**C and **120**D be connected to flex PCB **120**. Electronic components **130** can be connected to flex PCB **120** and/or mounted thereon. In some embodiments, electronic components **130** can be mounted on the additional PCB's.

Electronic components **130** comprise components to take physiologic measurements, transmit data to remote center **106** and receive commands from remote center **106**. In many embodiments, electronics components **130** may comprise known low power circuitry, for example complementary metal oxide semiconductor (CMOS) circuitry components. Electronics components **130** comprise an activity sensor and activity circuitry **134**, impedance circuitry **136** and electrocardiogram circuitry, for example ECG circuitry **136**. In some embodiments, electronics circuitry **130** may comprise a microphone and microphone circuitry **142** to detect an audio signal from within the patient, and the audio signal may comprise a heart sound and/or a respiratory sound, for example an S3 heart sound and a respiratory sound with rales and/or crackles. Electronics circuitry **130** may comprise a temperature sensor, for example a thermistor, and temperature sensor circuitry **144** to measure a temperature of the patient, for example a temperature of a skin of the patient. Electronics circuitry may comprise a heat flux sensor and heat flux sensor circuitry to measure a skin heat flow of a patient.

Work in relation to embodiments of the present invention suggests that skin temperature may effect impedance and/or hydration measurements, and that skin temperature measurements may be used to correct impedance and/or hydration measurements. In some embodiments, increase in skin temperature can be associated with increased vaso-dilation near the skin surface, such that measured impedance measurement decreased, even through the hydration of the patient in deeper tissues under the skin remains substantially unchanged. Thus, use of the temperature sensor can allow for correction of the hydration signals to more accurately assess the hydration, for example extra cellular hydration, of deeper tissues of the patient, for example deeper tissues in the thorax.

Electronics circuitry **130** may comprise a processor **146**. Processor **146** comprises a tangible medium, for example read only memory (ROM), electrically erasable programmable read only memory (EEPROM) and/or random access memory (RAM). Electronic circuitry **130** may comprise real time clock and frequency generator circuitry **148**. In some embodiments, processor **136** may comprise the frequency generator and real time clock. The processor can be configured to control a collection and transmission of data from the impedance circuitry electrocardiogram circuitry and the accelerometer. In many embodiments, device **100** comprise a distributed processor system, for example with multiple processors on device **100**.

In many embodiments, electronics components **130** comprise wireless communications circuitry **132** to communicate with remote center **106**. The wireless communication circuitry can be coupled to the impedance circuitry, the electrocardiogram circuitry and the accelerometer to transmit to a remote center with a communication protocol at least one of the hydration signal, the electrocardiogram signal or the accelerometer signal. In specific embodiments, wireless communication circuitry is configured to transmit the hydration signal, the electrocardiogram signal and the accelerometer signal to the remote center with a single wireless hop, for example from wireless communication circuitry **132** to intermediate device **102**. The communication protocol comprises at least one of Bluetooth, Zigbee, WiFi, WiMax, IR, amplitude modulation or frequency modulation. In many embodiments, the communications protocol comprises a two way protocol such that the remote center is capable of issuing commands to control data collection.

In some embodiments, intermediate device **102** comprises a data collection system to collect and store data from the wireless transmitter. The data collection system can be configured to communicate periodically with the remote center. In many embodiments, the data collection system can transmit data in response to commands from remote center **106** and/or in response to commands from the adherent device.

Activity sensor and activity circuitry **134** can comprise many known activity sensors and circuitry. In many embodiments, the accelerometer comprises at least one of a piezoelectric accelerometer, capacitive accelerometer or electromechanical accelerometer. The accelerometer may comprise a 3-axis accelerometer to measure at least one of an inclination, a position, an orientation or acceleration of the patient in three dimensions. Work in relation to embodiments of the present invention suggests that three dimensional orientation of the patient and associated positions, for example sitting, standing, lying down, can be very useful when combined with data from other sensors, for example ECG data and/or hydration data.

Impedance circuitry **136** can generate both hydration data and respiration data. In many embodiments, impedance circuitry **136** is electrically connected to electrodes **112**A, **112**B, **112**C and **112**D such that electrodes **112**A and **112**D comprise outer electrodes that are driven with a current, or force electrodes. The current delivered between electrodes **112**A and **112**D generates a measurable voltage between electrodes **112**B and **112**C, such that electrodes **112**B and **112**C comprise inner electrodes, or sense electrodes that measure the voltage in response to the current from the force electrodes. The voltage measured by the sense electrodes can be used to determine the hydration of the patient.

FIG. **1**D-**1** shows an equivalent circuit **152** that can be used to determine optimal frequencies for measuring patient hydration. Work in relation to embodiments of the present invention indicates that the frequency of the current and/or

voltage at the force electrodes can be selected so as to provide impedance signals related to the extracellular and/or intracellular hydration of the patient tissue. Equivalent circuit **152** comprises an intracellular resistance **156**, or R(ICW) in series with a capacitor **154**, and an extracellular resistance **158**, or R(ECW). Extracellular resistance **158** is in parallel with intracellular resistance **156** and capacitor **154** related to capacitance of cell membranes. In many embodiments, impedances can be measured and provide useful information over a wide range of frequencies, for example from about 0.5 kHz to about 200 KHz. Work in relation to embodiments of the present invention suggests that extracellular resistance **158** can be significantly related extracellular fluid and to cardiac decompensation, and that extracellular resistance **158** and extracellular fluid can be effectively measured with frequencies in a range from about 0.5 kHz to about 20 kHz, for example from about 1 kHz to about 10 kHz. In some embodiments, a single frequency can be used to determine the extracellular resistance and/or fluid. As sample frequencies increase from about 10 kHz to about 20 kHz, capacitance related to cell membranes decrease the impedance, such that the intracellular fluid contributes to the impedance and/or hydration measurements. Thus, many embodiments of the present invention employ measure hydration with frequencies from about 0.5 kHz to about 20 kHz to determine patient hydration.

In many embodiments, impedance circuitry **136** can be configured to determine respiration of the patient. In specific embodiments, the impedance circuitry can measure the hydration at 25 Hz intervals, for example at 25 Hz intervals using impedance measurements with a frequency from about 0.5 kHz to about 20 kHz.

ECG circuitry **138** can generate electrocardiogram signals and data from electrodes **112**A, **112**B, **112**C and **112**D. In some embodiments, ECG circuitry **138** is connected to inner electrodes **12**B and **122**C, which may comprise sense electrodes of the impedance circuitry as described above. In some embodiments, the inner electrodes may be positioned near the outer electrodes to increase the voltage of the ECG signal measured by ECG circuitry **138**. In some embodiments, the ECG circuitry can share components with the impedance circuitry.

FIG. **1**E shows batteries **150** positioned over the flex printed circuit board and electronic components as in FIG. **1**D. Batteries **150** may comprise rechargeable batteries that can be removed and/or recharged. In some embodiments, batteries **150** can be removed from the adherent patch and recharged and/or replaced.

FIG. **1**F shows a top view of a cover **162** over the batteries, electronic components and flex printed circuit board as in FIG. **1**E. In many embodiments, an electronics housing **160** may be disposed under cover **162** to protect the electronic components, and in some embodiments electronics housing **160** may comprise an encapsulant over the electronic components and PCB. In many embodiments, electronics housing **160** may comprise a water proof material, for example a sealant adhesive such as epoxy or silicone coated over the electronics components and/or PCB. In some embodiments, electronics housing **160** may comprise metal and/or plastic, which may be potted with silicone, epoxy, etc.

Cover **162** may comprise many known biocompatible cover, casing and/or housing materials, such as elastomers, for example silicone. The elastomer may be fenestrated to improve breathability. In some embodiments, cover **162** may comprise many known breathable materials, for example polyester or polyamide fabric. The breathable fabric may be coated to make it water resistant, waterproof, and/or to aid in wicking moisture away from the patch. The breathable fabric may be coated in order to make the outside hydrophobic and the inside hydrophilic.

FIG. **1**G shows a side view of adherent device **100** as in FIGS. **1**A to **1**F. Adherent device **100** comprises a maximum dimension, for example a length **170** from about 4 to 10 inches (from about 100 mm to about 250 mm), for example from about 6 to 8 inches (from about 150 mm to about 200 mm). In some embodiments, length **170** may be no more than about 6 inches (no more than about 150 mm). Adherent device **100** comprises a thickness **172**. Thickness **172** may comprise a maximum thickness along a profile of the device. Thickness **172** can be from about 0.2 inches to about 0.4 inches (from about 5 mm to about 10 mm), for example about 0.3 inches (about 7.5 mm).

FIG. **1**H shown a bottom isometric view of adherent device **100** as in FIGS. **1**A to **1**G. Adherent device **100** comprises a width **174**, for example a maximum width along a width profile of adherent device **100**. Width **174** can be from about 2 to about 4 inches (from about 50 mm to 100 mm), for example about 3 inches (about 75 mm).

FIG. **2**A shows a method **200** of predicting an impending cardiac decompensation. A step **205** measures an ECG signal. The ECG signal may comprise a differential signal measured with at least two electrodes and may be measured in many known ways. A step **210** measures an hydration signal. The hydration signal may comprise an impedance signal, for example a four pole impedance signal, and may be measured in many known ways. A step **215** measures a respiration signal. The respiration signal may comprise an impedance signal, and may be measured in many known ways. A step **220** measures an activity signal. The activity signal may be measured in many known ways and may comprise a three dimensional accelerometer signal to determine a position of the patient, for example from a three dimensional accelerometer signal. A step **225** measures a temperature signal. The temperature signal may be measured in many ways, for example with a thermistor, a thermocouple, and known temperature measurement devices. A step **230** records a time of day of the signals, for example a local time of day such as morning, afternoon, evening, and/or nighttime.

A step **235** processes the signals. The signals may be processed in many known ways, for example to generate at least one of a derived signal, a time averaged signal, a filtered signal. In some embodiments, the signals may comprise raw signals. The ECG signal may comprise at least one of a heart rate signal, a heart rate variability signal, an average heart rate signal, a maximum heart rate signal or a minimum heart rate signal. The hydration signal may comprise an impedance measurement signal. The activity signal may comprise at least one of an accelerometer signal, a position signal indicating the orientation of the patient, such as standing, lying, or sitting. The respiration signal may comprise a least one of a respiration rate, a maximum respiration rate, a minimum respiration rate, an average respiration rate or respiration rate variability. The temperature may comprise an average temperature or a peak temperature.

A step **240** compares the signals with baseline values. In many embodiments, the baseline values may comprise measurements from the same patient at an earlier time. In some embodiments, the baseline values comprise values for a patient population. In some embodiments, the baseline values for a patient population may comprise empirical data from a suitable patient population size, for example at least about 144 patients, depending on the number of variables measured,

statistical confidence and power used. The measured signals may comprise changes and/or deviations from the baseline values.

A step **245** transmits the signals. In many embodiments, the measurement signals, which may comprise derived and/or processed measurement signals, are transmitted to the remote site for comparison. In some embodiments, the signals may be transmitted to a processor supported with the patient for comparison.

A step **250** combines at least two of the ECG signal, the hydration signal, the respiration signal, the activity signal and the temperature signal to detect the impending decompensation. In many embodiments, at least three of the signals are combined. In some embodiments, at least four signals comprising ECG signal, the hydration signal, the respiration signal and the activity signal are combined to detect the impending decompensation. In specific embodiments, at least four signals comprising the ECG signal, the hydration signal, the respiration signal, the activity signal and the temperature signal are combined to detect the impending decompensation.

The signals can be combined in many ways. In some embodiments, the signals can be used simultaneously to determine the impending cardiac decompensation.

In some embodiments, the signals can be combined by using the at least two of the electrocardiogram signal, the hydration signal, the respiration signal or the activity signal to look up a value in a previously existing array.

TABLE 1

Lookup Table for ECG and Hydration Signals

Heart Rate/Hydration	0-49 bpm	50-69 bpm	70-90 bpm
>60 Ohms	N	N	Y
41-59 Ohms	N	Y	Y
0-40 Ohms	Y	Y	Y

Table 1 shows combination of the electrocardiogram signal with the hydration signal to look up a value in a pre-existing array. For example at a heart rate of 89 bpm and a hydration of 35 Ohms, the value in the table may comprise Y. In specific embodiments, the values of the look up table can be determined in response to empirical data measured for a patient population of at least about 100 patients, for example measurements on about 1000 to 10,000 patients.

In some embodiments, the table may comprise a three or more dimensional look up table.

In some embodiments, the signals may be combined with at least one of adding, subtracting, multiplying, scaling or dividing the at least two of the electrocardiogram signal, the hydration signal, the respiration signal or the activity signal. In specific embodiments, the measurement signals can be combined with positive and or negative coefficients determined in response to empirical data measured for a patient population of at least about 100 patients, for example data on about 1000 to 10,000 patients.

In some embodiments, a weighted combination may combine at least 3 measurement signals to generate an output value according to a formula of the general form

$$OUTPUT=aX+bY+cZ$$

where a, b and c comprise positive or negative coefficients determined from empirical data and X, Y and Z comprise measured signals for the patient, for example at least three of the electrocardiogram signal, the hydration signal, the respiration signal or the activity signal. While three coefficients and three variables are shown, the data may be combined with multiplication and/or division. One or more of the variables may be the inverse of a measured variable.

In some embodiments, the ECG signal comprises a heart rate signal that can be divided by the activity signal. Work in relation to embodiments of the present invention suggest that an increase in heart rate with a decrease in activity can indicate an impending decompensation. The signals can be combined to generate an output value with an equation of the general form

$$OUTPUT=aX/Y+bZ$$

where X comprise a heart rate signal, Y comprises a hydration rate signal and Z comprises a respiration signal, with each of the coefficients determined in response to empirical data as described above.

In some embodiments, the data may be combined with a tiered combination. While many tiered combinations can be used a tiered combination with three measurement signals can be expressed as

$$OUTPUT=(\Delta X)+(\Delta Y)+(\Delta Z)$$

where (ΔX), (ΔY), (ΔZ) may comprise change in heart rate signal from baseline, change in hydration signal from baseline and change in respiration signal from baseline, and each may have a value of zero or one, based on the values of the signals. For example if the heart rate increase by 10%, (ΔX) can be assigned a value of 1. If hydration increases by 5%, (ΔY) can be assigned a value of 1. If activity decreases below 10% of a baseline value (ΔZ) can be assigned a value of 1. When the output signal is three, a flag may be set to trigger an alarm.

In some embodiments, the data may be combined with a logic gated combination. While many logic gated combinations can be used a logic gated combination with three measurement signals can be expressed as

$$OUTPUT=(\Delta X)AND(\Delta Y)AND(\Delta Z)$$

where (ΔX), (ΔY), (ΔZ) may comprise change in heart rate signal from baseline, change in hydration signal from baseline and change in respiration signal from baseline, and each may have a value of zero or one, based on the values of the signals. For example if the heart rate increase by 10%, (ΔX) can be assigned a value of 1. If hydration increases by 5%, (ΔY) can be assigned a value of 1. If activity decreases below 10% of a baseline value (ΔZ) can be assigned a value of 1. When each of (ΔX), (ΔY), (ΔZ) is one, the output signal is one, and a flag may be set to trigger an alarm. If any one of (ΔX), (ΔY) or (ΔZ) is zero, the output signal is zero and a flag may be set so as not to trigger an alarm. While a specific example with AND gates has been shown the data can be combined in may ways with known gates for example NAND, NOR, OR, NOT, XOR, XNOR gates. In some embodiments, the gated logic may be embodied in a truth table.

A step **255** sets a flag. The flag can be set in response to the output of the combined signals. In some embodiments, the flag may comprise a binary parameter in which a value of zero does not triggers an alarm and a value of one triggers an alarm.

A step **260** communicates with the patient and/or a health care provider. In some embodiments, the remote site may contact the patient to determine if he or she is okay and communicate the impending decompensation such that the patient can receive needed medical care. In some embodiments, the remote site contacts the health care provider to

warn the provider of the impending decompensation and the need for the patient to receive medical care.

A step **265** collects additional measurements. Additional measurements may comprise additional measurements with the at least two signals, for example with greater sampling rates and or frequency of the measurements. Additional measurements may comprise measurements with a additional sensors, for example an onboard microphone to detect at least one of rales, S1 heart sounds, S2 heart sounds, S3 heart sounds, or arrhythmias. In some embodiments, the additional measurements, for example sounds, can be transmitted to the health care provider to diagnose the patient in real time.

The processor system, as described above, can be configured to perform the method **200**, including many of the steps described above. It should be appreciated that the specific steps illustrated in FIG. **2**A provide a particular method of predicting an impending cardiac decompensation, according to an embodiment of the present invention. Other sequences of steps may also be performed according to alternative embodiments. For example, alternative embodiments of the present invention may perform the steps outlined above in a different order. Moreover, the individual steps illustrated in FIG. **2**A may include multiple sub-steps that may be performed in various sequences as appropriate to the individual step. Furthermore, additional steps may be added or removed depending on the particular applications. One of ordinary skill in the art would recognize many variations, modifications, and alternatives.

Experimental Clinical Study

The protocol below has been used to measure signals from actual patients with an adherent device. These data show that an adherent patch as described above can be continuously adhered for at least one week. These data also show that 90 day continuous in home monitoring can be achieved with a set of 13 patches in which one of the patches is replaced each week. The clinical testing device used an adherent device with modifications, as described more fully below and referred to as the MS system (multi-sensor). Although the clinical device did not include wireless circuitry and processor circuitry supported with the patch adhered to the skin of the patient, these data do show that such a device, as described above, can be made by one of ordinary skill in the art based on the teachings described herein. Additional empirical studies can be conducted on a suitable number of patients.

MS Clinical System Description

The MS clinical system includes many of the structure components described above. There is a flexible connection between the electrodes and the flex PCB, for example wires or polyurethane with silver ink. The cover can stretch with the breathable tape on both the clinical device and the above described wireless device. There is generally a gap between the flex PCB and breathable tape in both clinical and above described wireless devices. The tested device used weights to at least partially simulate the weight of wireless and processor circuitry. The adherent device of the MS clinical system comprises four electrodes to measure bioimpedance and ECG signals and a 3-axis accelerometer, as described above. Bioimpedance signals were used to determine patient respiration and patient hydration, and accelerometer signals were used to determine patient activity and posture. The MS clinical adherent patch device comprising the sensors and at least some sensor circuitry were connected to a processor to record data. The processor was connected to the tested adherent device with wires and supported away from the tested adherent patch device, for example around the patient's waist. Data were collected at regular intervals and uploaded to a remote site, as described above.

Clinical testing of the MS clinical system shows the effectiveness of the structures for continuous adherence of at least one week and data collection, and that patches can be successively removed and replaced by the patient for in-home monitoring. This effectiveness has been shown without requiring fully functional electronics circuitry such as a battery, wireless circuitry and process circuitry on the adherent device. For example, the MS system includes an insert with about 20 g of additional weight. Although an insert with a 20 gram weight was used for the MS clinical device, greater amounts of weight and circuitry can be used, for example about 30-50 g. The patch device may be modified to accommodate additional weight, for example by increasing the size of the adherent surface. The shape of the MS clinical patch is generally elongate, similar to the elongate shape shown above.

Study Design and Rationale

The MS System is used in a clinical study of heart failure patients to gather data that can be used to develop an algorithm for diagnosing and predicting impending heart failure decompensation events. Events typically manifest as heart failure-related hospitalization, emergency room or urgent care visits leading to a change in oral or IV diuretic treatment.

The purpose of the clinical study is to correlate physiological signals recorded by the system to clinical events of acute heart failure decompensation (AHFD). Signals from the patch can be weighted and combined to determine an index that associates physiologic parameters to impending events of decompensation. Patients who have been classified as New York Heart Association class III and IV within the last 12 months and have had a recent AHFD event can be enrolled into the study and are monitored with the MS system for approximately 90 days.

AHFD events are defined as any of the following:

1) Any heart failure related ER, Urgent Care, in-office visit or hospitalization requiring administration of IV diuretics, administration of IV inotropes, or ultrafiltration for fluid removal.

2) A change in diuretic, defined as a change in diuretic directed by the health care provider occurring inside a hospital, emergency room, or urgent care setting (i.e. no patient self-directed changes to medications not approved by a health care provider would be included), that satisfies one or more of the following: a) a change in the type of diuretic the patient is taking, b) a dose increase of an existing diuretic, or c) the addition of another diuretic.

3) A heart failure decompensation event for which death is the outcome.

Patients enrolled in the study were asked to replace the patch weekly. The study can enroll at least about 550 patients. The patient was provided with a kit comprising 13 patches for replacement. The patches were placed on alternating left and right sides of the patient's thorax, as described above, to minimize progressive irritation.

The data collected in the study can be used to develop an algorithm to at least one of detect, diagnose or predict an impending cardiac decompensation. The algorithm can be implemented on a processor system as described above. Known methods can be used to analyze the data, for example splitting the patients into two groups, one to develop parameters for the algorithm and a second group to test the algorithm developed with the first group. In many embodiments, the signal of the algorithm may comprise a simple binary output for impending cardiac decompensation of the patient. The logic output, yes or no, can be determined in response to patient data combined as described above. The logic output may comprise a signal, such as a binary Y or N signal.

The developed algorithm can be evaluated with composite sensitivity and false positive patient signal status rates. The sensitivity may be defined as the percent of true positive events out of all condition present events, and the false positive patient status signal status rate can be defined as the number of false positive patient status signals per patient-years of follow up. For example, the sensitivity can be at least 50%, for example at least 60%, at least 70%, or even at least 80%. The false positive patient signal status rate may be limited to no more than about 1.1 false positive patient status signals per patient year, for example no more than about 1.0 false positive patient status signals per patient year, no more than about 0.9 false positive patient status signals per patient year, and even no more than about 0.8 false positive patient status signals per patient year.

Clinical Results

Clinical data are available for the first **180** patients enrolled in the study.

FIGS. **3**A and **3**B show clinical data measured with an adherent patch device, in accordance with the above protocol. FIG. **3**A shows data from a patient with the MS patch adhered to a first patient, and the data was acquired over the 90 day period with the series of 13 patches. The signals measured included Heart Rate (beats per minute), Heart Rate Variability (ms), Respiratory Rate (breaths per minute), Activity (m-G's) and Body Fluid (Ohms). FIG. **3**B shows data from a second patient similar to FIG. **3**A.

Of the 180 patients who have completed the study with the MS adherent patch, as described above, all patches in all patients adhered continuously without patch failure. In all patients, the first patch adhered continuously for the first week. With the exception of a handful of patient deaths and early withdrawals that were unrelated to device failure, all patients reached the end of 90-day follow-up period having used 13 weekly patches without incident. None of the 180 patients showed skin irritation or damage that required withdrawal from the study.

The above data show that the wireless adherent patch device can be constructed for in home wireless patient monitoring for an extended period of at least 90 day, in which each patch of a set is continuously adhered to a patient for at least one week and each patch is configured to support the measurement circuitry, the processor, the wireless communication circuitry and the battery with the skin of the patient.

While the exemplary embodiments have been described in some detail, by way of example and for clarity of understanding, those of skill in the art will recognize that a variety of modifications, adaptations, and changes may be employed. Hence, the scope of the present invention should be limited solely by the appended claims.

What is claimed is:

1. A system to detect impending acute cardiac decompensation of a patient, the patient having a skin and an extracellular fluid, the system comprising:

impedance circuitry to measure, a hydration signal of the patient and a respiration signal of the patient, wherein the hydration signal corresponds to a tissue hydration of the patient; and

a processor system comprising a computer readable memory in communication with the impedance circuitry, wherein the computer readable memory of the processor system embodies instructions to combine the hydration signal and the respiration signal to detect the impending acute cardiac decompensation.

2. The system of claim **1** wherein the processor system comprises at least one processor at a location remote from the patient configured to detect impending acute cardiac decompensation.

3. The system of claim **1** wherein the processor system, supported with the patient, receives instructions transmitted from a remote site and combines the hydration signal and the respiration signal in response to the instructions to detect the impending acute cardiac decompensation.

4. The system of claim **1**, further comprising circuitry to measure an electrocardiogram signal of the patient, wherein the computer readable memory of the processor system embodies instructions to combine the electrocardiogram signal, the hydration signal, and the respiration signal to detect the impending acute cardiac decompensation.

5. The system of claim **4**, further comprising circuitry to measure an activity signal of the patient, wherein the computer readable memory of the processor system embodies instructions to combine the electrocardiogram signal, the hydration signal, the respiration signal and the activity signal to detect the impending acute cardiac decompensation.

6. The system of claim **1** wherein the processor system simultaneously uses the hydration signal and the respiration signal to detect the impending acute cardiac decompensation.

7. The system of claim **1** wherein combing comprises the processor system using the hydration signal and the respiration signal to look up a value in a previously existing array.

8. The system of claim **1** wherein combining comprises at least one of adding, subtracting, multiplying, scaling or dividing the hydration signal and the respiration signal.

9. The system of claim **1** wherein the processor system combines the hydration signal and the respiration signal with at least one of a weighted combination, a tiered combination or a logic gated combination, a time weighted combination or a rate of change.

10. The system of claim **1** wherein the processor system determines a flag status in response to the hydration signal and the respiration signal.

11. The system of claim **8** wherein the processor system determines the flag status in response to a change in the hydration signal and the respiration signal.

12. The system of claim **8** wherein the processor system affects the circuitry to make additional signal measurements of the patient in response to the flag status.

13. The system of claim **1** wherein the processor system combines the hydration signal and the respiration signal in response to a time of day.

14. The system of claim **1** wherein the hydration signal and the respiration signal comprise at least one of a derived signal, a time averaged signal, a filtered signal or a raw signal.

15. The system of claim **1**, further comprising an accelerometer to measure an activity signal of the patient, wherein the activity signal is combined with the hydration signal and the respiration signal.

16. The system of claim **1**, further comprising circuitry to measure an activity signal of the patient, wherein the activity signal comprises an accelerometer signal to determine a posture of the patient.

17. The system of claim **16** wherein the accelerometer signal comprises a three dimensional inclination signal to determine a three dimensional orientation of the patient.

18. The system of claim **1** wherein the processor transmits the hydration signal and the respiration signal to a remote site where the hydration signal and the respiration signal are combined to detect the impending acute cardiac decompensation.

19. The system of claim 1 wherein the processor system comprises a remote processor located at a site remote from the patient and a processor coupled to a support configured to adhere to the skin of the patient and wherein the remote processor is configured to transmit instructions from the site remote from the patient to the processor coupled to the support, and wherein the processor coupled to the support is configured to combine the hydration signal and the respiration signal in response to the instructions to detect the impending acute cardiac decompensation.

20. The system of claim 1 wherein the circuitry comprises circuitry to measure a skin temperature signal of the patient and wherein the computer readable memory of the processor system embodies instructions to correct the hydration signal such that the hydration signal remains substantially unchanged when the measured impedance decreases and the skin temperature increases.

21. The system of claim 1 wherein the patient exhibits heart failure corresponding to a New York Heart Association classification of class III and wherein the computer readable memory embodies instructions to detect the impending acute cardiac decompensation with a sensitivity of at least about 50% and a false positive patient status signal rate of no more than about 1.1 false positive patient status signals per patient year.

22. The system of claim 1 wherein the hydration signal of the patient and the respiration signal of the patient are based on impedance measurements made at a single frequency within a range from about 0.5 kHz to about 20 kHz to determine a tissue impedance.

23. The system of claim 1 wherein the hydration signal of the patient and the respiration signal of the patient are based on impedance measurements made at a single frequency within a range from about 0.5 kHz to about 10 kHz to determine a tissue impedance.

24. The system of claim 1 wherein the computer readable memory embodies instructions to determine the change of the hydration signal based on a baseline hydration value of the patient measured at least one week before the hydration signal and instructions to determine the change of the respiration signal based on a baseline respirations value of the patient measured at least one week before the respiration signal.

25. The system of claim 1 wherein the computer readable memory embodies instructions to determine the change of the hydration signal based on a baseline hydration value of the patient measured with a first adherent device at least one week before the hydration signal measured with a second adherent device and instructions to determine the change of the respiration signal based on a baseline respiration value of the patient measured with the first adherent device at least one week before the respiration signal measured with the second adherent device.

26. A system to predict an impending acute cardiac decompensation of a patient having heart failure, the patient having a skin and extracellular fluid, the system comprising:

circuitry to measure an activity signal of the patient, a hydration signal of the patient and a respiration signal of the patient, the circuitry comprising an accelerometer to measure the activity signal of the patient, the circuitry comprising impedance circuitry to measure the hydration signal of the patient and the respiration signal of the patient based on impedance measurements, the impedance measurements having a single frequency within a range from about 1 kHz to about 10 kHz such that the hydration signal corresponds to a tissue hydration of the patient; and

a processor system comprising a computer readable memory in communication with the circuitry, wherein the computer readable memory of the processor system embodies instructions to combine the hydration signal and the respirations signal to predict the impending acute cardiac decompensation, wherein the computer readable memory embodies instructions to determine a baseline hydration value of the patient and compare the baseline hydration value to the hydration signal to determine a change of the hydration signal from the baseline hydration value over a 90 day period and instructions to determine a baseline respiration value of the patient and compare the baseline respiration value to the respiration signal over the 90 day period to determine a change of the respiration signal from the baseline respiration value and wherein the processor system embodies instructions to predict the impending acute cardiac decopmensation based on the change of the hydration signal and the change of the respiration signal.

27. The system of claim 1, wherein the computer readable memory embodies instructions to determine a baseline hydration value of the patient and compare the baseline hydration value to the hydration signal to determine a change of the hydration signal from the baseline hydration value and instructions to detect the impending acute cardiac decompensation based in part on the change of the hydration signal.

28. A system to detect impending acute cardiac decompensation of a patient, the system comprising:

impedance circuitry to measure a hydration signal of the patient such that the hydration signal corresponds to a tissue hydration of the patient, wherein a respiration signal of the patient is derived from the impedance circuitry; and

a processor system in communication with the impedance circuitry, the processor system comprising a computer readable memory storing instructions to detect the impending acute cardiac decompensation based at least in part on the hydration signal of the patient and the respiration signal of the patient.

29. The system of claim 28, wherein the computer readable memory stores instructions to determine a baseline hydration value of the patient and compare the baseline hydration value to the hydration signal to determine a change of the hydration signal from the baseline hydration value and instructions to detect the impending acute cardiac decompensation based at least in part on the change of the hydration signal.

30. The system of claim 29, wherein the hydration signal is based on impedance measurements having a frequency within a range from about 0.5 kHz to about 20 kHz.

31. The system of claim 28, wherein the computer readable memory stores instructions to determine a baseline respiration value of the patient and compare the baseline respiration value to the respiration signal to determine a change of the respiration signal from the baseline respiration value and instructions to detect the impending acute cardiac decompensation based in part on the change of the respiration signal.

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(12) **United States Patent**
Libbus et al.

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(54) **MULTI-SENSOR PATIENT MONITOR TO DETECT IMPENDING CARDIAC DECOMPENSATION**

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(58) **Field of Classification Search**

None

See application file for complete search history.

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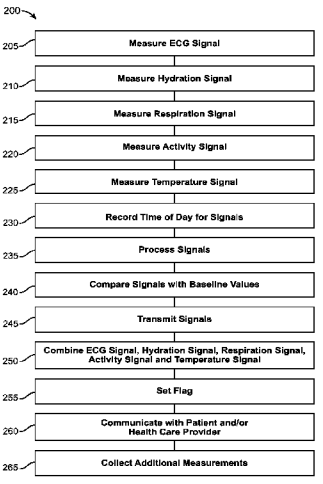
(57) **ABSTRACT**

Systems and methods of detecting an impending cardiac decompensation of a patient measure at least two of an electrocardiogram signal of the patient, a hydration signal of the patient, a respiration signal of the patient or an activity signal of the patient. The at least two of the electrocardiogram signal, the hydration signal, the respiration signal or the activity signal are combined with an algorithm to detect the impending cardiac decompensation.

20 Claims, 10 Drawing Sheets



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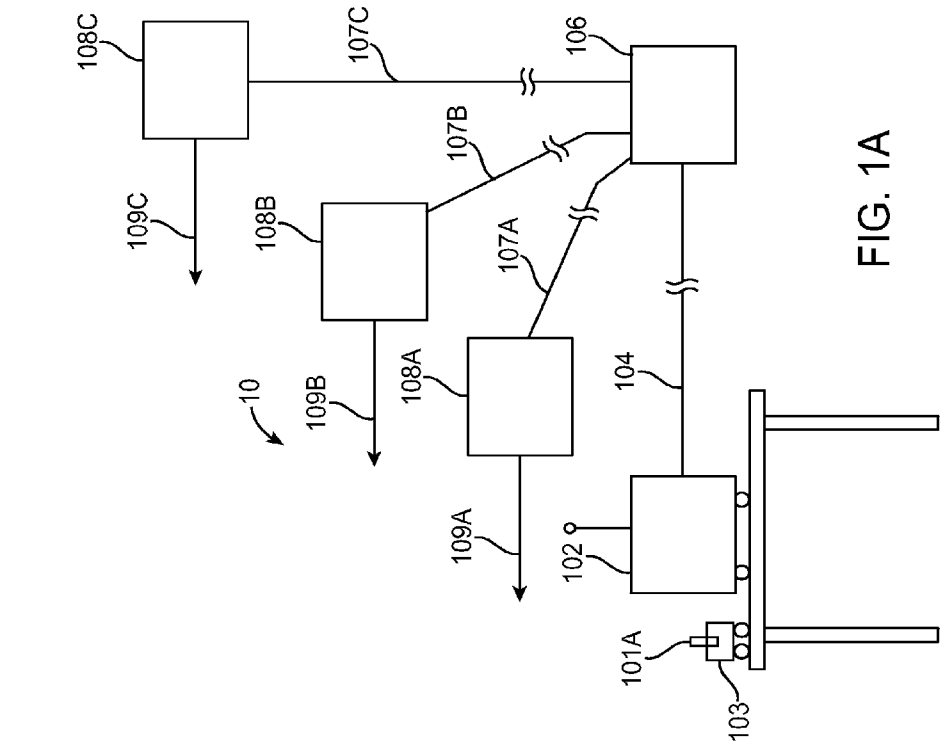
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109B
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101A
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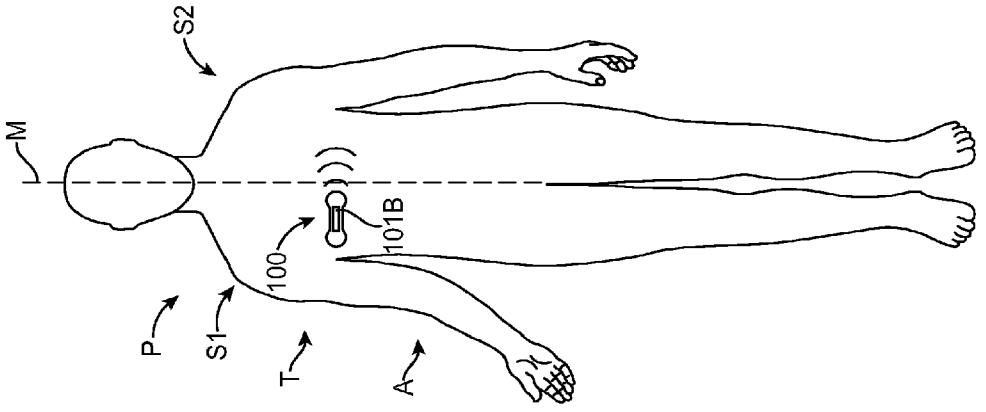
FIG. 1A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P
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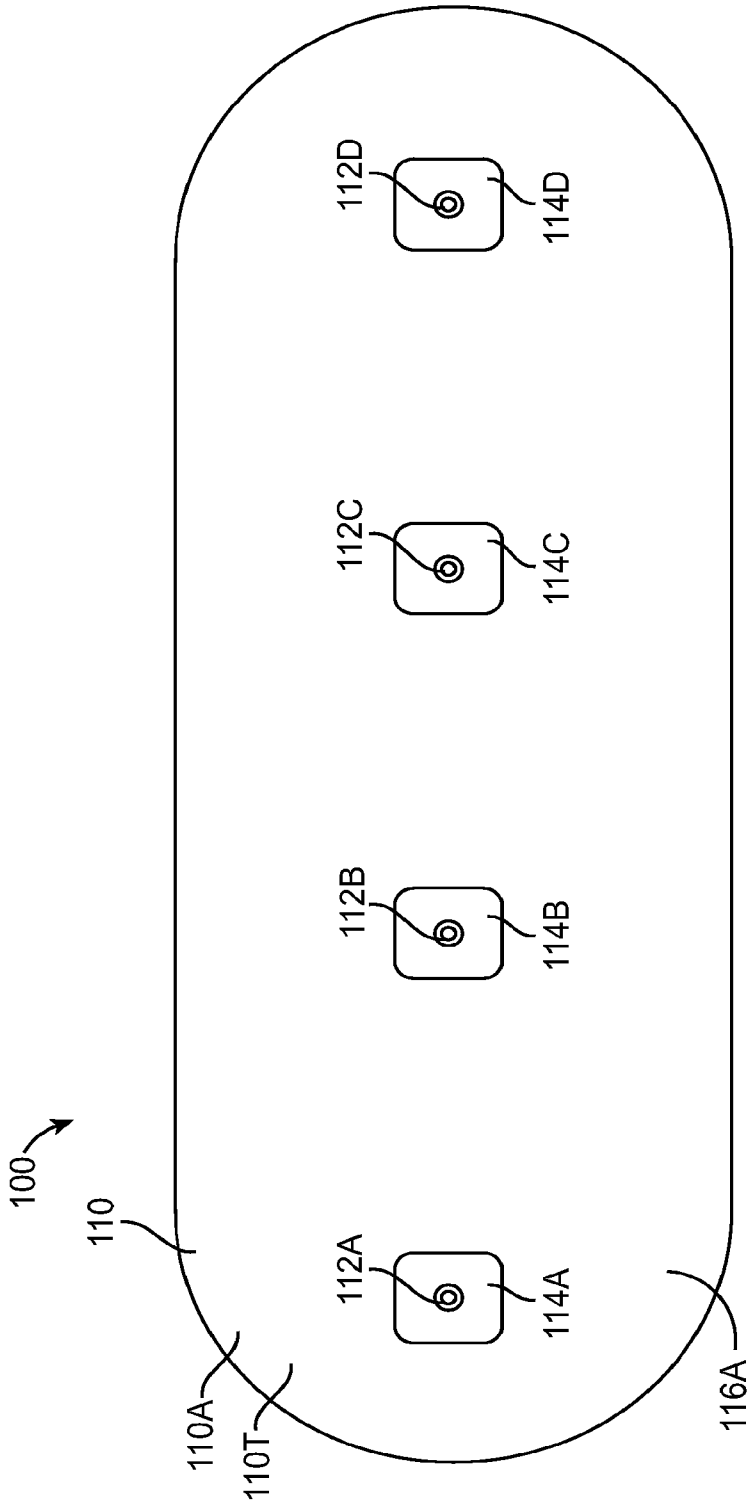
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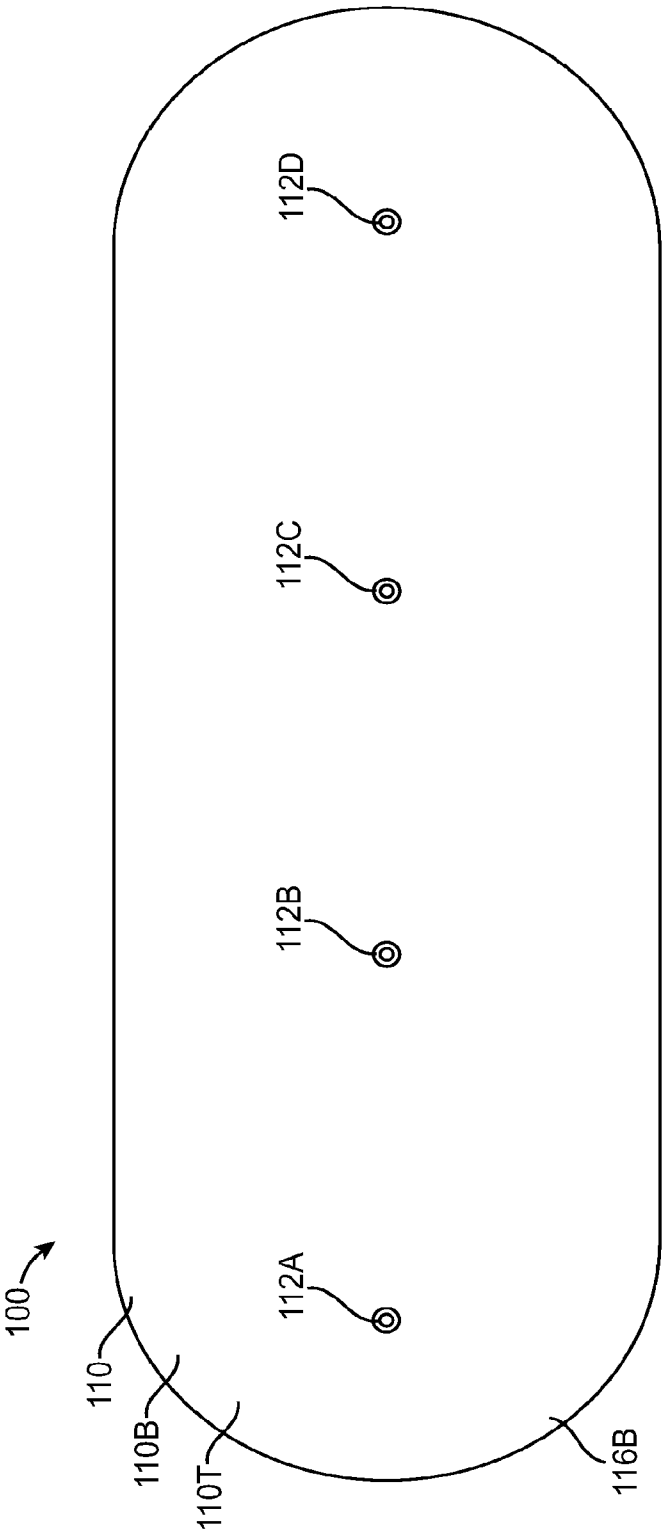
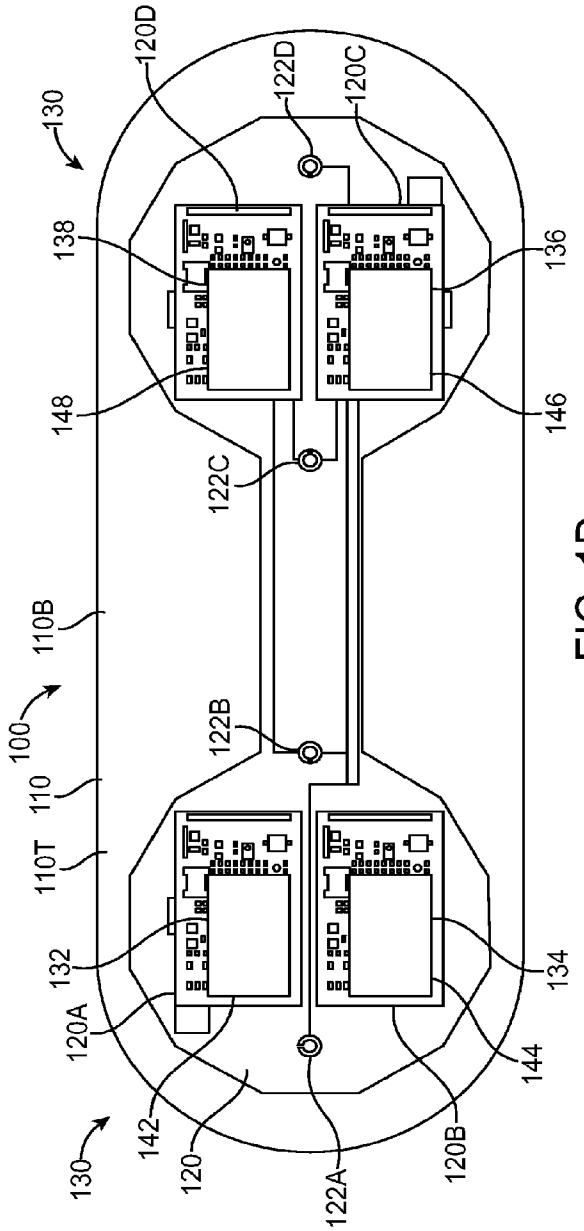


FIG. 1C



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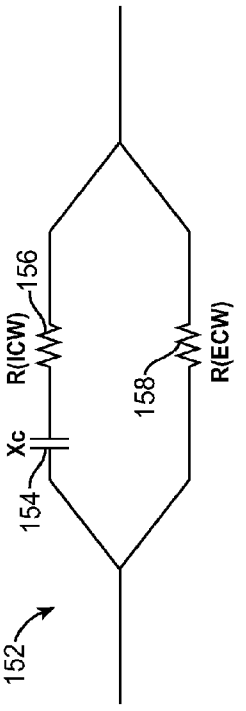

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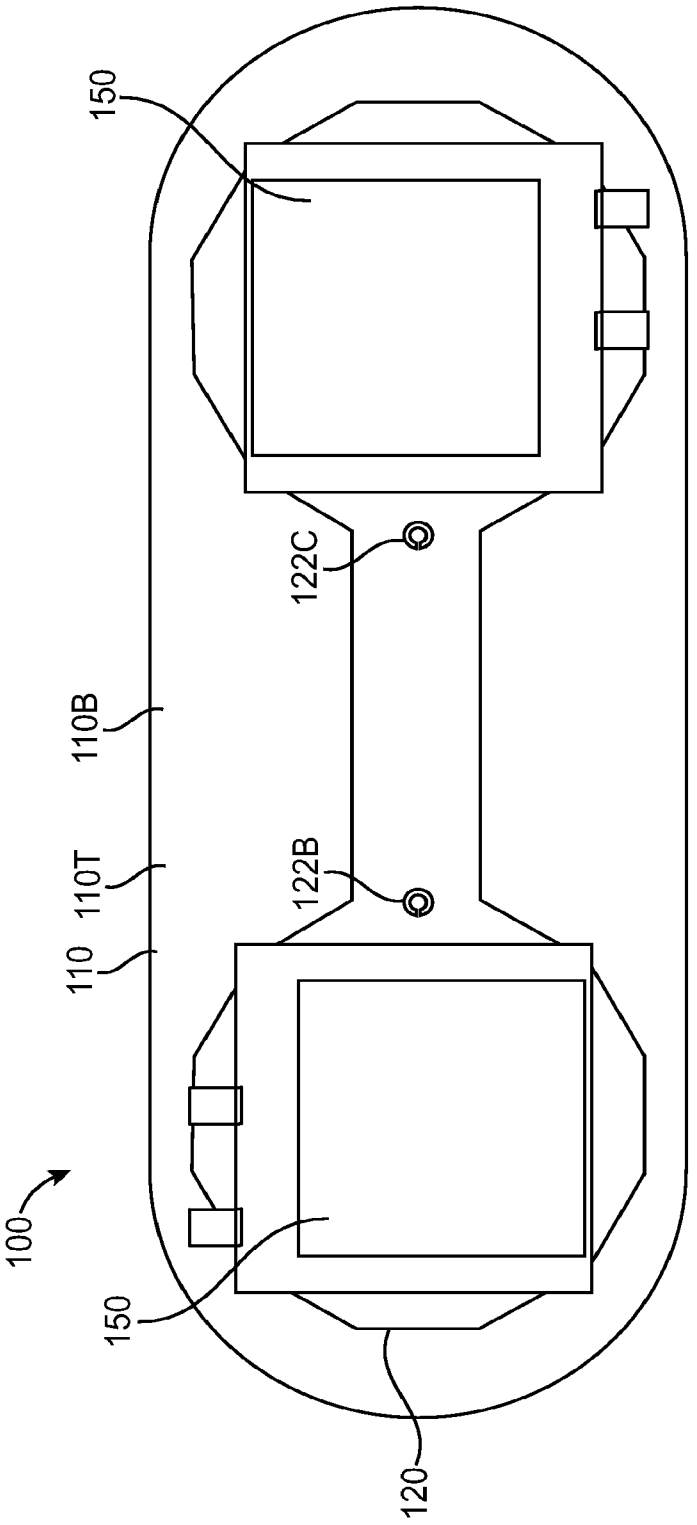
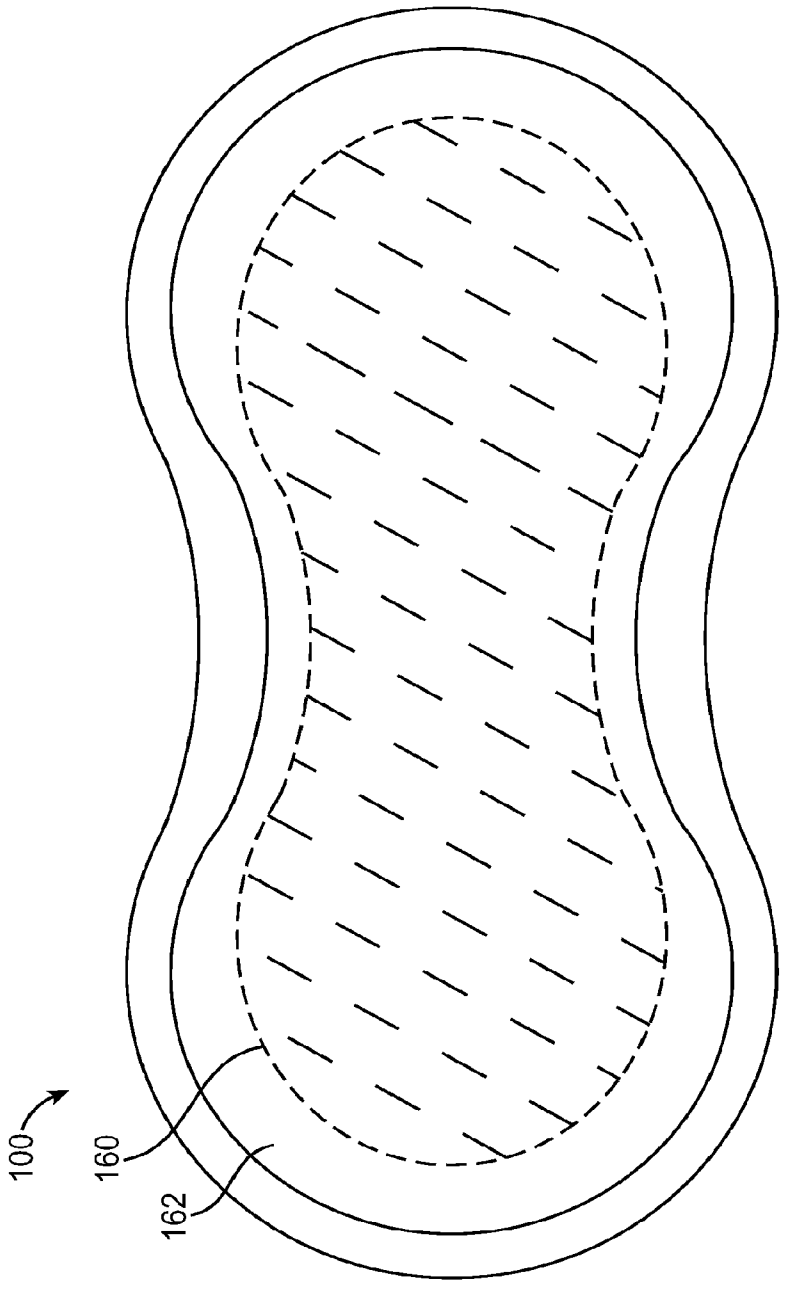


FIG. 1E



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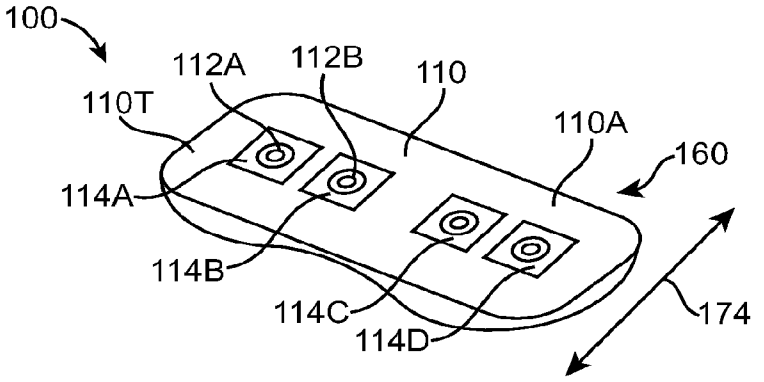
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FIG. 1H

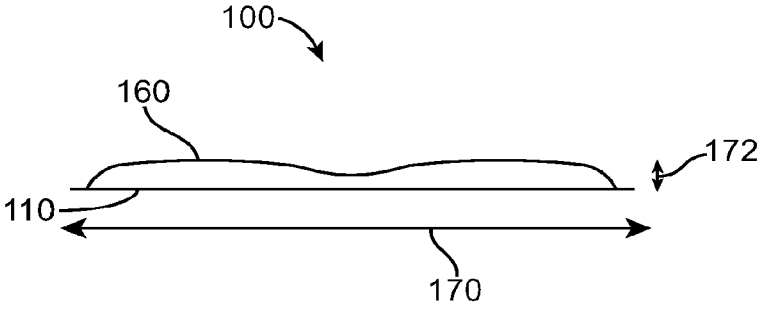
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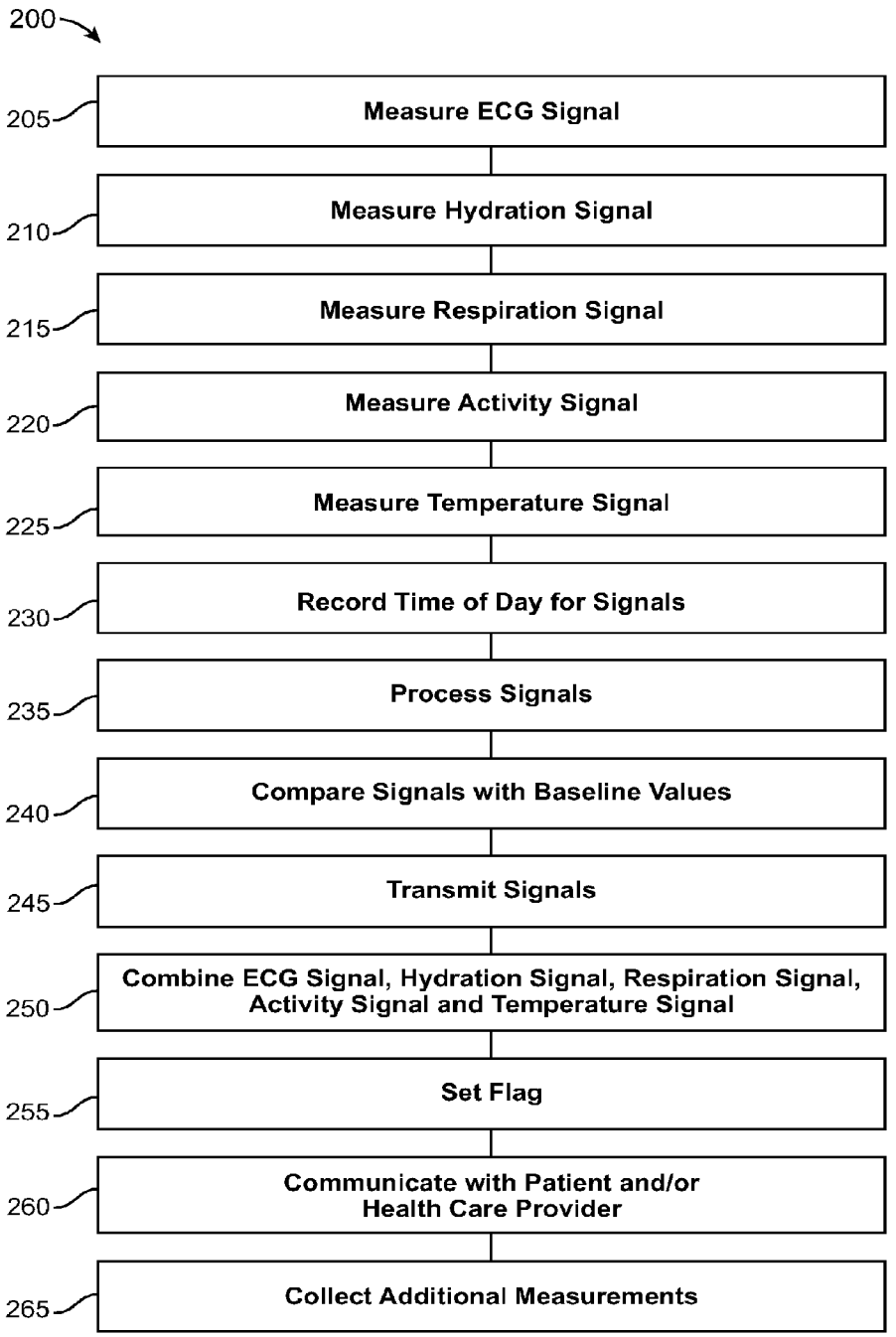
FIG. 1G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Measure Hydration Signal
215
Measure Respiration Signal
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Measure Activity Signal
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Measure Temperature Signal
230
Record Time of Day for Signals
235
Process Signals
240
Compare Signals with Baseline Values
245
Transmit Signals
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Combine ECG Signal, Hydration Signal, Respiration Signal, Activity Signal and Temperature Signal
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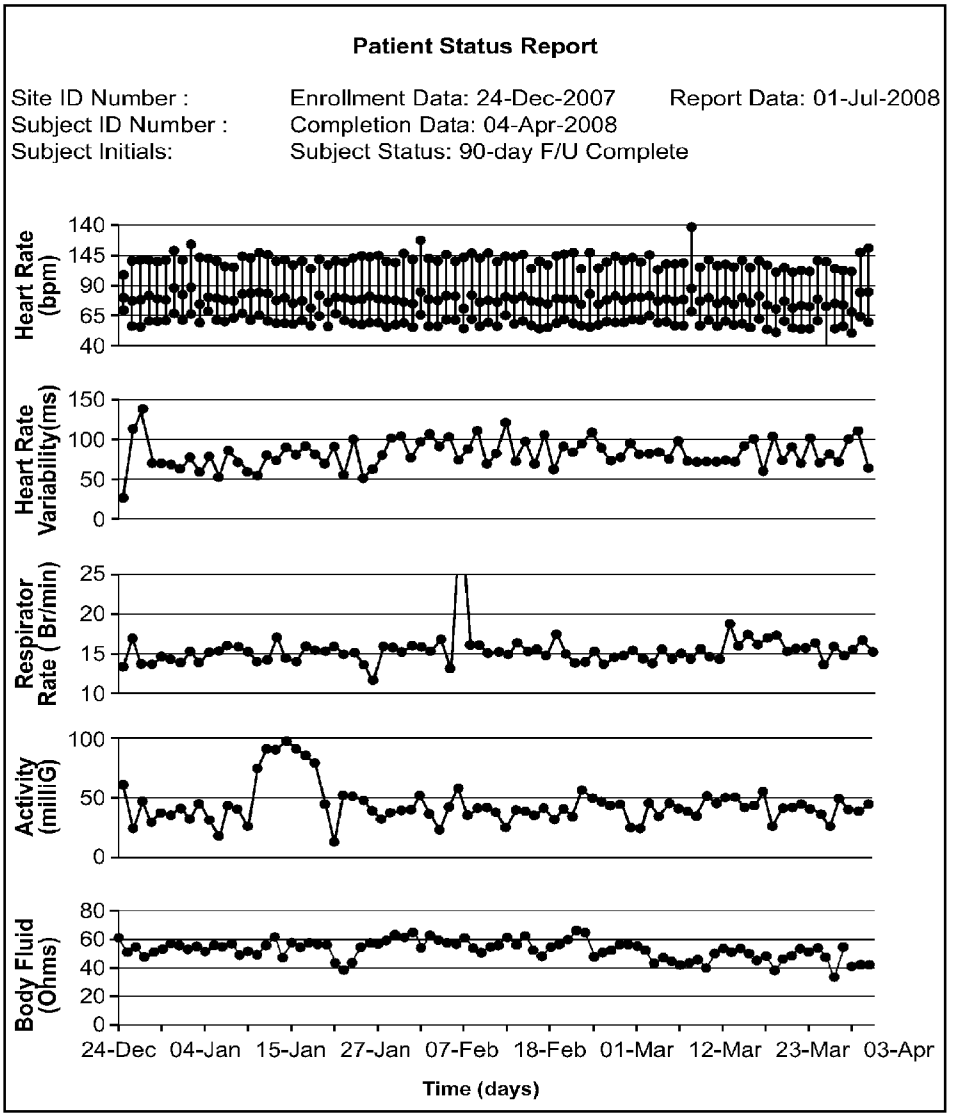
Set Flag
260
Communicate with Patient and/or Health Care Provider
265
Collect Additional Measurements

FIG. 2A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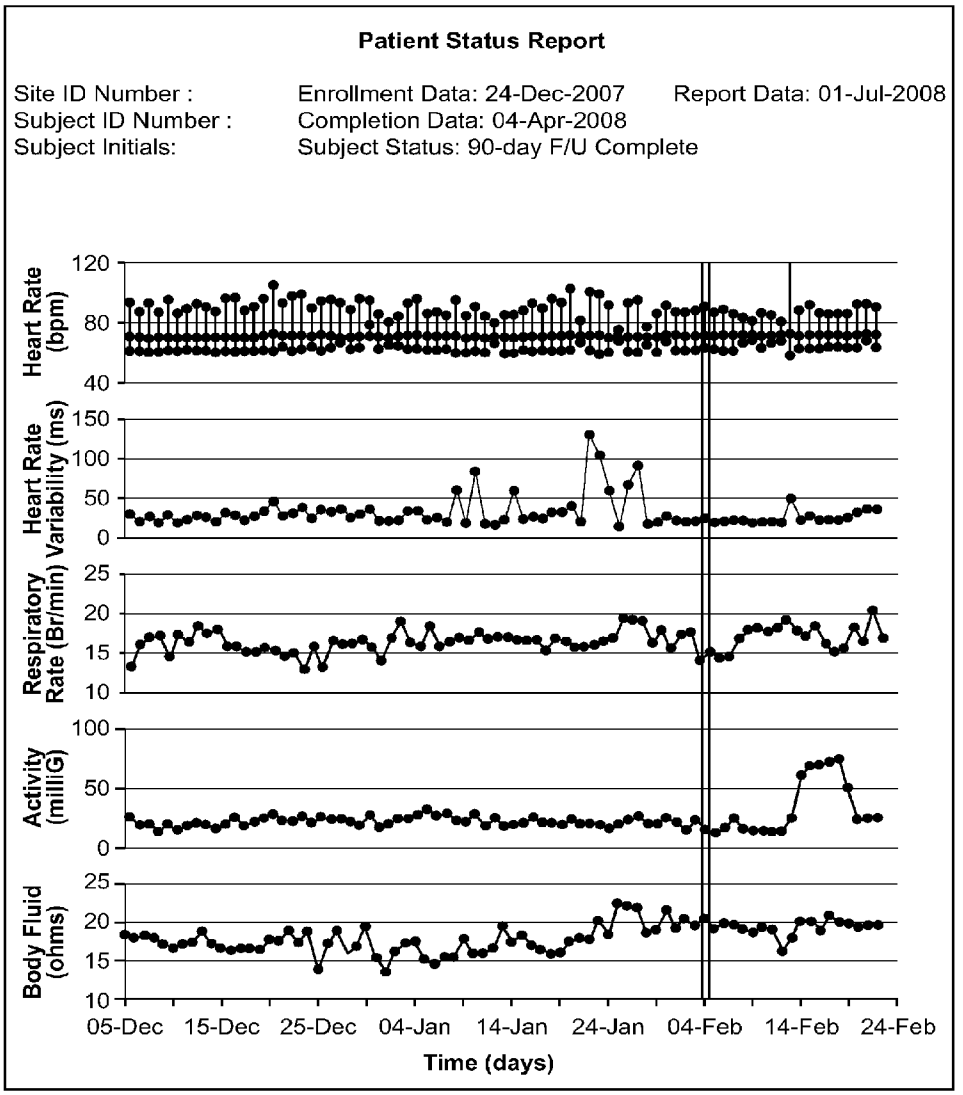
Completion Data: 04-Apr-2008
Subject Status: 90-day F/U Complete
Report Data: 01-Jul-2008
Heart Rate (bpm)
140
145
90
65
40
Heart Rate Variability(ms)
150
100
50
0
Respirator Rate (Br/min)
25
20
15
10
Activity (milliG)
100
50
0
Body Fluid (Ohms)
80
60
40
20
0
24-Dec 04-Jan 15-Jan 27-Jan 07-Feb 18-Feb 01-Mar 12-Mar 23-Mar 03-Apr
Time (days)

FIG. 3A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Heart Rate (bpm)
120
80
40
Heart Rate Variability (ms)
150
100
50
0
Respiratory Rate (Br/min)
25
20
15
10
Activity (milliG)
100
50
0
Body Fluid (ohms)
25
20
15
10
05-Dec
15-Dec
25-Dec
04-Jan
14-Jan
24-Jan
04-Feb
14-Feb
24-Feb
Time (days)

FIG. 3B

MULTI-SENSOR PATIENT MONITOR TO DETECT IMPENDING CARDIAC DECOMPENSATION

CROSS-REFERENCES TO RELATED APPLICATIONS

This application is a Continuation of U.S. application Ser. No. 12/209,279, filed on 12 Sep. 2008, which claims the benefit of U.S. Provisional Application No. 61/055,666, filed on 23 May 2008, and of U.S. Provisional Application No. 60/972,512, filed on 14 Sep. 2007, and which applications are incorporated herein by reference. A claim of priority to all, to the extent appropriate, is made.

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates to patient monitoring, and more specifically to patient monitoring to detect and/or avoid impending cardiac decompensation. Although embodiments make specific reference to monitoring impedance and electrocardiogram signals with an adherent patch, the system methods and device described herein may be applicable to many applications in which physiological monitoring is used, for example wireless physiological monitoring with implantable devices for extended periods.

Patients are often treated for diseases and/or conditions associated with a compromised status of the patient, for example a compromised physiologic status such as heart disease. In some instances a patient may have suffered a heart attack and require care and/or monitoring after release from the hospital. While such long term care may be at least partially effective, many patients are not sufficiently monitored and eventually succumb to cardiac decompensation, or heart failure. One example of a device that may be used to monitor a patient is the Holter monitor, or ambulatory electrocardiography device. Although such a device may be effective in measuring electrocardiography, such measurements alone may not be sufficient to reliably detect and/or avoid an impending cardiac decompensation.

In addition to measuring heart signals with electrocardiograms, known physiologic measurements include impedance measurements. For example, transthoracic impedance measurements can be used to measure hydration and respiration. Although transthoracic measurements can be useful, such measurements may use electrodes that are positioned across the midline of the patient, and may be somewhat uncomfortable and/or cumbersome for the patient to wear.

Work in relation to embodiments of the present invention suggests that known methods and apparatus for long term monitoring of patients may be less than ideal to detect and/or avoid an impending cardiac decompensation. In at least some instances, cardiac decompensation can be difficult to detect, for example in the early stages. At least some of the known devices may not collect the right kinds of data to treat patients optimally. For example, although successful at detecting and storing electrocardiogram signals, devices such as the Holter monitor can be somewhat bulky and may not collect all of the kinds of data that would be ideal to diagnose and/or treat a patient, for example to detect decompensation. In at least some instances, devices that are worn by the patient may be somewhat uncomfortable, which may lead to patients not wearing the devices and not complying with direction from the health care provider, such that data collected may be less than ideal. Although implantable devices may be used in some instances, many of these devices can be invasive and/or

costly, and may suffer at least some of the shortcomings of known wearable devices. As a result, at least some patient are not adequately monitored, and may go into cardiac decompensation, or even die. Work in relation to embodiments of the present invention suggests that improved monitoring may avoid patient trauma, save lives, and decrease health care costs.

Therefore, a need exists for improved patient monitoring. Ideally, such improved patient monitoring would avoid at least some of the short-comings of the present methods and devices.

2. Description of the Background Art

The following U.S. patents and Publications may describe relevant background art: U.S. Pat. Nos. 4,121,573; 4,955,381; 4,981,139; 5,080,099; 5,353,793; 5,469,859; 5,511,553; 5,544,661; 5,558,638; 5,724,025; 5,772,586; 5,862,802; 6,047,203; 6,117,077; 6,129,744; 6,225,901; 6,308,094; 6,385,473; 6,416,471; 6,454,707; 6,454,708; 6,527,711; 6,527,729; 6,551,252; 6,595,927; 6,595,929; 6,605,038; 6,645,153; 6,821,249; 6,980,851; 7,020,508; 7,054,679; 7,153,262; 7,160,252; 2004/133079; 2004/152956; 2005/0113703; 2005/0131288; 2006/0010090; 2006/0031102; 2006/0089679; 2006/122474; 2006/0155183; 2006/0224051; 2006/0264730; 2007/0021678; 2007/0038038; 2005/256418; 2005/137626; and 2006/161459. The following PCT Publication(s) may also describe relevant background art: WO2006/111878.

BRIEF SUMMARY OF THE INVENTION

Embodiments of the present invention provide systems and methods for the detection of an impending cardiac decompensation. In many embodiments, the impending decompensation can be detected early enough to avoid, or at least delay, the impending decompensation, such that patient trauma and/or expensive ICU care can be avoided. Although embodiments make specific reference to monitoring impedance and electrocardiogram signals with an adherent patch, the system methods and device described herein may be applicable to many applications in which physiological monitoring is used, for example wireless physiological monitoring with implanted sensors for extended periods.

In a first aspect, embodiments of the present invention provide a method of detecting an impending cardiac decompensation of a patient. At least two of an electrocardiogram signal of the patient, a hydration signal of the patient, a respiration signal of the patient or an activity signal of the patient are measured. The at least two of the electrocardiogram signal, the hydration signal, the respiration signal or the activity signal are combined to detect the impending cardiac decompensation. In many embodiments, the impending decompensation can be detected at least 24 hours before the decompensation occurs, for example 72 hours, and in many embodiments with a confidence level of at least 80%, for example 90%.

In many embodiments, the at least two comprise at least three of the electrocardiogram signal, the hydration signal, the respiration signal or the activity signal, and the at least three are measured and combined to detect the impending cardiac decompensation. In specific embodiments, the at least three comprise at least four of the electrocardiogram signal, the hydration signal, the respiration signal or the activity signal, and the at least four are measured and combined to detect the impending cardiac decompensation.

In specific embodiments, the electrocardiogram signal, the hydration signal, the respiration signal and the activity signal are measured combined to detect the impending cardiac decompensation.

In many embodiments, the at least two of the electrocardiogram signal, the hydration signal, the respiration signal or the activity signal can be used simultaneously to determine impending cardiac decompensation. The at least two signals can be used simultaneously in many ways.

In many embodiments, combining comprises using the at least two of the electrocardiogram signal, the hydration signal, the respiration signal or the activity signal to look up a value in a previously existing array. In some embodiments, combining may comprise at least one of adding, subtracting, multiplying, scaling or dividing the at least two of the electrocardiogram signal, the hydration signal, the respiration signal or the activity signal. In some embodiments, the at least two of the electrocardiogram signal, the hydration signal, the respiration signal or the activity signal can be combined with at least one of a weighted combination, a tiered combination or a logic gated combination, a time weighted combination or a rate of change.

In many embodiments, a flag status is determined in response to the at least two of the electrocardiogram signal, the hydration signal, the respiration signal or the activity signal. The flag status can be determined in response to a change in the at least two of the electrocardiogram signal, the hydration signal, the respiration signal or the activity signal. In some embodiments, additional signal measurements of the patient can be made in response to the flag status.

In many embodiments, the at least two of the electrocardiogram signal, the hydration signal, the respiration signal or the activity signal are combined in response to a time of day.

In many embodiments, the at least two of the electrocardiogram signal, the hydration signal, the respiration signal or the activity signal may comprise at least one of a derived signal, a time averaged signal, a filtered signal or a raw signal.

In many embodiments, baseline values of the patient for the at least two of the electrocardiogram signal, the hydration signal, the respiration signal or the activity signal are determined, and the at least two of the electrocardiogram signal, the hydration signal, the respiration signal or the activity signal signals comprise changes from the baseline values.

In many embodiments, the at least two of the electrocardiogram signal, the hydration signal, the respiration signal or the activity signal comprise differences from population baseline values, and the impending decompensation is detected in response to the differences from the baseline values of the patient population.

In many embodiments, the hydration signal comprises an impedance signal and the activity signal comprise an accelerometer signal.

In many embodiments, the activity signal may comprise an accelerometer signal to indicate a posture of the patient. In specific embodiments, the accelerometer signal may comprise a three dimensional inclination signal to determine a three dimensional orientation of the patient.

In many embodiments, a temperature signal is combined with the at least two of the electrocardiogram signal, the hydration signal, the respiration signal or the activity signal to detect the impending cardiac decompensation.

In many embodiments, the at least two of the electrocardiogram signal, the hydration signal, the respiration signal or the activity signal are transmitted to a remote site where the at least two of the electrocardiogram signal, the hydration signal, the respiration signal or the activity signal are combined to detect the impending cardiac decompensation.

In many embodiments, instructions are transmitted from a remote site to a processor supported with the patient, and the at least two of the electrocardiogram signal, the hydration signal, the respiration signal or the activity signal are combined with the processor in response to the instructions to detect the impending cardiac decompensation.

In another aspect, embodiments of the present invention provide a system to detect impending cardiac decompensation of a patient. The system comprises circuitry to measure at least two of an electrocardiogram signal of the patient, a hydration signal of the patient, or an activity signal of the patient. A processor system comprising a tangible medium in communication with the circuitry is configured to combine the at least two of the electrocardiogram signal, the hydration signal, the respiration signal or the activity signal to detect the impending cardiac decompensation.

In some embodiments, the processor system comprises a least one processor remote from the patient configured to combine the at least two to detect the decompensation.

In some embodiments, the processor system comprises a processor supported with the patient configured to receive instructions transmitted from a remote site and combine the at least two in response to the instructions to detect the impending cardiac decompensation.

In many embodiments, the at least two comprise at least three of the electrocardiogram signal, the hydration signal, the respiration signal or the activity signal and the at least three are measured and combined to detect the impending cardiac decompensation. In specific embodiments, the at least three comprise at least four of the electrocardiogram signal, the hydration signal, the respiration signal or the activity signal and the at least four are measured and combined to detect the impending cardiac decompensation.

In specific embodiments, the processor system simultaneously uses the at least two of the electrocardiogram signal, the hydration signal, the respiration signal or the activity signal to determine impending cardiac decompensation. The at least two signals can be used simultaneously in many ways,

In many embodiments, combining comprises the processor system using the at least two of the electrocardiogram signal, the hydration signal, the respiration signal or the activity signal to look up a value in a previously existing array. In some embodiments, combining comprises at least one of adding, subtracting, multiplying, scaling or dividing the at least two of the electrocardiogram signal, the hydration signal, the respiration signal or the activity signal. In some embodiments, the at least two of the electrocardiogram signal, the hydration signal, the respiration signal, or the activity signal can be combined with at least one of a weighted combination, a tiered combination or a logic gated combination, a time weighted combination or a rate of change.

In many embodiments, the processor system determines a flag status in response to the at least two of the electrocardiogram signal, the hydration signal, the respiration signal or the activity signal. The processor system determines the flag status in response to a change in the at least two of the electrocardiogram signal, the hydration signal, the respiration signal or the activity signal. In some embodiments, the processor system affects the circuitry to make additional signal measurements of the patient in response to the flag status.

In many embodiments, the processor system combines the at least two of the electrocardiogram signal, the hydration signal, the respiration signal or the activity signal in response to a time of day.

In many embodiments, the at least two of the electrocardiogram signal, the hydration signal, the respiration signal or

the activity signal comprise at least one of a derived signal, a time averaged signal, a filtered signal or a raw signal.

In many embodiments, the processor determines baseline values of the patient for the at least two of the electrocardiogram signal, the hydration signal, the respiration signal or the activity signal. The at least two of the electrocardiogram signal, the hydration signal, the respiration signal or the activity signal signals may comprise changes from the baseline values.

In many embodiments, the at least two of the electrocardiogram signal, the hydration signal, the respiration signal or the activity signal comprise differences from baseline values of a patient population. The impending decompensation is detected in response to the differences from the baseline value of the patient population.

In many embodiments, the hydration signal comprises an impedance signal and the activity signal comprise an accelerometer signal.

In many embodiments, the activity signal may comprise an accelerometer signal to determine a posture of the patient. In specific embodiments, the accelerometer signal may comprise a three dimensional inclination signal to determine a three dimensional orientation of the patient.

In many embodiments, the processor system combines a temperature signal with the at least two of the electrocardiogram signal, the hydration signal, the respiration signal or the activity signal to detect the impending cardiac decompensation.

In many embodiments, the processor transmits the at least two of the electrocardiogram signal, the hydration signal, the respiration signal or the activity signal to a remote site where the at least two of the electrocardiogram signal, the hydration signal, the respiration signal or the activity signal are combined to detect the impending cardiac decompensation.

In many embodiments, instructions are transmitted from a remote site to a processor supported with the patient. The processor combines at least two of the electrocardiogram signal, the hydration signal, the respiration signal or the activity signal in response to the instructions to detect the impending cardiac decompensation

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1**A shows a patient and a monitoring system comprising an adherent device, according to embodiments of the present invention;

FIG. **1**B shows a bottom view of the adherent device as in FIG. **1**A comprising an adherent patch;

FIG. **1**C shows a top view of the adherent patch, as in FIG. **1**B;

FIG. **1**D shows a printed circuit boards and electronic components over the adherent patch, as in FIG. **1**C;

FIG. **1**D-**1** shows an equivalent circuit that can be used to determine optimal frequencies for determining patient hydration, according to embodiments of the present invention;

FIG. **1**E shows batteries positioned over the printed circuit board and electronic components as in FIG. **1**D;

FIG. **1**F shows a top view of an electronics housing and a breathable cover over the batteries, electronic components and printed circuit board as in FIG. **1**E;

FIG. **1**G shows a side view of the adherent device as in FIGS. **1**A to **1**F;

FIG. **1**H shown a bottom isometric view of the adherent device as in FIGS. **1**A to **1**G;

FIG. **2**A shows a method of predicting an impending cardiac decompensation, according to embodiments of the present invention; and

FIGS. **3**A and **3**B show clinical data measured with an adherent patch device.

DETAILED DESCRIPTION OF THE INVENTION

Embodiments of the present invention provide systems and methods for the detection of an impending cardiac decompensation. In many embodiments, the impending decompensation can be detected early enough to avoid, or at least delay, the impending decompensation, such that patient trauma and/or expensive ICU care can be avoided. Although embodiments make specific reference to monitoring impedance and electrocardiogram signals with an adherent patch, the system methods and device described herein may be applicable to many applications in which physiological monitoring is used, for example wireless physiological monitoring with implanted sensors for extended periods. In some embodiments, implanted sensors may be used, for example as described in U.S. Pat. Nos. 6,208,894; 6,315,721; 6,185,452; and U.S. Application No. 60/972,329, entitled "Injectable Device for Physiological Monitoring" filed on Sep. 14, 2007, the same day as the present application with the same assignee, the full disclosures of which are incorporated by reference.

Decompensation is failure of the heart to maintain adequate blood circulation. Although the heart can maintain at least some pumping of blood, the quantity is inadequate to maintain healthy tissues. Several symptoms can result from decompensation including pulmonary congestion, breathlessness, faintness, cardiac palpitation, edema of the extremities, and enlargement of the liver. Cardiac decompensation can result in slow or sudden death. Sudden Cardiac Arrest (hereinafter "SCA"), also referred to as sudden cardiac death, is an abrupt loss of cardiac pumping function that can be caused by a ventricular arrhythmia, for example ventricular tachycardia and/or ventricular fibrillation. Although decompensation and SCA can be related in that patients with decompensation are also at an increased risk for SCA, decompensation is primarily a mechanical dysfunction caused by inadequate blood flow, and SCA is primarily an electrical dysfunction caused by inadequate and/or inappropriate electrical signals of the heart.

FIG. **1**A shows a patient P and a monitoring system **10**. Patient P comprises a midline M, a first side S**1**, for example a right side, and a second side S**2**, for example a left side. Monitoring system **10** comprises an adherent device **100**. Adherent device **100** can be adhered to a patient P at many locations, for example thorax T of patient P. In many embodiments, the adherent device may adhere to one side of the patient, from which data from the one side can be collected. Work in relation with embodiments of the present invention suggests that location on a side of the patient can provide comfort for the patient while the device is adhered to the patient.

Monitoring system **10** includes components to transmit data to a remote center **106**. Adherent device **100** can communicate wirelessly to an intermediate device **102**, for example with a single wireless hop from the adherent device on the patient to the intermediate device. Intermediate device **102** can communicate with remote center **106** in many ways, for example with an internet connection. In many embodiments, monitoring system **10** comprises a distributed processing system with at least one processor on device **100**, at least one processor on intermediate device **102**, and at least one process at remote center **106**, each of which processors is in electronic communication with the other processors. Remote center **106** can be in communication with a health care pro-

vider **108**A with a communication system **107**A, such as the Internet, an intranet, phone lines, wireless and/or satellite phone. Health care provider **108**A, for example a family member, can be in communication with patient P with a communication, for example with a two way communication system, as indicated by arrow **109**A, for example by cell phone, email, landline. Remote center **106** can be in communication with a health care professional, for example a physician **108**B, with a communication system **107**B, such as the Internet, an intranet, phone lines, wireless and/or satellite phone. Physician **108**B can be in communication with patient P with a communication, for example with a two way communication system, as indicated by arrow **109**B, for example by cell phone, email, landline. Remote center **106** can be in communication with an emergency responder **108**C, for example a 911 operator and/or paramedic, with a communication system **107**C, such as the Internet, an intranet, phone lines, wireless and/or satellite phone. Emergency responder **108**C can travel to the patient as indicated by arrow **109**C. Thus, in many embodiments, monitoring system **10** comprises a closed loop system in which patient care can be monitored and implemented from the remote center in response to signals from the adherent device.

In many embodiments, the adherent device may continuously monitor physiological parameters, communicate wirelessly with a remote center, and provide alerts when necessary.

The system may comprise an adherent patch, which attaches to the patient's thorax and contains sensing electrodes, battery, memory, logic, and wireless communication capabilities. In some embodiments, the patch can communicate with the remote center, via the intermediate device in the patient's home. In the many embodiments, the remote center receives the data and applies the prediction algorithm. When a flag is raised, the center may communicate with the patient, hospital, nurse, and/or physician to allow for therapeutic intervention to prevent decompensation.

The adherent device may be affixed and/or adhered to the body in many ways. For example, with at least one of the following an adhesive tape, a constant-force spring, suspenders around shoulders, a screw-in microneedle electrode, a pre-shaped electronics module to shape fabric to a thorax, a pinch onto roll of skin, or transcutaneous anchoring. Patch and/or device replacement may occur with a keyed patch (e.g. two-part patch), an outline or anatomical mark, a low-adhesive guide (place guide|remove old patch|place new patch|remove guide), or a keyed attachment for chatter reduction. The patch and/or device may comprise an adhesiveless embodiment (e.g. chest strap), and/or a low-irritation adhesive model for sensitive skin. The adherent patch and/or device can comprise many shapes, for example at least one of a dogbone, an hourglass, an oblong, a circular or an oval shape.

In many embodiments, the adherent device may comprise a reusable electronics module with replaceable patches (the module collects cumulative data for approximately 90 days) and/or the entire adherent component (electronics+patch) may be disposable. In a completely disposable embodiment, a "baton" mechanism may be used for data transfer and retention, for example baton transfer may include baseline information. In some embodiments, the device may have a rechargeable module, and may use dual battery and/or electronics modules, wherein one module **101**A can be recharged using a charging station **103** while the other module **101**B is placed on the adherent device. In some embodiments, the intermediate device **102** may comprise the charging module, data transfer, storage and/or transmission, such that one of the electronics modules can be placed in the intermediate device for charging and/or data transfer while the other electronics module is worn by the patient.

In many embodiments, the system can perform the following functions: initiation, programming, measuring, storing, analyzing, communicating, predicting, and displaying. The adherent device may contain a subset of the following physiological sensors: bioimpedance, respiration, respiration rate variability, heart rate (average, minimum, maximum), heart rhythm, HRV, HRT, heart sounds (e.g. S**3**), respiratory sounds, blood pressure, activity, posture, wake/sleep, orthopnea, temperature/heat flux, and weight. The activity sensor may be one of the following: ball switch, accelerometer, minute ventilation, HR, bioimpedance noise, skin temperature/heat flux, BP, muscle noise, posture.

In many embodiments, the patch wirelessly communicates with a remote center. In some embodiments, the communication may occur directly (via a cellular or Wi-Fi network), or indirectly through intermediate device **102**. Intermediate device **102** may consist of multiple devices which communicate wired or wirelessly to relay data to remote center **106**.

FIG. **1**B shows a bottom view of adherent device **100** as in FIG. **1**A comprising an adherent patch **110**. Adherent patch **110** comprises a first side, or a lower side **110**A, that is oriented toward the skin of the patient when placed on the patient. In many embodiments, adherent patch **110** comprises a tape **110**T which is a material, preferably breathable, with an adhesive **116**A. Patient side **110**A comprises adhesive **116**A to adhere the patch **110** and adherent device **100** to patient P. Electrodes **112**A, **112**B, **112**C and **112**D are affixed to adherent patch **110**. In many embodiments, at least four electrodes are attached to the patch, for example six electrodes. In some embodiments the patch comprises at least two electrodes, for example two electrodes to measure an electrocardiogram (ECG) of the patient. Gel **114**A, gel **114**B, gel **114**C and gel **114**D can each be positioned over electrodes **112**A, **112**B, **112**C and **112**D, respectively, to provide electrical conductivity between the electrodes and the skin of the patient. In many embodiments, the electrodes can be affixed to the patch **110**, for example with known methods and structures such as rivets, adhesive, stitches, etc. In many embodiments, patch **110** comprises a breathable material to permit air and/or vapor to flow to and from the surface of the skin.

FIG. **1**C shows a top view of the adherent patch **100**, as in FIG. **1**B. Adherent patch **100** comprises a second side, or upper side **110**B. In many embodiments, electrodes **110**A, **110**B, **110**C and **110**D extend from lower side **110**A through the adherent patch to upper side **110**B. In some embodiments, an adhesive **116**B can be applied to upper side **110**B to adhere structures, for example, a cover, to the patch such that the patch can support the electronics and other structures when the patch is adhered to the patient. The printed circuit board (PCB) comprise completely flex PCB, rigid PCB combined flex PCB and/or rigid PCB boards connected by cable.

FIG. **1**D shows a printed circuit boards and electronic components over adherent patch **110**, as in FIG. **1**C. A printed circuit board (PCB), for example flex PCB **120**, can be positioned above **110**B of patch **110**. Flex PCB **120** can include traces that extends to connectors **122**A, **122**B, **122**C and **122**D on the flex PCB. Connectors **122**A, **122**B, **122**C and **122**D can be positioned on flex PCB **120** in alignment with electrodes **112**A, **112**B, **112**C and **112**D so as to electrically couple the flex PCB with the electrodes. In some embodiments, connectors **122**A, **122**B, **122**C and **122**D may comprise insulated wires or a flex circuit that provide strain relief between the PCB and the electrodes. In some embodiments, additional PCB's for example PCB **120**A, **120**B, **120**C and

120D be connected to flex PCB **120**. Electronic components **130** can be connected to flex PCB **120** and/or mounted thereon. In some embodiments, electronic components **130** can be mounted on the additional PCB's.

Electronic components **130** comprise components to take physiologic measurements, transmit data to remote center **106** and receive commands from remote center **106**. In many embodiments, electronics components **130** may comprise known low power circuitry, for example complementary metal oxide semiconductor (CMOS) circuitry components. Electronics components **130** comprise an activity sensor and activity circuitry **134**, impedance circuitry **136** and electrocardiogram circuitry, for example ECG circuitry **136**. In some embodiments, electronics circuitry **130** may comprise a microphone and microphone circuitry **142** to detect an audio signal from within the patient, and the audio signal may comprise a heart sound and/or a respiratory sound, for example an S3 heart sound and a respiratory sound with rales and/or crackles. Electronics circuitry **130** may comprise a temperature sensor, for example a thermistor, and temperature sensor circuitry **144** to measure a temperature of the patient, for example a temperature of a skin of the patient. Electronics circuitry may comprise a heat flux sensor and heat flux sensor circuitry to measure a skin heat flow of a patient.

Work in relation to embodiments of the present invention suggests that skin temperature may effect impedance and/or hydration measurements, and that skin temperature measurements may be used to correct impedance and/or hydration measurements. In some embodiments, increase in skin temperature can be associated with increased vaso-dilation near the skin surface, such that measured impedance measurement decreased, even through the hydration of the patient in deeper tissues under the skin remains substantially unchanged. Thus, use of the temperature sensor can allow for correction of the hydration signals to more accurately assess the hydration, for example extra cellular hydration, of deeper tissues of the patient, for example deeper tissues in the thorax.

Electronics circuitry **130** may comprise a processor **146**. Processor **146** comprises a tangible medium, for example read only memory (ROM), electrically erasable programmable read only memory (EEPROM) and/or random access memory (RAM). Electronic circuitry **130** may comprise real time clock and frequency generator circuitry **148**. In some embodiments, processor **136** may comprise the frequency generator and real time clock. The processor can be configured to control a collection and transmission of data from the impedance circuitry electrocardiogram circuitry and the accelerometer. In many embodiments, device **100** comprise a distributed processor system, for example with multiple processors on device **100**.

In many embodiments, electronics components **130** comprise wireless communications circuitry **132** to communicate with remote center **106**. The wireless communication circuitry can be coupled to the impedance circuitry, the electrocardiogram circuitry and the accelerometer to transmit to a remote center with a communication protocol at least one of the hydration signal, the electrocardiogram signal or the accelerometer signal. In specific embodiments, wireless communication circuitry is configured to transmit the hydration signal, the electrocardiogram signal and the accelerometer signal to the remote center with a single wireless hop, for example from wireless communication circuitry **132** to intermediate device **102**. The communication protocol comprises at least one of Bluetooth, Zigbee, WiFi, WiMax, IR, amplitude modulation or frequency modulation. In many embodiments, the communications protocol comprises a two way protocol such that the remote center is capable of issuing commands to control data collection.

In some embodiments, intermediate device **102** comprises a data collection system to collect and store data from the wireless transmitter. The data collection system can be configured to communicate periodically with the remote center. In many embodiments, the data collection system can transmit data in response to commands from remote center **106** and/or in response to commands from the adherent device.

Activity sensor and activity circuitry **134** can comprise many known activity sensors and circuitry. In many embodiments, the accelerometer comprises at least one of a piezoelectric accelerometer, capacitive accelerometer or electromechanical accelerometer. The accelerometer may comprise a 3-axis accelerometer to measure at least one of an inclination, a position, an orientation or acceleration of the patient in three dimensions. Work in relation to embodiments of the present invention suggests that three dimensional orientation of the patient and associated positions, for example sitting, standing, lying down, can be very useful when combined with data from other sensors, for example ECG data and/or hydration data.

Impedance circuitry **136** can generate both hydration data and respiration data. In many embodiments, impedance circuitry **136** is electrically connected to electrodes **112**A, **112**B, **112**C and **112**D such that electrodes **112**A and **112**D comprise outer electrodes that are driven with a current, or force electrodes. The current delivered between electrodes **112**A and **112**D generates a measurable voltage between electrodes **112**B and **112**C, such that electrodes **112**B and **112**C comprise inner electrodes, or sense electrodes that measure the voltage in response to the current from the force electrodes. The voltage measured by the sense electrodes can be used to determine the hydration of the patient.

FIG. **1**D-**1** shows an equivalent circuit **152** that can be used to determine optimal frequencies for measuring patient hydration. Work in relation to embodiments of the present invention indicates that the frequency of the current and/or voltage at the force electrodes can be selected so as to provide impedance signals related to the extracellular and/or intracellular hydration of the patient tissue. Equivalent circuit **152** comprises an intracellular resistance **156**, or R(ICW) in series with a capacitor **154**, and an extracellular resistance **158**, or R(ECW). Extracellular resistance **158** is in parallel with intracellular resistance **156** and capacitor **154** related to capacitance of cell membranes. In many embodiments, impedances can be measured and provide useful information over a wide range of frequencies, for example from about 0.5 kHz to about 200 KHz. Work in relation to embodiments of the present invention suggests that extracellular resistance **158** can be significantly related extracellular fluid and to cardiac decompensation, and that extracellular resistance **158** and extracellular fluid can be effectively measured with frequencies in a range from about 0.5 kHz to about 20 kHz, for example from about 1 kHz to about 10 kHz. In some embodiments, a single frequency can be used to determine the extracellular resistance and/or fluid. As sample frequencies increase from about 10 kHz to about 20 kHz, capacitance related to cell membranes decrease the impedance, such that the intracellular fluid contributes to the impedance and/or hydration measurements. Thus, many embodiments of the present invention employ measure hydration with frequencies from about 0.5 kHz to about 20 kHz to determine patient hydration.

In many embodiments, impedance circuitry **136** can be configured to determine respiration of the patient. In specific embodiments, the impedance circuitry can measure the

hydration at 25 Hz intervals, for example at 25 Hz intervals using impedance measurements with a frequency from about 0.5 kHz to about 20 kHz.

ECG circuitry **138** can generate electrocardiogram signals and data from electrodes **112**A, **112**B, **112**C and **112**D. In some embodiments, ECG circuitry **138** is connected to inner electrodes **12**B and **122**C, which may comprise sense electrodes of the impedance circuitry as described above. In some embodiments, the inner electrodes may be positioned near the outer electrodes to increase the voltage of the ECG signal measured by ECG circuitry **138**. In some embodiments, the ECG circuitry can share components with the impedance circuitry.

FIG. **1**E shows batteries **150** positioned over the flex printed circuit board and electronic components as in FIG. **1**D. Batteries **150** may comprise rechargeable batteries that can be removed and/or recharged. In some embodiments, batteries **150** can be removed from the adherent patch and recharged and/or replaced.

FIG. **1**F shows a top view of a cover **162** over the batteries, electronic components and flex printed circuit board as in FIG. **1**E. In many embodiments, an electronics housing **160** may be disposed under cover **162** to protect the electronic components, and in some embodiments electronics housing **160** may comprise an encapsulant over the electronic components and PCB. In many embodiments, electronics housing **160** may comprise a water proof material, for example a sealant adhesive such as epoxy or silicone coated over the electronics components and/or PCB. In some embodiments, electronics housing **160** may comprise metal and/or plastic, which may be potted with silicone, epoxy, etc.

Cover **162** may comprise many known biocompatible cover, casing and/or housing materials, such as elastomers, for example silicone. The elastomer may be fenestrated to improve breathability. In some embodiments, cover **162** may comprise many known breathable materials, for example polyester or polyamide fabric. The breathable fabric may be coated to make it water resistant, waterproof, and/or to aid in wicking moisture away from the patch. The breathable fabric may be coated in order to make the outside hydrophobic and the inside hydrophilic.

FIG. **1**G shows a side view of adherent device **100** as in FIGS. **1**A to **1**F. Adherent device **100** comprises a maximum dimension, for example a length **170** from about 4 to 10 inches (from about 100 mm to about 250 mm), for example from about 6 to 8 inches (from about 150 mm to about 200 mm). In some embodiments, length **170** may be no more than about 6 inches (no more than about 150 mm). Adherent device **100** comprises a thickness **172**. Thickness **172** may comprise a maximum thickness along a profile of the device. Thickness **172** can be from about 0.2 inches to about 0.4 inches (from about 5 mm to about 10 mm), for example about 0.3 inches (about 7.5 mm).

FIG. **1**H shown a bottom isometric view of adherent device **100** as in FIGS. **1**A to **1**G. Adherent device **100** comprises a width **174**, for example a maximum width along a width profile of adherent device **100**. Width **174** can be from about 2 to about 4 inches (from about 50 mm to 100 mm), for example about 3 inches (about 75 mm).

FIG. **2**A shows a method **200** of predicting an impending cardiac decompensation. A step **205** measures an ECG signal. The ECG signal may comprise a differential signal measured with at least two electrodes and may be measured in many known ways. A step **210** measures an hydration signal. The hydration signal may comprise an impedance signal, for example a four pole impedance signal, and may be measured in many known ways. A step **215** measures a respiration signal. The respiration signal may comprise an impedance signal, and may be measured in many known ways. A step **220** measures an activity signal. The activity signal may be measured in many known ways and may comprise a three dimensional accelerometer signal to determine a position of the patient, for example from a three dimensional accelerometer signal. A step **225** measures a temperature signal. The temperature signal may be measured in many ways, for example with a thermistor, a thermocouple, and known temperature measurement devices. A step **230** records a time of day of the signals, for example a local time of day such as morning, afternoon, evening, and/or nighttime.

A step **235** processes the signals. The signals may be processed in many known ways, for example to generate at least one of a derived signal, a time averaged signal, a filtered signal. In some embodiments, the signals may comprise raw signals. The ECG signal may comprise at least one of a heart rate signal, a heart rate variability signal, an average heart rate signal, a maximum heart rate signal or a minimum heart rate signal. The hydration signal may comprise an impedance measurement signal. The activity signal may comprise at least one of an accelerometer signal, a position signal indicating the orientation of the patient, such as standing, lying, or sitting. The respiration signal may comprise a least one of a respiration rate, a maximum respiration rate, a minimum respiration rate, an average respiration rate or respiration rate variability. The temperature may comprise an average temperature or a peak temperature.

A step **240** compares the signals with baseline values. In many embodiments, the baseline values may comprise measurements from the same patient at an earlier time. In some embodiments, the baseline values comprise values for a patient population. In some embodiments, the baseline values for a patient population may comprise empirical data from a suitable patient population size, for example at least about 144 patients, depending on the number of variables measured, statistical confidence and power used. The measured signals may comprise changes and/or deviations from the baseline values.

A step **245** transmits the signals. In many embodiments, the measurement signals, which may comprise derived and/or processed measurement signals, are transmitted to the remote site for comparison. In some embodiments, the signals may be transmitted to a processor supported with the patient for comparison.

A step **250** combines at least two of the ECG signal, the hydration signal, the respiration signal, the activity signal and the temperature signal to detect the impending decompensation. In many embodiments, at least three of the signals are combined. In some embodiments, at least four signals comprising ECG signal, the hydration signal, the respiration signal and the activity signal are combined to detect the impending decompensation. In specific embodiments, at least four signals comprising the ECG signal, the hydration signal, the respiration signal, the activity signal and the temperature signal are combined to detect the impending decompensation.

The signals can be combined in many ways. In some embodiments, the signals can be used simultaneously to determine the impending cardiac decompensation.

In some embodiments, the signals can be combined by using the at least two of the electrocardiogram signal, the hydration signal, the respiration signal or the activity signal to look up a value in a previously existing array.

TABLE 1

Lookup Table for ECG and Hydration Signals

Heart Rate/Hydration	0-49 bpm	50-69 bpm	70-90 bpm
>60 Ohms	N	N	Y
41-59 Ohms	N	Y	Y
0-40 Ohms	Y	Y	Y

Table 1 shows combination of the electrocardiogram signal with the hydration signal to look up a value in a pre-existing array. For example at a heart rate of 89 bpm and a hydration of 35 Ohms, the value in the table may comprise Y. In specific embodiments, the values of the look up table can be determined in response to empirical data measured for a patient population of at least about 100 patients, for example measurements on about 1000 to 10,000 patients.

In some embodiments, the table may comprise a three or more dimensional look up table.

In some embodiments, the signals may be combined with at least one of adding, subtracting, multiplying, scaling or dividing the at least two of the electrocardiogram signal, the hydration signal, the respiration signal or the activity signal. In specific embodiments, the measurement signals can be combined with positive and or negative coefficients determined in response to empirical data measured for a patient population of at least about 100 patients, for example data on about 1000 to 10,000 patients.

In some embodiments, a weighted combination may combine at least 3 measurement signals to generate an output value according to a formula of the general form

$$OUTPUT=aX+bY+cZ$$

where a, b and c comprise positive or negative coefficients determined from empirical data and X, Y and Z comprise measured signals for the patient, for example at least three of the electrocardiogram signal, the hydration signal, the respiration signal or the activity signal. While three coefficients and three variables are shown, the data may be combined with multiplication and/or division. One or more of the variables may be the inverse of a measured variable.

In some embodiments, the ECG signal comprises a heart rate signal that can be divided by the activity signal. Work in relation to embodiments of the present invention suggest that an increase in heart rate with a decrease in activity can indicate an impending decompensation. The signals can be combined to generate an output value with an equation of the general form

$$OUTPUT=aX/Y+bZ$$

where X comprise a heart rate signal, Y comprises a hydration rate signal and Z comprises a respiration signal, with each of the coefficients determined in response to empirical data as described above.

In some embodiments, the data may be combined with a tiered combination. While many tiered combinations can be used a tiered combination with three measurement signals can be expressed as

$$OUTPUT=(\Delta X)+(\Delta Y)+(\Delta Z)$$

where (ΔX), (ΔY), (ΔZ) may comprise change in heart rate signal from baseline, change in hydration signal from baseline and change in respiration signal from baseline, and each may have a value of zero or one, based on the values of the signals. For example if the heart rate increase by 10%, (ΔX) can be assigned a value of 1. If hydration increases by 5%, (ΔY) can be assigned a value of 1. If activity decreases below 10% of a baseline value (ΔZ) can be assigned a value of 1. When the output signal is three, a flag may be set to trigger an alarm.

In some embodiments, the data may be combined with a logic gated combination. While many logic gated combinations can be used a logic gated combination with three measurement signals can be expressed as

$$OUTPUT=(\Delta X)\ AND\ (\Delta Y)\ AND\ (\Delta Z)$$

where (ΔX), (ΔY), (ΔZ) may comprise change in heart rate signal from baseline, change in hydration signal from baseline and change in respiration signal from baseline, and each may have a value of zero or one, based on the values of the signals. For example if the heart rate increase by 10%, (ΔX) can be assigned a value of 1. If hydration increases by 5%, (ΔY) can be assigned a value of 1. If activity decreases below 10% of a baseline value (ΔZ) can be assigned a value of 1. When each of (ΔX), (ΔY), (ΔZ) is one, the output signal is one, and a flag may be set to trigger an alarm. If any one of (ΔX), (ΔY) or (ΔZ) is zero, the output signal is zero and a flag may be set so as not to trigger an alarm. While a specific example with AND gates has been shown the data can be combined in may ways with known gates for example NAND, NOR, OR, NOT, XOR, XNOR gates. In some embodiments, the gated logic may be embodied in a truth table.

A step **255** sets a flag. The flag can be set in response to the output of the combined signals. In some embodiments, the flag may comprise a binary parameter in which a value of zero does not triggers an alarm and a value of one triggers an alarm.

A step **260** communicates with the patient and/or a health care provider. In some embodiments, the remote site may contact the patient to determine if he or she is okay and communicate the impending decompensation such that the patient can receive needed medical care. In some embodiments, the remote site contacts the health care provider to warn the provider of the impending decompensation and the need for the patient to receive medical care.

A step **265** collects additional measurements. Additional measurements may comprise additional measurements with the at least two signals, for example with greater sampling rates and or frequency of the measurements. Additional measurements may comprise measurements with a additional sensors, for example an onboard microphone to detect at least one of rales, S1 heart sounds, S**2** heart sounds, S**3** heart sounds, or arrhythmias. In some embodiments, the additional measurements, for example sounds, can be transmitted to the health care provider to diagnose the patient in real time.

The processor system, as described above, can be configured to perform the method **200**, including many of the steps described above. It should be appreciated that the specific steps illustrated in FIG. **2**A provide a particular method of predicting an impending cardiac decompensation, according to an embodiment of the present invention. Other sequences of steps may also be performed according to alternative embodiments. For example, alternative embodiments of the present invention may perform the steps outlined above in a different order. Moreover, the individual steps illustrated in FIG. **2**A may include multiple sub-steps that may be performed in various sequences as appropriate to the individual step. Furthermore, additional steps may be added or removed depending on the particular applications. One of ordinary skill in the art would recognize many variations, modifications, and alternatives.

Experimental Clinical Study

The protocol below has been used to measure signals from actual patients with an adherent device. These data show that an adherent patch as described above can be continuously adhered for at least one week. These data also show that 90 day continuous in home monitoring can be achieved with a set of 13 patches in which one of the patches is replaced each week. The clinical testing device used an adherent device with modifications, as described more fully below and referred to as the MS system (multi-sensor). Although the clinical device did not include wireless circuitry and processor circuitry supported with the patch adhered to the skin of the patient, these data do show that such a device, as described above, can be made by one of ordinary skill in the art based on the teachings described herein. Additional empirical studies can be conducted on a suitable number of patients.

MS Clinical System Description

The MS clinical system includes many of the structure components described above. There is a flexible connection between the electrodes and the flex PCB, for example wires or polyurethane with silver ink. The cover can stretch with the breathable tape on both the clinical device and the above described wireless device. There is generally a gap between the flex PCB and breathable tape in both clinical and above described wireless devices. The tested device used weights to at least partially simulate the weight of wireless and processor circuitry. The adherent device of the MS clinical system comprises four electrodes to measure bioimpedance and ECG signals and a 3-axis accelerometer, as described above. Bioimpedance signals were used to determine patient respiration and patient hydration, and accelerometer signals were used to determine patient activity and posture. The MS clinical adherent patch device comprising the sensors and at least some sensor circuitry were connected to a processor to record data. The processor was connected to the tested adherent device with wires and supported away from the tested adherent patch device, for example around the patient's waist. Data were collected at regular intervals and uploaded to a remote site, as described above.

Clinical testing of the MS clinical system shows the effectiveness of the structures for continuous adherence of at least one week and data collection, and that patches can be successively removed and replaced by the patient for in-home monitoring. This effectiveness has been shown without requiring fully functional electronics circuitry such as a battery, wireless circuitry and process circuitry on the adherent device. For example, the MS system includes an insert with about 20 g of additional weight. Although an insert with a 20 gram weight was used for the MS clinical device, greater amounts of weight and circuitry can be used, for example about 30-50 g. The patch device may be modified to accommodate additional weight, for example by increasing the size of the adherent surface. The shape of the MS clinical patch is generally elongate, similar to the elongate shape shown above.

Study Design and Rationale

The MS System is used in a clinical study of heart failure patients to gather data that can be used to develop an algorithm for diagnosing and predicting impending heart failure decompensation events. Events typically manifest as heart failure-related hospitalization, emergency room or urgent care visits leading to a change in oral or IV diuretic treatment.

The purpose of the clinical study is to correlate physiological signals recorded by the system to clinical events of acute heart failure decompensation (AHFD). Signals from the patch can be weighted and combined to determine an' index that associates physiologic parameters to impending events of decompensation. Patients who have been classified as New York Heart Association class III and IV within the last 12 months and have had a recent AHFD event can be enrolled into the study and are monitored with the MS system for approximately 90 days.

AHFD events are defined as any of the following:

1) Any heart failure related ER, Urgent Care, in-office visit or hospitalization requiring administration of IV diuretics, administration of IV inotropes, or ultrafiltration for fluid removal.

2) A change in diuretic, defined as a change in diuretic directed by the health care provider occurring inside a hospital, emergency room, or urgent care setting (i.e. no patient self-directed changes to medications not approved by a health care provider would be included), that satisfies one or more of the following: a) a change in the type of diuretic the patient is taking, b) a dose increase of an existing diuretic, or c) the addition of another diuretic.

3) A heart failure decompensation event for which death is the outcome.

Patients enrolled in the study were asked to replace the patch weekly. The study can enroll at least about 550 patients. The patient was provided with a kit comprising 13 patches for replacement. The patches were placed on alternating left and right sides of the patient's thorax, as described above, to minimize progressive irritation.

The data collected in the study can be used to develop an algorithm to at least one of detect, diagnose or predict an impending cardiac decompensation. The algorithm can be implemented on a processor system as described above. Known methods can be used to analyze the data, for example splitting the patients into two groups, one to develop parameters for the algorithm and a second group to test the algorithm developed with the first group. In many embodiments, the signal of the algorithm may comprise a simple binary output for impending cardiac decompensation of the patient. The logic output, yes or no, can be determined in response to patient data combined as described above. The logic output may comprise a signal, such as a binary Y or N signal.

The developed algorithm can be evaluated with composite sensitivity and false positive patient signal status rates. The sensitivity may be defined as the percent of true positive events out of all condition present events, and the false positive patient status signal status rate can be defined as the number of false positive patient status signals per patient-years of follow up. For example, the sensitivity can be at least 50%, for example at least 60%, at least 70%, or even at least 80%. The false positive patient signal status rate may be limited to no more than about 1.1 false positive patient status signals per patient year, for example no more than about 1.0 false positive patient status signals per patient year, no more than about 0.9 false positive patient status signals per patient year, and even no more than about 0.8 false positive patient status signals per patient year.

Clinical Results

Clinical data are available for the first 180 patients enrolled in the study.

FIGS. **3**A and **3**B show clinical data measured with an adherent patch device, in accordance with the above protocol. FIG. **3**A shows data from a patient with the MS patch adhered to a first patient, and the data was acquired over the 90 day period with the series of 13 patches. The signals measured included Heart Rate (beats per minute), Heart Rate Variability (ms), Respiratory Rate (breaths per minute), Activity (m-G's) and Body Fluid (Ohms). FIG. **3**B shows data from a second patient similar to FIG. **3**A.

Of the 180 patients who have completed the study with the MS adherent patch, as described above, all patches in all

patients adhered continuously without patch failure. In all patients, the first patch adhered continuously for the first week. With the exception of a handful of patient deaths and early withdrawals that were unrelated to device failure, all patients reached the end of 90-day follow-up period having used 13 weekly patches without incident. None of the 180 patients showed skin irritation or damage that required withdrawal from the study.

The above data show that the wireless adherent patch device can be constructed for in home wireless patient monitoring for an extended period of at least 90 day, in which each patch of a set is continuously adhered to a patient for at least one week and each patch is configured to support the measurement circuitry, the processor, the wireless communication circuitry and the battery with the skin of the patient.

While the exemplary embodiments have been described in some detail, by way of example and for clarity of understanding, those of skill in the art will recognize that a variety of modifications, adaptations, and changes may be employed. Hence, the scope of the present invention should be limited solely by the appended claims.

What is claimed is:

1. A system to predict impending acute cardiac decompensation of a patient, the system comprising:

an adherent patch including at least four electrodes connected to the patch and capable of electrically coupling to the patient;

impedance circuitry coupled to two or more of the at least four electrodes to measure an impedance associated with the patient;

a temperature sensor configured to measure a temperature of a skin of the patient; and

a processor system in communication with the impedance circuitry and the temperature sensor, wherein the processor system calculates a hydration measurement based on the measured impedance and corrects the calculated hydration measurement based on the measured skin temperature of the patient, wherein the processor system utilizes the calculated hydration measurement to predict an impending acute cardiac decompensation of the patient.

2. The system of claim **1**, wherein the impedance circuitry places a voltage and/or current at one or more of the electrodes having a frequency between 0.5 kHz and about 20 kHz such that the hydration measurement corresponds to the extracellular fluid of the patient.

3. The system of claim **1**, wherein the processor system corrects the calculated hydration measurement by lowering the hydration measurement in response to an increase in measured skin temperature.

4. The system of claim **3**, wherein the processor system corrects the calculated hydration measurement by increasing the hydration measurement in response to a decrease in the measured skin temperature.

5. The system of claim **1**, wherein the processor system corrects the calculated hydration measurement such that the hydration measurement remains substantially unchanged when the measured impedance decreases and the skin temperature increases.

6. The system of claim **1**, wherein the processor system comprises at least one processor at a location remote from the patient and configured to predict the impending acute cardiac decompensation.

7. The system of claim **1**, further including:

electrocardiogram circuitry coupled to at least two of the four electrodes and configured to measure an electrocardiogram signal of the patient, wherein the processor system utilizes the electrocardiogram signal in combination with the calculated hydration measurement to predict an impending acute cardiac decompensation of the patient.

8. The system of claim **7**, wherein the processor system utilizes a previously existing array of electrocardiogram signals and hydration values to predict an impending acute cardiac decompensation of the patient.

9. The system of claim **7**, further including:

an activity sensor that measures an activity level of the patient, including at least one of inclination, position, orientation, and acceleration of the patient;

wherein the processor system utilizes the calculated hydration measurement and at least one of the electrocardiogram signal and the activity level to predict an impending acute cardiac decompensation of the patient.

10. The system of claim **9**, wherein the processor system utilizes the electrocardiogram signal to determine a heart rate of the patient, and wherein the processor system correlates the heart rate of the patient with the activity level, wherein an increase in heart rate combined with a decrease in the activity level is indicative of an impending acute cardiac decompensation of the patient.

11. The system of claim **9**, wherein the processor system combines the calculated hydration measurement with at least one of the electrocardiogram signal and the activity level with at least one of a weighted combination, a tiered combination or a logic gated combination, a time-weighted combination or a rate of change to detect an impending acute cardiac decompensation of the patient.

12. A system to predict an impending acute cardiac decompensation of a patient having heart failure, the system comprising:

an adherent device including at least four electrodes capable of electrically coupling to the patient;

impedance circuitry coupled to two or more of the at least four electrodes to measure an impedance value related to a hydration value of the patient, and a respiration signal;

electrocardiogram circuitry coupled to two or more of the at least four electrodes to measure an electrocardiogram signal associated with the patient; and

a processor system in communication with the impedance circuitry and the electrocardiogram circuitry, wherein the processor system receives the measured hydration value, the respiration signal and the electrocardiogram signal and compares the received signals with baseline values established for each, wherein the processor sets a flag indicating an impending acute cardiac decompensation based on a combination of the compared values.

13. The system of claim **12**, wherein the baseline values are generated by measuring a hydration value, a respiration signal, and an electrocardiogram signal associated with the patient at a first time, wherein the processor system stores the baseline values for comparison to subsequently measured hydration values, respiration signals, and electrocardiogram signals.

14. The system of claim **12**, wherein the baseline values are generated based on measurements taken from a population of patients.

15. The system of claim **12**, wherein the processor system sets the flag indicating an impending acute cardiac decompensation based on a logic gated combination of the outputs of the comparison between two or more baseline values and measured values.

16. The system of claim 15, wherein the logic gated combination is a logical AND combination of the outputs of the comparison between two or more baseline values and measured values.

17. The system of claim 12, wherein the processor system affects one or more of the impedance circuitry and electrocardiogram signal to make additional signal measurements of the patient in response to the flag status.

18. The system of claim 12, further including a temperature sensor configured to measure a temperature of a skin of the patient, wherein the processor system corrects the measured hydration value based on the measured skin temperature of the patient.

19. The system of claim 18, wherein the processor system corrects the measured hydration value by lowering the hydration value in response to an increase in measured skin temperature and by increasing the hydration value in response to a decrease in the measured skin temperature.

20. The system of claim 18, wherein the processor system corrects the measured hydration value such that the hydration value remains substantially unchanged when a measured impedance decreases and the skin temperature increases.

* * * * *

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(54) **MULTI-SENSOR PATIENT MONITOR TO DETECT IMPENDING CARDIAC DECOMPENSATION**

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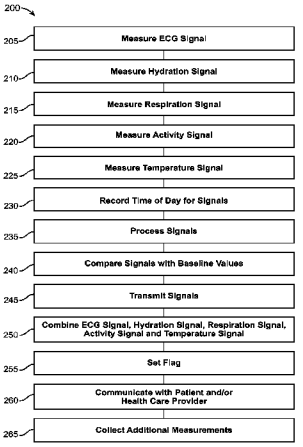
(57) **ABSTRACT**

A system for detecting impending acute cardiac decompensation of a patient includes impedance circuitry, an activity sensor, and a processor system. The impedance circuitry measures a hydration signal of the patient, wherein the hydration signal corresponds to a tissue hydration of the patient. The activity sensor to measure an activity level of the patient, and the processor system includes a computer readable memory in communication with the impedance circuitry and the activity sensor, wherein the computer readable memory of the processor system embodies instructions to combine the hydration signal and the activity level of the patient to detect the impending acute cardiac decompensation.

12 Claims, 10 Drawing Sheets



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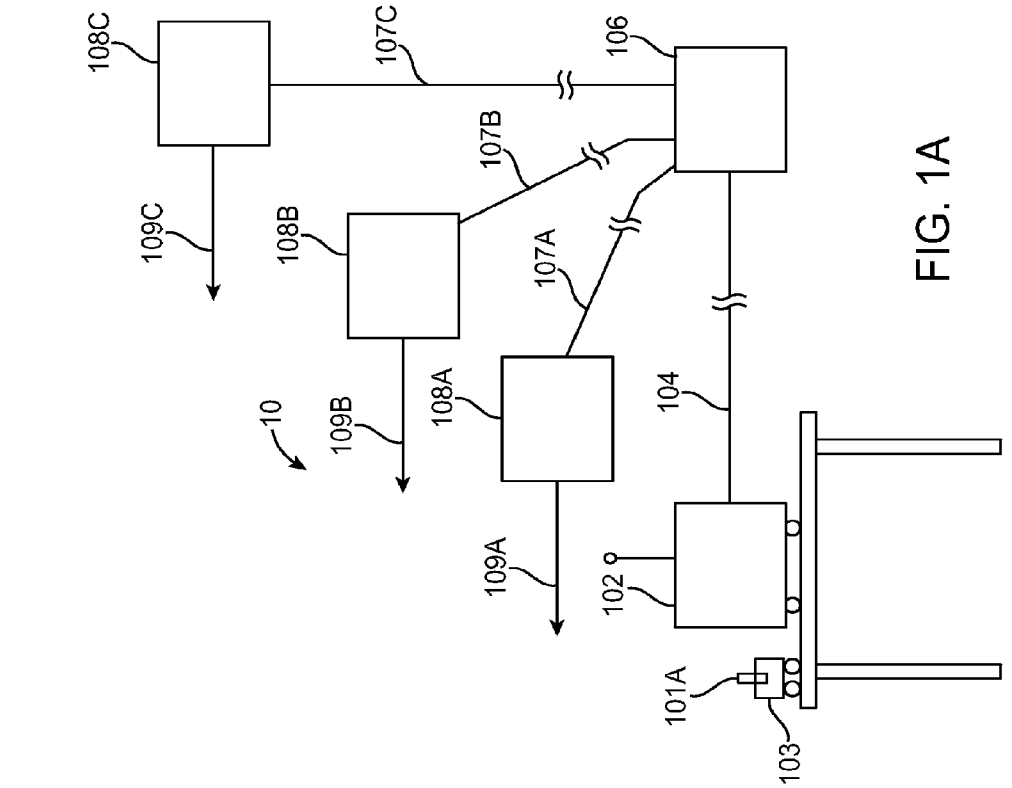
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101A
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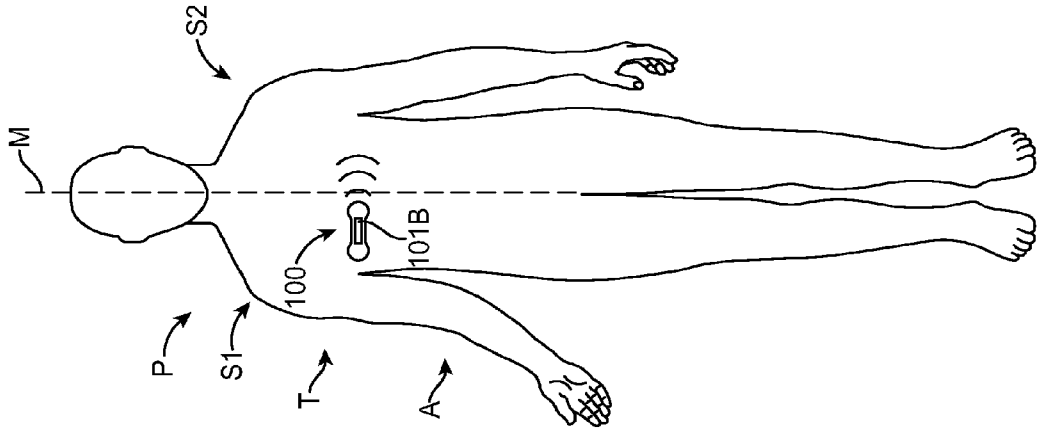
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P
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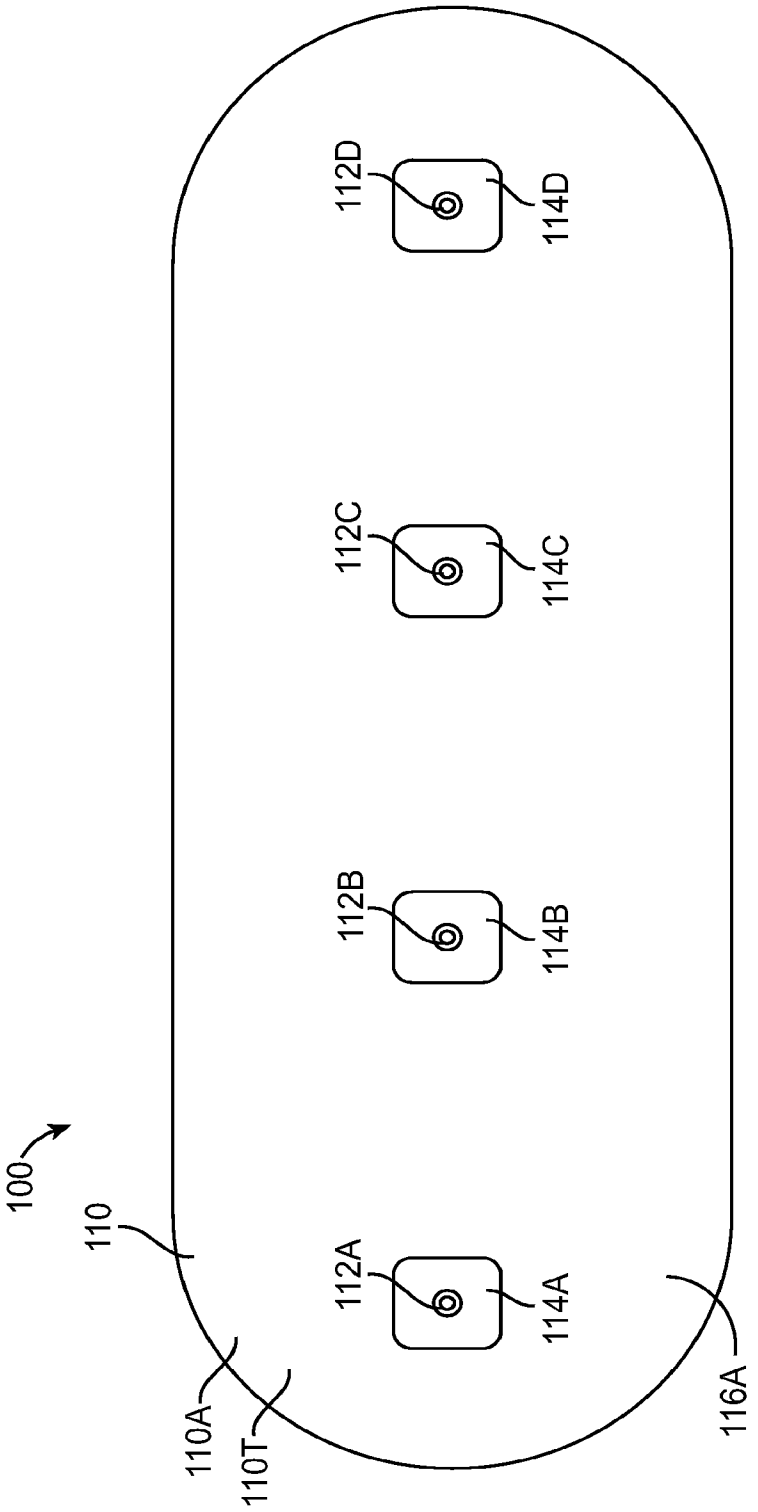
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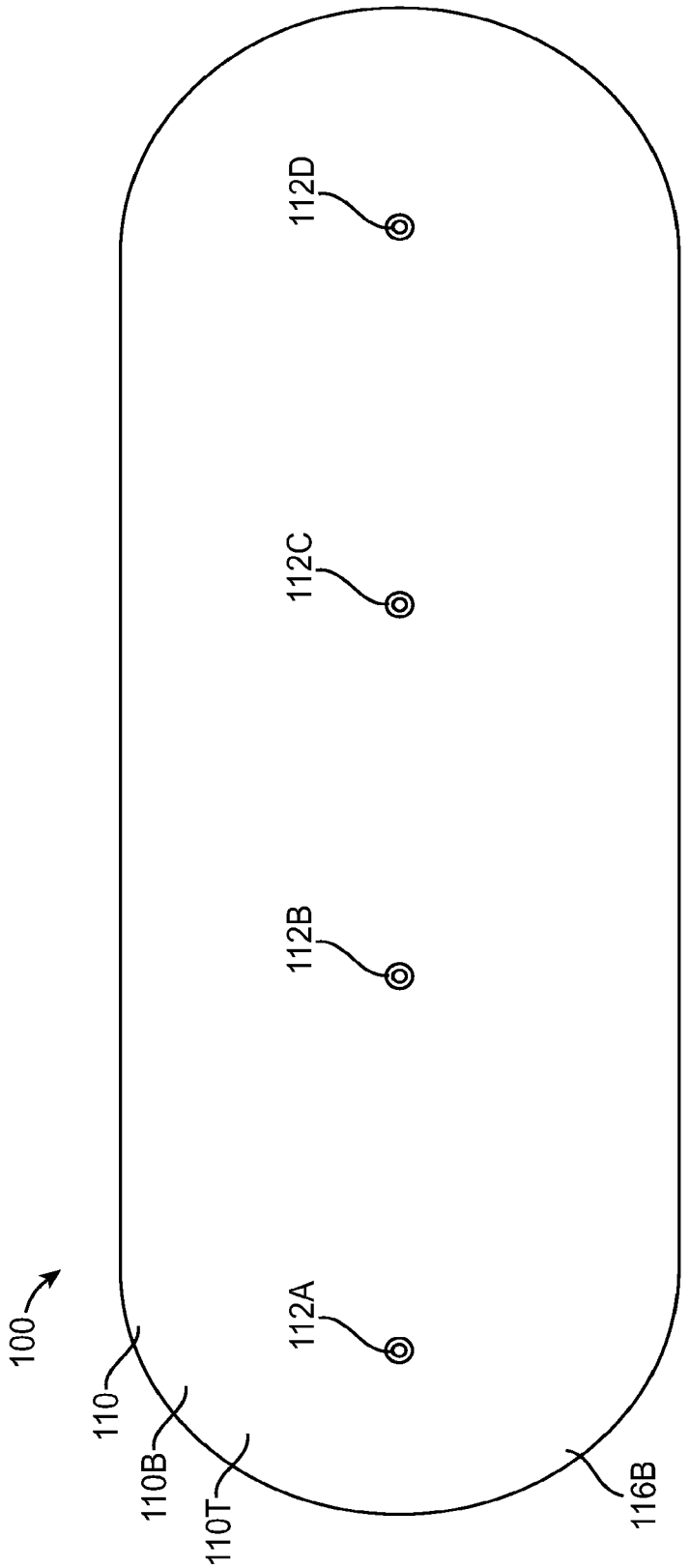

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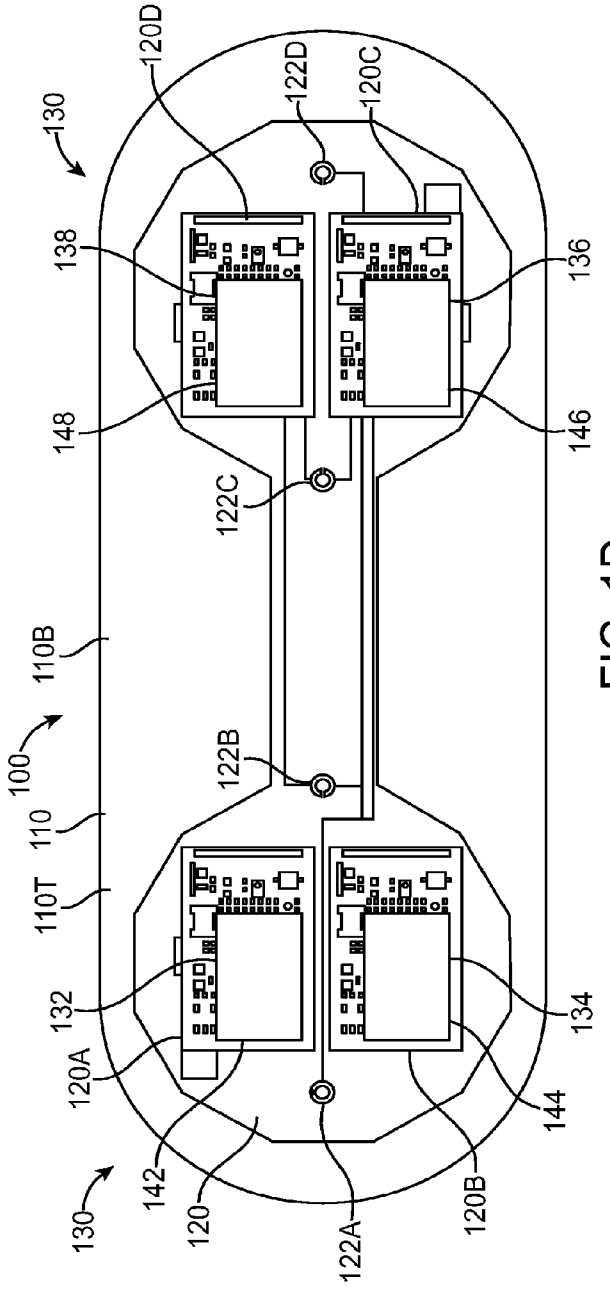

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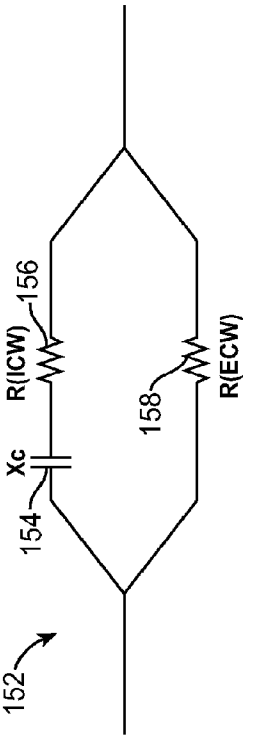

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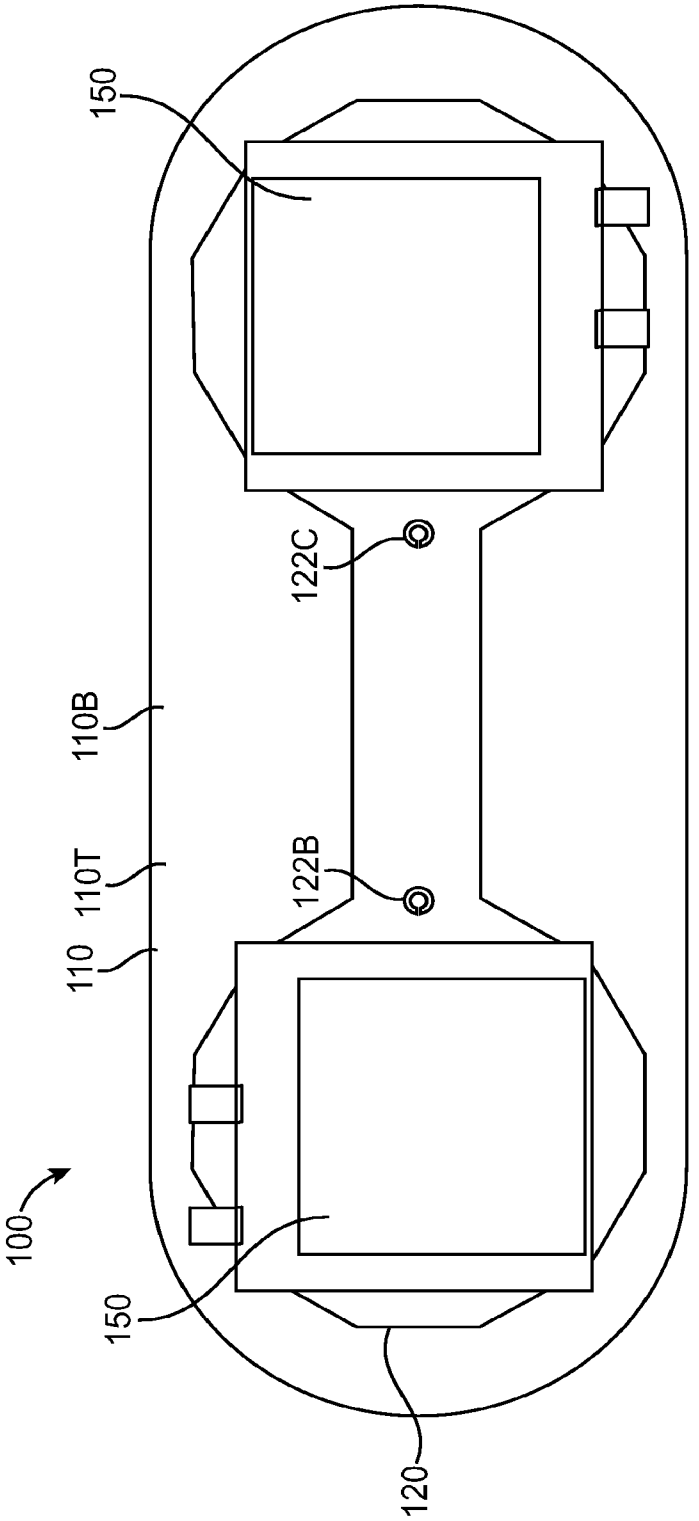

FIG. 1E

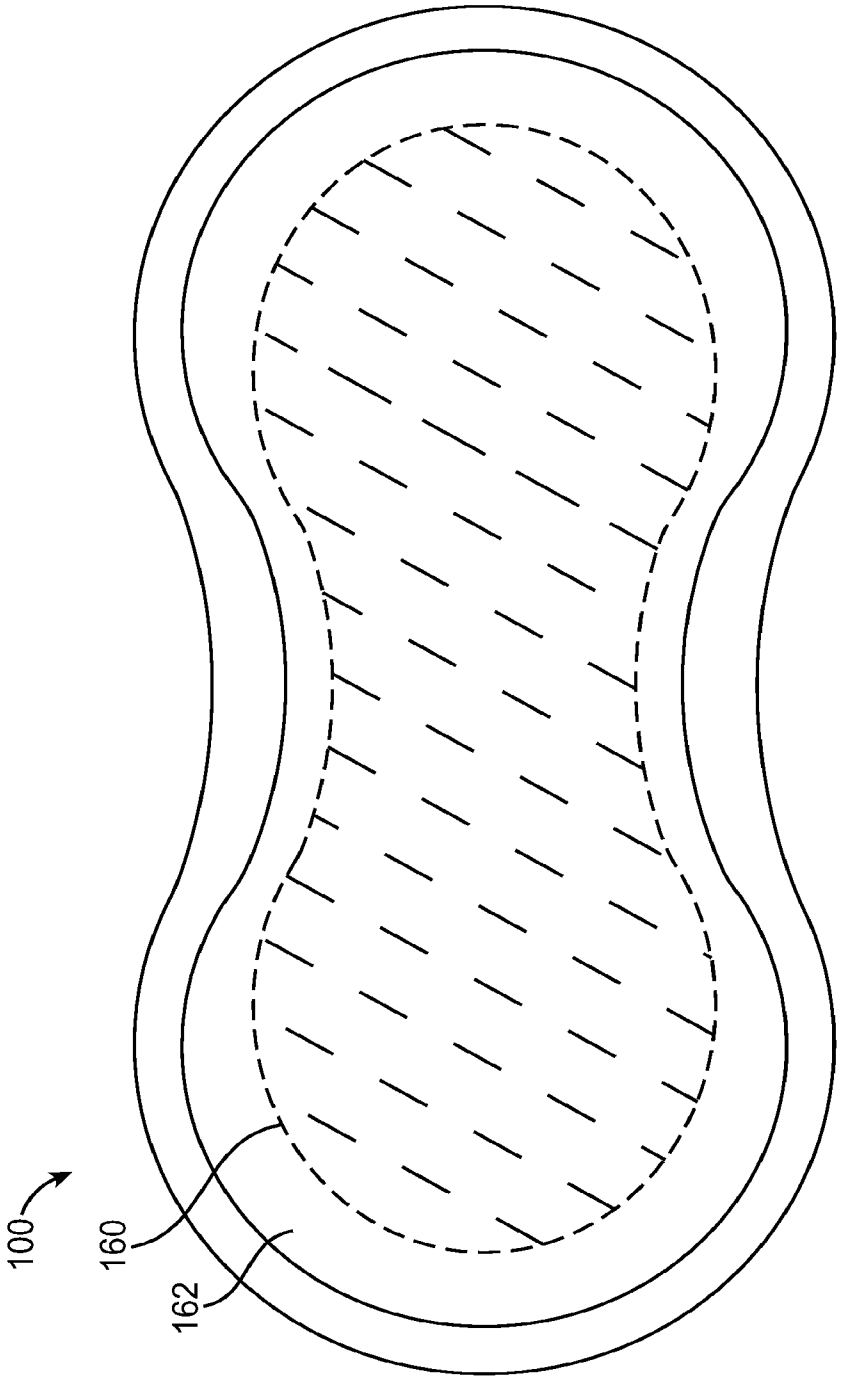

FIG. 1F

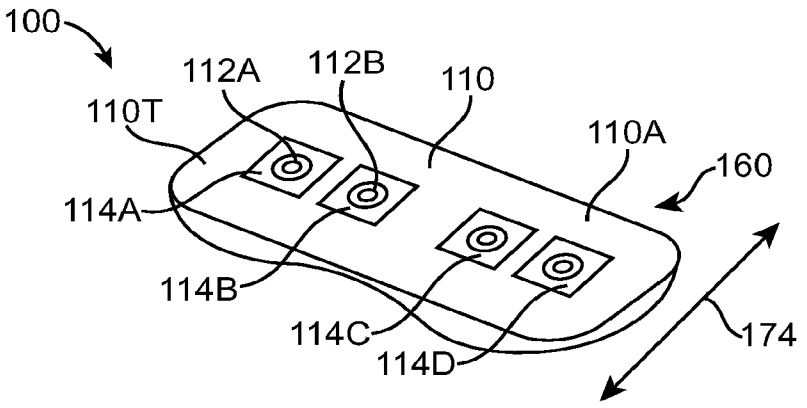
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FIG. 1H

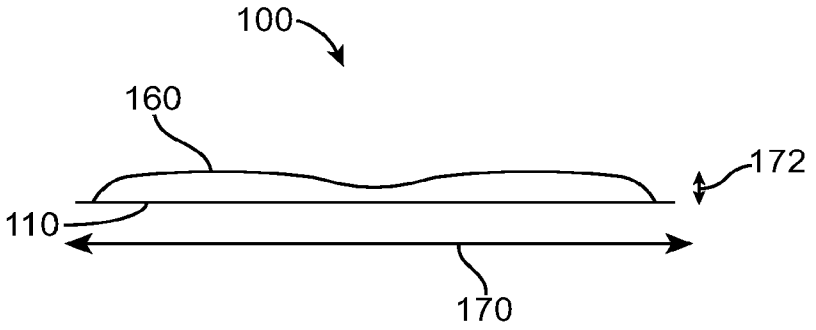
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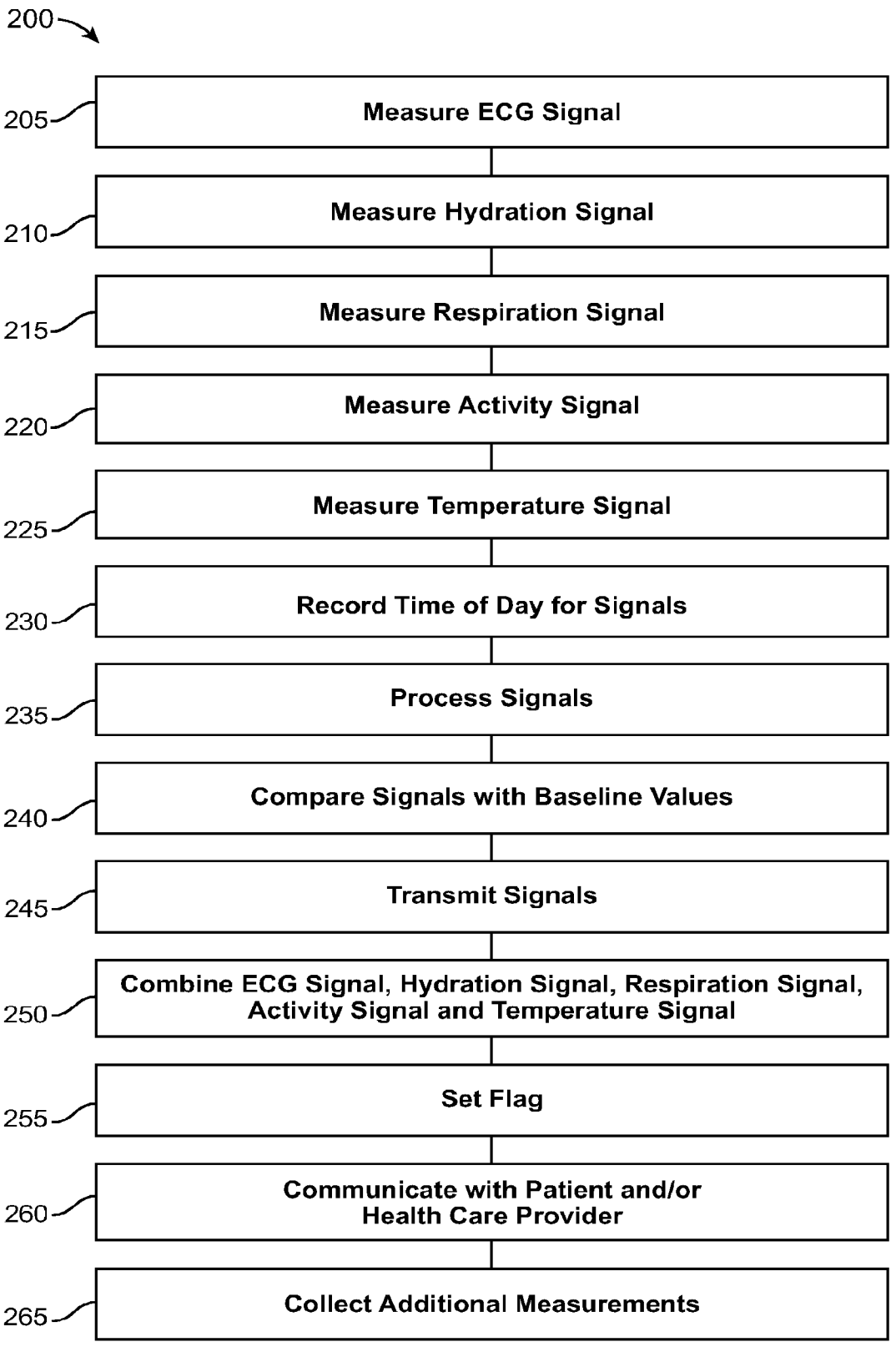
FIG. 1G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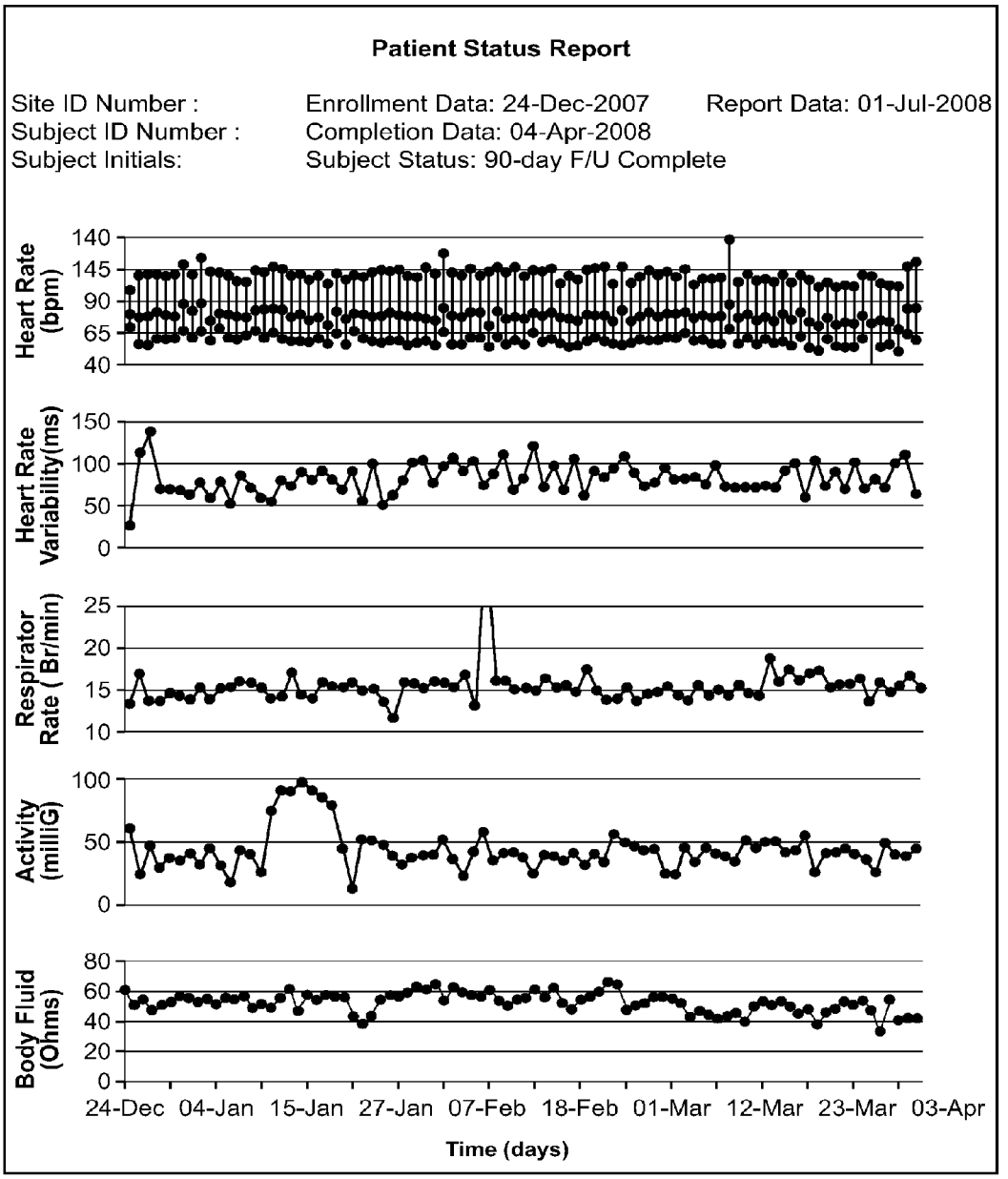
Measure ECG Signal
210
Measure Hydration Signal
215
Measure Respiration Signal
220
Measure Activity Signal
225
Measure Temperature Signal
230
Record Time of Day for Signals
235
Process Signals
240
Compare Signals with Baseline Values
245
Transmit Signals
250
Combine ECG Signal, Hydration Signal, Respiration Signal, Activity Signal and Temperature Signal
255
Set Flag
260
Communicate with Patient and/or Health Care Provider
265
Collect Additional Measurements

FIG. 2A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Subject ID Number :
Subject Initials:
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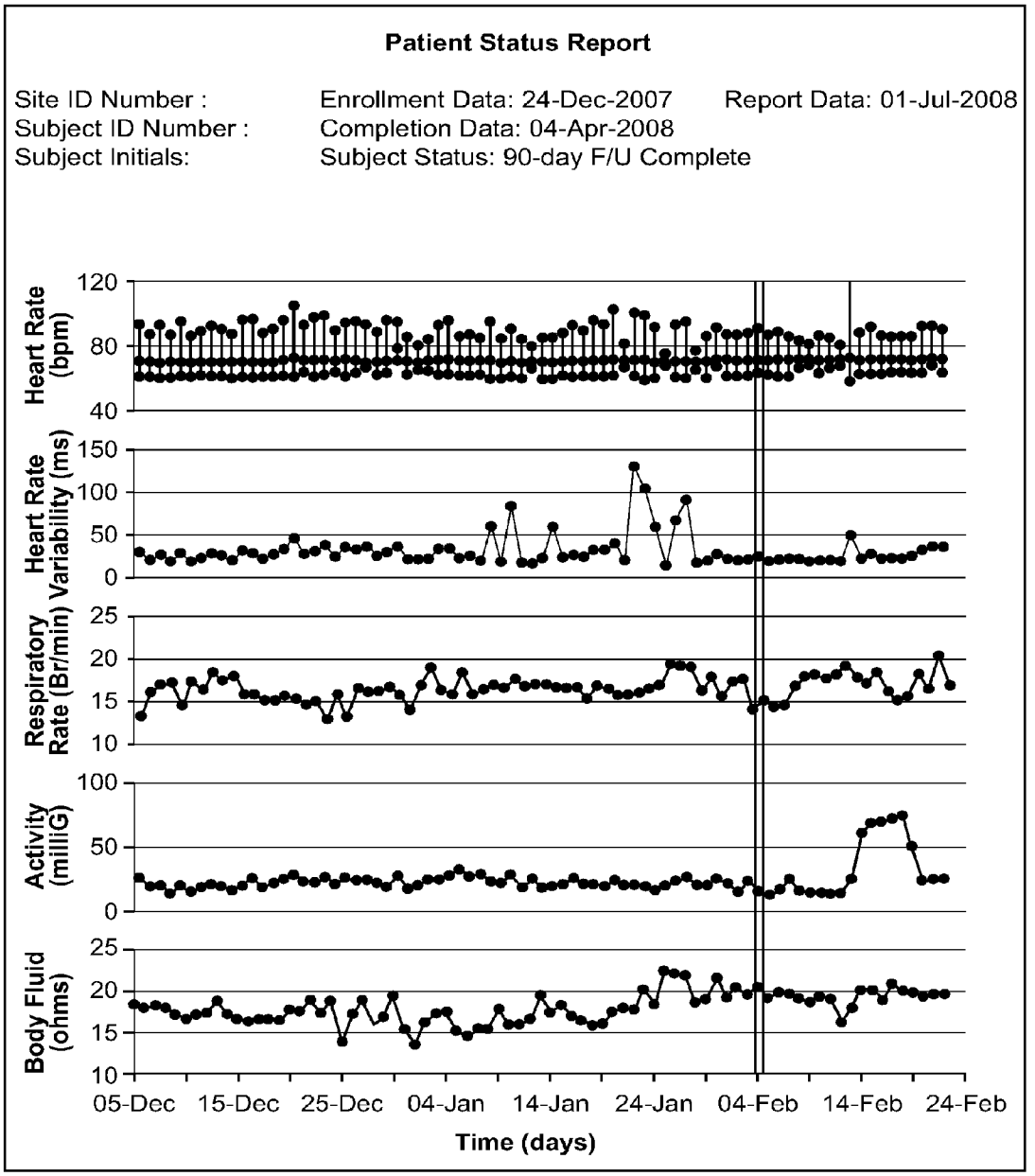
Completion Data: 04-Apr-2008
Subject Status: 90-day F/U Complete
Report Data: 01-Jul-2008
Heart Rate (bpm)
140
145
90
65
40
Heart Rate Variability(ms)
150
100
50
0
Respirator Rate (Br/min)
25
20
15
10
Activity (milliG)
100
50
0
Body Fluid (Ohms)
80
60
40
20
0
24-Dec 04-Jan 15-Jan 27-Jan 07-Feb 18-Feb 01-Mar 12-Mar 23-Mar 03-Apr
Time (days)

FIG. 3A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Subject ID Number :
Subject Initials:
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Completion Data: 04-Apr-2008
Subject Status: 90-day F/U Complete
Report Data: 01-Jul-2008
Heart Rate (bpm)
120
80
40
Heart Rate Variability (ms)
150
100
50
0
Respiratory Rate (Br/min)
25
20
15
10
Activity (milliG)
100
50
0
Body Fluid (ohms)
25
20
15
10
05-Dec
15-Dec
25-Dec
04-Jan
14-Jan
24-Jan
04-Feb
14-Feb
24-Feb
Time (days)

FIG. 3B

MULTI-SENSOR PATIENT MONITOR TO DETECT IMPENDING CARDIAC DECOMPENSATION

CROSS-REFERENCES TO RELATED APPLICATIONS

This application is a Continuation of U.S. application Ser. No. 14/325,968, filed on 8 Jul. 2014, which is a Continuation of U.S. application Ser. No. 12/209,279, filed on 12 Sep. 2008, which claims the benefit of U.S. Provisional Application No. 61/055,666, filed on 23 May 2008, and of U.S. Provisional Application No. 60/972,537, filed on 14 Sep. 2007, and of U.S. Provisional Application No. 60/972,512, filed on 14 Sep. 2007, and which applications are incorporated herein by reference. A claim of priority to all, to the extent appropriate, is made.

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates to patient monitoring, and more specifically to patient monitoring to detect and/or avoid impending cardiac decompensation. Although embodiments make specific reference to monitoring impedance and electrocardiogram signals with an adherent patch, the system methods and device described herein may be applicable to many applications in which physiological monitoring is used, for example wireless physiological monitoring with implantable devices for extended periods.

Patients are often treated for diseases and/or conditions associated with a compromised status of the patient, for example a compromised physiologic status such as heart disease. In some instances a patient may have suffered a heart attack and require care and/or monitoring after release from the hospital. While such long term care may be at least partially effective, many patients are not sufficiently monitored and eventually succumb to cardiac decompensation, or heart failure. One example of a device that may be used to monitor a patient is the Holter monitor, or ambulatory electrocardiography device. Although such a device may be effective in measuring electrocardiography, such measurements alone may not be sufficient to reliably detect and/or avoid an impending cardiac decompensation.

In addition to measuring heart signals with electrocardiograms, known physiologic measurements include impedance measurements. For example, transthoracic impedance measurements can be used to measure hydration and respiration. Although transthoracic measurements can be useful, such measurements may use electrodes that are positioned across the midline of the patient, and may be somewhat uncomfortable and/or cumbersome for the patient to wear.

Work in relation to embodiments of the present invention suggests that known methods and apparatus for long term monitoring of patients may be less than ideal to detect and/or avoid an impending cardiac decompensation. In at least some instances, cardiac decompensation can be difficult to detect, for example in the early stages. At least some of the known devices may not collect the right kinds of data to treat patients optimally. For example, although successful at detecting and storing electrocardiogram signals, devices such as the Holter monitor can be somewhat bulky and may not collect all of the kinds of data that would be ideal to diagnose and/or treat a patient, for example to detect decompensation. In at least some instances, devices that are worn by the patient may be somewhat uncomfortable, which may lead to patients not wearing the devices and not complying with direction from the health care provider, such that data collected may be less than ideal. Although implantable devices may be used in some instances, many of these devices can be invasive and/or costly, and may suffer at least some of the shortcomings of known wearable devices. As a result, at least some patient are not adequately monitored, and may go into cardiac decompensation, or even die. Work in relation to embodiments of the present invention suggests that improved monitoring may avoid patient trauma, save lives, and decrease health care costs.

Therefore, a need exists for improved patient monitoring. Ideally, such improved patient monitoring would avoid at least some of the short-comings of the present methods and devices.

2. Description of the Background Art

The following U.S. Patents and Publications may describe relevant background art: U.S. Pat. Nos. 4,121,573; 4,955,381; 4,981,139; 5,080,099; 5,353,793; 5,469,859; 5,511,553; 5,544,661; 5,558,638; 5,724,025; 5,772,586; 5,862,802; 6,047,203; 6,117,077; 6,129,744; 6,225,901; 6,308,094; 6,385,473; 6,416,471; 6,454,707; 6,454,708; 6,527,711; 6,527,729; 6,551,252; 6,595,927; 6,595,929; 6,605,038; 6,645,153; 6,821,249; 6,980,851; 7,020,508; 7,054,679; 7,153,262; 7,160,252; 2004/133079; 2004/152956; 2005/0113703; 2005/0131288; 2006/0010090; 2006/0031102; 2006/0089679; 2006/122474; 2006/0155183; 2006/0224051; 2006/0264730; 2007/0021678; 2007/0038038; 2005/256418; 2005/137626; and 2006/161459. The following PCT Publication(s) may also describe relevant background art: WO2006/111878.

BRIEF SUMMARY OF THE INVENTION

Embodiments of the present invention provide systems and methods for the detection of an impending cardiac decompensation. In many embodiments, the impending decompensation can be detected early enough to avoid, or at least delay, the impending decompensation, such that patient trauma and/or expensive ICU care can be avoided. Although embodiments make specific reference to monitoring impedance and electrocardiogram signals with an adherent patch, the system methods and device described herein may be applicable to many applications in which physiological monitoring is used, for example wireless physiological monitoring with implanted sensors for extended periods.

In a first aspect, embodiments of the present invention provide a method of detecting an impending cardiac decompensation of a patient. At least two of an electrocardiogram signal of the patient, a hydration signal of the patient, a respiration signal of the patient or an activity signal of the patient are measured. The at least two of the electrocardiogram signal, the hydration signal, the respiration signal or the activity signal are combined to detect the impending cardiac decompensation. In many embodiments, the impending decompensation can be detected at least 24 hours before the decompensation occurs, for example 72 hours, and in many embodiments with a confidence level of at least 80%, for example 90%.

In many embodiments, the at least two comprise at least three of the electrocardiogram signal, the hydration signal, the respiration signal or the activity signal, and the at least three are measured and combined to detect the impending cardiac decompensation. In specific embodiments, the at least three comprise at least four of the electrocardiogram signal, the hydration signal, the respiration signal or the activity signal, and the at least four are measured and combined to detect the impending cardiac decompensation.

In specific embodiments, the electrocardiogram signal, the hydration signal, the respiration signal and the activity signal are measured combined to detect the impending cardiac decompensation.

In many embodiments, the at least two of the electrocardiogram signal, the hydration signal, the respiration signal or the activity signal can be used simultaneously to determine impending cardiac decompensation. The at least two signals can be used simultaneously in many ways.

In many embodiments, combining comprises using the at least two of the electrocardiogram signal, the hydration signal, the respiration signal or the activity signal to look up a value in a previously existing array. In some embodiments, combining may comprise at least one of adding, subtracting, multiplying, scaling or dividing the at least two of the electrocardiogram signal, the hydration signal, the respiration signal or the activity signal. In some embodiments, the at least two of the electrocardiogram signal, the hydration signal, the respiration signal or the activity signal can be combined with at least one of a weighted combination, a tiered combination or a logic gated combination, a time weighted combination or a rate of change.

In many embodiments, a flag status is determined in response to the at least two of the electrocardiogram signal, the hydration signal, the respiration signal or the activity signal. The flag status can be determined in response to a change in the at least two of the electrocardiogram signal, the hydration signal, the respiration signal or the activity signal. In some embodiments, additional signal measurements of the patient can be made in response to the flag status.

In many embodiments, the at least two of the electrocardiogram signal, the hydration signal, the respiration signal or the activity signal are combined in response to a time of day.

In many embodiments, the at least two of the electrocardiogram signal, the hydration signal, the respiration signal or the activity signal may comprise at least one of a derived signal, a time averaged signal, a filtered signal or a raw signal.

In many embodiments, baseline values of the patient for the at least two of the electrocardiogram signal, the hydration signal, the respiration signal or the activity signal are determined, and the at least two of the electrocardiogram signal, the hydration signal, the respiration signal or the activity signal signals comprise changes from the baseline values.

In many embodiments, the at least two of the electrocardiogram signal, the hydration signal, the respiration signal or the activity signal comprise differences from population baseline values, and the impending decompensation is detected in response to the differences from the baseline values of the patient population.

In many embodiments, the hydration signal comprises an impedance signal and the activity signal comprise an accelerometer signal.

In many embodiments, the activity signal may comprise an accelerometer signal to indicate a posture of the patient. In specific embodiments, the accelerometer signal may comprise a three dimensional inclination signal to determine a three dimensional orientation of the patient.

In many embodiments, a temperature signal is combined with the at least two of the electrocardiogram signal, the hydration signal, the respiration signal or the activity signal to detect the impending cardiac decompensation.

In many embodiments, the at least two of the electrocardiogram signal, the hydration signal, the respiration signal or the activity signal are transmitted to a remote site where the at least two of the electrocardiogram signal, the hydration signal, the respiration signal or the activity signal are combined to detect the impending cardiac decompensation.

In many embodiments, instructions are transmitted from a remote site to a processor supported with the patient, and the at least two of the electrocardiogram signal, the hydration signal, the respiration signal or the activity signal are combined with the processor in response to the instructions to detect the impending cardiac decompensation.

In another aspect, embodiments of the present invention provide a system to detect impending cardiac decompensation of a patient. The system comprises circuitry to measure at least two of an electrocardiogram signal of the patient, a hydration signal of the patient, or an activity signal of the patient. A processor system comprising a tangible medium in communication with the circuitry is configured to combine the at least two of the electrocardiogram signal, the hydration signal, the respiration signal or the activity signal to detect the impending cardiac decompensation.

In some embodiments, the processor system comprises a least one processor remote from the patient configured to combine the at least two to detect the decompensation.

In some embodiments, the processor system comprises a processor supported with the patient configured to receive instructions transmitted from a remote site and combine the at least two in response to the instructions to detect the impending cardiac decompensation.

In many embodiments, the at least two comprise at least three of the electrocardiogram signal, the hydration signal, the respiration signal or the activity signal and the at least three are measured and combined to detect the impending cardiac decompensation. In specific embodiments, the at least three comprise at least four of the electrocardiogram signal, the hydration signal, the respiration signal or the activity signal and the at least four are measured and combined to detect the impending cardiac decompensation.

In specific embodiments, the processor system simultaneously uses the at least two of the electrocardiogram signal, the hydration signal, the respiration signal or the activity signal to determine impending cardiac decompensation. The at least two signals can be used simultaneously in many ways,

In many embodiments, combining comprises the processor system using the at least two of the electrocardiogram signal, the hydration signal, the respiration signal or the activity signal to look up a value in a previously existing array. In some embodiments, combining comprises at least one of adding, subtracting, multiplying, scaling or dividing the at least two of the electrocardiogram signal, the hydration signal, the respiration signal or the activity signal. In some embodiments, the at least two of the electrocardiogram signal, the hydration signal, the respiration signal, or the activity signal can be combined with at least one of a weighted combination, a tiered combination or a logic gated combination, a time weighted combination or a rate of change.

In many embodiments, the processor system determines a flag status in response to the at least two of the electrocardiogram signal, the hydration signal, the respiration signal or the activity signal. The processor system determines the flag status in response to a change in the at least two of the electrocardiogram signal, the hydration signal, the respiration signal or the activity signal. In some embodiments, the processor system affects the circuitry to make additional signal measurements of the patient in response to the flag status.

In many embodiments, the processor system combines the at least two of the electrocardiogram signal, the hydration signal, the respiration signal or the activity signal in response to a time of day.

In many embodiments, the at least two of the electrocardiogram signal, the hydration signal, the respiration signal or

the activity signal comprise at least one of a derived signal, a time averaged signal, a filtered signal or a raw signal.

In many embodiments, the processor determines baseline values of the patient for the at least two of the electrocardiogram signal, the hydration signal, the respiration signal or the activity signal. The at least two of the electrocardiogram signal, the hydration signal, the respiration signal or the activity signal signals may comprise changes from the baseline values.

In many embodiments, the at least two of the electrocardiogram signal, the hydration signal, the respiration signal or the activity signal comprise differences from baseline values of a patient population. The impending decompensation is detected in response to the differences from the baseline value of the patient population.

In many embodiments, the hydration signal comprises an impedance signal and the activity signal comprise an accelerometer signal.

In many embodiments, the activity signal may comprise an accelerometer signal to determine a posture of the patient. In specific embodiments, the accelerometer signal may comprise a three dimensional inclination signal to determine a three dimensional orientation of the patient.

In many embodiments, the processor system combines a temperature signal with the at least two of the electrocardiogram signal, the hydration signal, the respiration signal or the activity signal to detect the impending cardiac decompensation.

In many embodiments, the processor transmits the at least two of the electrocardiogram signal, the hydration signal, the respiration signal or the activity signal to a remote site where the at least two of the electrocardiogram signal, the hydration signal, the respiration signal or the activity signal are combined to detect the impending cardiac decompensation.

In many embodiments, instructions are transmitted from a remote site to a processor supported with the patient. The processor combines at least two of the electrocardiogram signal, the hydration signal, the respiration signal or the activity signal in response to the instructions to detect the impending cardiac decompensation

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1**A shows a patient and a monitoring system comprising an adherent device, according to embodiments of the present invention;

FIG. **1**B shows a bottom view of the adherent device as in FIG. **1**A comprising an adherent patch;

FIG. **1**C shows a top view of the adherent patch, as in FIG. **1**B;

FIG. **1**D shows a printed circuit boards and electronic components over the adherent patch, as in FIG. **1**C;

FIG. **1**D-**1** shows an equivalent circuit that can be used to determine optimal frequencies for determining patient hydration, according to embodiments of the present invention;

FIG. **1**E shows batteries positioned over the printed circuit board and electronic components as in FIG. **1**D;

FIG. **1**F shows a top view of an electronics housing and a breathable cover over the batteries, electronic components and printed circuit board as in FIG. **1**E;

FIG. **1**G shows a side view of the adherent device as in FIGS. **1**A to **1**F;

FIG. **1**H shown a bottom isometric view of the adherent device as in FIGS. **1**A to **1**G;

FIG. **2**A shows a method of predicting an impending cardiac decompensation, according to embodiments of the present invention; and

FIGS. **3**A and **3**B show clinical data measured with an adherent patch device.

DETAILED DESCRIPTION OF THE INVENTION

Embodiments of the present invention provide systems and methods for the detection of an impending cardiac decompensation. In many embodiments, the impending decompensation can be detected early enough to avoid, or at least delay, the impending decompensation, such that patient trauma and/or expensive ICU care can be avoided. Although embodiments make specific reference to monitoring impedance and electrocardiogram signals with an adherent patch, the system methods and device described herein may be applicable to many applications in which physiological monitoring is used, for example wireless physiological monitoring with implanted sensors for extended periods. In some embodiments, implanted sensors may be used, for example as described in U.S. Pat. Nos. 6,208,894; 6,315,721; 6,185,452; and U.S. Application No. 60/972,329, entitled "Injectable Device for Physiological Monitoring" filed on Sep. 14, 2007, the same day as the present application with the same assignee, the full disclosures of which are incorporated by reference.

Decompensation is failure of the heart to maintain adequate blood circulation. Although the heart can maintain at least some pumping of blood, the quantity is inadequate to maintain healthy tissues. Several symptoms can result from decompensation including pulmonary congestion, breathlessness, faintness, cardiac palpitation, edema of the extremities, and enlargement of the liver. Cardiac decompensation can result in slow or sudden death. Sudden Cardiac Arrest (hereinafter "SCA"), also referred to as sudden cardiac death, is an abrupt loss of cardiac pumping function that can be caused by a ventricular arrhythmia, for example ventricular tachycardia and/or ventricular fibrillation. Although decompensation and SCA can be related in that patients with decompensation are also at an increased risk for SCA, decompensation is primarily a mechanical dysfunction caused by inadequate blood flow, and SCA is primarily an electrical dysfunction caused by inadequate and/or inappropriate electrical signals of the heart.

FIG. **1**A shows a patient P and a monitoring system **10**. Patient P comprises a midline M, a first side S**1**, for example a right side, and a second side S**2**, for example a left side. Monitoring system **10** comprises an adherent device **100**. Adherent device **100** can be adhered to a patient P at many locations, for example thorax T of patient P. In many embodiments, the adherent device may adhere to one side of the patient, from which data from the one side can be collected. Work in relation with embodiments of the present invention suggests that location on a side of the patient can provide comfort for the patient while the device is adhered to the patient.

Monitoring system **10** includes components to transmit data to a remote center **106**. Adherent device **100** can communicate wirelessly to an intermediate device **102**, for example with a single wireless hop from the adherent device on the patient to the intermediate device. Intermediate device **102** can communicate with remote center **106** in many ways, for example with an internet connection. In many embodiments, monitoring system **10** comprises a distributed processing system with at least one processor on device **100**, at least one processor on intermediate device **102**, and at least one process at remote center **106**, each of which processors is in electronic communication with the other processors. Remote center **106** can be in communication with a health care pro-

vider **108**A with a communication system **107**A, such as the Internet, an intranet, phone lines, wireless and/or satellite phone. Health care provider **108**A, for example a family member, can be in communication with patient P with a communication, for example with a two way communication system, as indicated by arrow **109**A, for example by cell phone, email, landline. Remote center **106** can be in communication with a health care professional, for example a physician **108**B, with a communication system **107**B, such as the Internet, an intranet, phone lines, wireless and/or satellite phone. Physician **108**B can be in communication with patient P with a communication, for example with a two way communication system, as indicated by arrow **109**B, for example by cell phone, email, landline. Remote center **106** can be in communication with an emergency responder **108**C, for example a **911** operator and/or paramedic, with a communication system **107**C, such as the Internet, an intranet, phone lines, wireless and/or satellite phone. Emergency responder **108**C can travel to the patient as indicated by arrow **109**C. Thus, in many embodiments, monitoring system **10** comprises a closed loop system in which patient care can be monitored and implemented from the remote center in response to signals from the adherent device.

In many embodiments, the adherent device may continuously monitor physiological parameters, communicate wirelessly with a remote center, and provide alerts when necessary. The system may comprise an adherent patch, which attaches to the patient's thorax and contains sensing electrodes, battery, memory, logic, and wireless communication capabilities. In some embodiments, the patch can communicate with the remote center, via the intermediate device in the patient's home. In the many embodiments, the remote center receives the data and applies the prediction algorithm. When a flag is raised, the center may communicate with the patient, hospital, nurse, and/or physician to allow for therapeutic intervention to prevent decompensation.

The adherent device may be affixed and/or adhered to the body in many ways. For example, with at least one of the following an adhesive tape, a constant-force spring, suspenders around shoulders, a screw-in microneedle electrode, a pre-shaped electronics module to shape fabric to a thorax, a pinch onto roll of skin, or transcutaneous anchoring. Patch and/or device replacement may occur with a keyed patch (e.g. two-part patch), an outline or anatomical mark, a low-adhesive guide (place guide|remove old patch|place new patch|remove guide), or a keyed attachment for chatter reduction. The patch and/or device may comprise an adhesiveless embodiment (e.g. chest strap), and/or a low-irritation adhesive model for sensitive skin. The adherent patch and/or device can comprise many shapes, for example at least one of a dogbone, an hourglass, an oblong, a circular or an oval shape.

In many embodiments, the adherent device may comprise a reusable electronics module with replaceable patches (the module collects cumulative data for approximately 90 days) and/or the entire adherent component (electronics+patch) may be disposable. In a completely disposable embodiment, a "baton" mechanism may be used for data transfer and retention, for example baton transfer may include baseline information. In some embodiments, the device may have a rechargeable module, and may use dual battery and/or electronics modules, wherein one module **101**A can be recharged using a charging station **103** while the other module **101**B is placed on the adherent device. In some embodiments, the intermediate device **102** may comprise the charging module, data transfer, storage and/or transmission, such that one of the electronics modules can be placed in the intermediate device for charging and/or data transfer while the other electronics module is worn by the patient.

In many embodiments, the system can perform the following functions: initiation, programming, measuring, storing, analyzing, communicating, predicting, and displaying. The adherent device may contain a subset of the following physiological sensors: bioimpedance, respiration, respiration rate variability, heart rate (average, minimum, maximum), heart rhythm, HRV, HRT, heart sounds (e.g. S**3**), respiratory sounds, blood pressure, activity, posture, wake/sleep, orthopnea, temperature/heat flux, and weight. The activity sensor may be one of the following: ball switch, accelerometer, minute ventilation, HR, bioimpedance noise, skin temperature/heat flux, BP, muscle noise, posture.

In many embodiments, the patch wirelessly communicates with a remote center. In some embodiments, the communication may occur directly (via a cellular or Wi-Fi network), or indirectly through intermediate device **102**. Intermediate device **102** may consist of multiple devices which communicate wired or wirelessly to relay data to remote center **106**.

FIG. **1**B shows a bottom view of adherent device **100** as in FIG. **1**A comprising an adherent patch **110**. Adherent patch **110** comprises a first side, or a lower side **11** OA, that is oriented toward the skin of the patient when placed on the patient. In many embodiments, adherent patch **110** comprises a tape **110**T which is a material, preferably breathable, with an adhesive **116**A. Patient side **11** OA comprises adhesive **116**A to adhere the patch **110** and adherent device **100** to patient P. Electrodes **112**A, **112**B, **112**C and **112**D are affixed to adherent patch **110**. In many embodiments, at least four electrodes are attached to the patch, for example six electrodes. In some embodiments the patch comprises at least two electrodes, for example two electrodes to measure an electrocardiogram (ECG) of the patient. Gel **114**A, gel **114**B, gel **114**C and gel **114**D can each be positioned over electrodes **112**A, **112**B, **112**C and **112**D, respectively, to provide electrical conductivity between the electrodes and the skin of the patient. In many embodiments, the electrodes can be affixed to the patch **110**, for example with known methods and structures such as rivets, adhesive, stitches, etc. In many embodiments, patch **110** comprises a breathable material to permit air and/or vapor to flow to and from the surface of the skin.

FIG. **1**C shows a top view of the adherent patch **100**, as in FIG. **1**B. Adherent patch **100** comprises a second side, or upper side **110**B. In many embodiments, electrodes **110**A, **110**B, **110**C and **110**D extend from lower side **110**A through the adherent patch to upper side **110**B. In some embodiments, an adhesive **116**B can be applied to upper side **110**B to adhere structures, for example, a cover, to the patch such that the patch can support the electronics and other structures when the patch is adhered to the patient. The printed circuit board (PCB) comprise completely flex PCB, rigid PCB combined flex PCB and/or rigid PCB boards connected by cable.

FIG. **1**D shows a printed circuit boards and electronic components over adherent patch **110**, as in FIG. **1**C. A printed circuit board (PCB), for example flex PCB **120**, can be positioned above **110**B of patch **110**. Flex PCB **120** can include traces that extends to connectors **122**A, **122**B, **122**C and **122**D on the flex PCB. Connectors **122**A, **122**B, **122**C and **122**D can be positioned on flex PCB **120** in alignment with electrodes **112**A, **112**B, **112**C and **112**D so as to electrically couple the flex PCB with the electrodes. In some embodiments, connectors **122**A, **122**B, **122**C and **122**D may comprise insulated wires or a flex circuit that provide strain relief between the PCB and the electrodes. In some embodiments, additional PCB's for example PCB **120**A, **120**B, **120**C and **120**D be connected to flex PCB **120**. Electronic components

130 can be connected to flex PCB 120 and/or mounted thereon. In some embodiments, electronic components 130 can be mounted on the additional PCB's.

Electronic components 130 comprise components to take physiologic measurements, transmit data to remote center 106 and receive commands from remote center 106. In many embodiments, electronics components 130 may comprise known low power circuitry, for example complementary metal oxide semiconductor (CMOS) circuitry components. Electronics components 130 comprise an activity sensor and activity circuitry 134, impedance circuitry 136 and electrocardiogram circuitry, for example ECG circuitry 136. In some embodiments, electronics circuitry 130 may comprise a microphone and microphone circuitry 142 to detect an audio signal from within the patient, and the audio signal may comprise a heart sound and/or a respiratory sound, for example an S3 heart sound and a respiratory sound with rales and/or crackles. Electronics circuitry 130 may comprise a temperature sensor, for example a thermistor, and temperature sensor circuitry 144 to measure a temperature of the patient, for example a temperature of a skin of the patient. Electronics circuitry may comprise a heat flux sensor and heat flux sensor circuitry to measure a skin heat flow of a patient.

Work in relation to embodiments of the present invention suggests that skin temperature may effect impedance and/or hydration measurements, and that skin temperature measurements may be used to correct impedance and/or hydration measurements. In some embodiments, increase in skin temperature can be associated with increased vaso-dilation near the skin surface, such that measured impedance measurement decreased, even through the hydration of the patient in deeper tissues under the skin remains substantially unchanged. Thus, use of the temperature sensor can allow for correction of the hydration signals to more accurately assess the hydration, for example extra cellular hydration, of deeper tissues of the patient, for example deeper tissues in the thorax.

Electronics circuitry 130 may comprise a processor 146. Processor 146 comprises a tangible medium, for example read only memory (ROM), electrically erasable programmable read only memory (EEPROM) and/or random access memory (RAM). Electronic circuitry 130 may comprise real time clock and frequency generator circuitry 148. In some embodiments, processor 136 may comprise the frequency generator and real time clock. The processor can be configured to control a collection and transmission of data from the impedance circuitry electrocardiogram circuitry and the accelerometer. In many embodiments, device 100 comprise a distributed processor system, for example with multiple processors on device 100.

In many embodiments, electronics components 130 comprise wireless communications circuitry 132 to communicate with remote center 106. The wireless communication circuitry can be coupled to the impedance circuitry, the electrocardiogram circuitry and the accelerometer to transmit to a remote center with a communication protocol at least one of the hydration signal, the electrocardiogram signal or the accelerometer signal. In specific embodiments, wireless communication circuitry is configured to transmit the hydration signal, the electrocardiogram signal and the accelerometer signal to the remote center with a single wireless hop, for example from wireless communication circuitry 132 to intermediate device 102. The communication protocol comprises at least one of Bluetooth, Zigbee, WiFi, WiMax, IR, amplitude modulation or frequency modulation. In many embodiments, the communications protocol comprises a two way protocol such that the remote center is capable of issuing commands to control data collection.

In some embodiments, intermediate device 102 comprises a data collection system to collect and store data from the wireless transmitter. The data collection system can be configured to communicate periodically with the remote center. In many embodiments, the data collection system can transmit data in response to commands from remote center 106 and/or in response to commands from the adherent device.

Activity sensor and activity circuitry 134 can comprise many known activity sensors and circuitry. In many embodiments, the accelerometer comprises at least one of a piezoelectric accelerometer, capacitive accelerometer or electromechanical accelerometer. The accelerometer may comprise a 3-axis accelerometer to measure at least one of an inclination, a position, an orientation or acceleration of the patient in three dimensions. Work in relation to embodiments of the present invention suggests that three dimensional orientation of the patient and associated positions, for example sitting, standing, lying down, can be very useful when combined with data from other sensors, for example ECG data and/or hydration data.

Impedance circuitry 136 can generate both hydration data and respiration data. In many embodiments, impedance circuitry 136 is electrically connected to electrodes 112A, 112B, 112C and 112D such that electrodes 112A and 112D comprise outer electrodes that are driven with a current, or force electrodes. The current delivered between electrodes 112A and 112D generates a measurable voltage between electrodes 112B and 112C, such that electrodes 112B and 112C comprise inner electrodes, or sense electrodes that measure the voltage in response to the current from the force electrodes. The voltage measured by the sense electrodes can be used to determine the hydration of the patient.

FIG. 1D-1 shows an equivalent circuit 152 that can be used to determine optimal frequencies for measuring patient hydration. Work in relation to embodiments of the present invention indicates that the frequency of the current and/or voltage at the force electrodes can be selected so as to provide impedance signals related to the extracellular and/or intracellular hydration of the patient tissue. Equivalent circuit 152 comprises an intracellular resistance 156, or R(ICW) in series with a capacitor 154, and an extracellular resistance 158, or R(ECW). Extracellular resistance 158 is in parallel with intracellular resistance 156 and capacitor 154 related to capacitance of cell membranes. In many embodiments, impedances can be measured and provide useful information over a wide range of frequencies, for example from about 0.5 kHz to about 200 KHz. Work in relation to embodiments of the present invention suggests that extracellular resistance 158 can be significantly related extracellular fluid and to cardiac decompensation, and that extracellular resistance 158 and extracellular fluid can be effectively measured with frequencies in a range from about 0.5 kHz to about 20 kHz, for example from about 1 kHz to about 10 kHz. In some embodiments, a single frequency can be used to determine the extracellular resistance and/or fluid. As sample frequencies increase from about 10 kHz to about 20 kHz, capacitance related to cell membranes decrease the impedance, such that the intracellular fluid contributes to the impedance and/or hydration measurements. Thus, many embodiments of the present invention employ measure hydration with frequencies from about 0.5 kHz to about 20 kHz to determine patient hydration.

In many embodiments, impedance circuitry 136 can be configured to determine respiration of the patient. In specific embodiments, the impedance circuitry can measure the

hydration at 25 Hz intervals, for example at 25 Hz intervals using impedance measurements with a frequency from about 0.5 kHz to about 20 kHz.

ECG circuitry **138** can generate electrocardiogram signals and data from electrodes **112**A, **112**B, **112**C and **112**D. In some embodiments, ECG circuitry **138** is connected to inner electrodes **12**B and **122**C, which may comprise sense electrodes of the impedance circuitry as described above. In some embodiments, the inner electrodes may be positioned near the outer electrodes to increase the voltage of the ECG signal measured by ECG circuitry **138**. In some embodiments, the ECG circuitry can share components with the impedance circuitry.

FIG. **1**E shows batteries **150** positioned over the flex printed circuit board and electronic components as in FIG. **1**D. Batteries **150** may comprise rechargeable batteries that can be removed and/or recharged. In some embodiments, batteries **150** can be removed from the adherent patch and recharged and/or replaced.

FIG. **1**F shows a top view of a cover **162** over the batteries, electronic components and flex printed circuit board as in FIG. **1**E. In many embodiments, an electronics housing **160** may be disposed under cover **162** to protect the electronic components, and in some embodiments electronics housing **160** may comprise an encapsulant over the electronic components and PCB. In many embodiments, electronics housing **160** may comprise a water proof material, for example a sealant adhesive such as epoxy or silicone coated over the electronics components and/or PCB. In some embodiments, electronics housing **160** may comprise metal and/or plastic, which may be potted with silicone, epoxy, etc.

Cover **162** may comprise many known biocompatible cover, casing and/or housing materials, such as elastomers, for example silicone. The elastomer may be fenestrated to improve breathability. In some embodiments, cover **162** may comprise many known breathable materials, for example polyester or polyamide fabric. The breathable fabric may be coated to make it water resistant, waterproof, and/or to aid in wicking moisture away from the patch. The breathable fabric may be coated in order to make the outside hydrophobic and the inside hydrophilic.

FIG. **1**G shows a side view of adherent device **100** as in FIGS. **1**A to **1**F. Adherent device **100** comprises a maximum dimension, for example a length **170** from about 4 to 10 inches (from about 100 mm to about 250 mm), for example from about 6 to 8 inches (from about 150 mm to about 200 mm). In some embodiments, length **170** may be no more than about 6 inches (no more than about 150 mm). Adherent device **100** comprises a thickness **172**. Thickness **172** may comprise a maximum thickness along a profile of the device. Thickness **172** can be from about 0.2 inches to about 0.4 inches (from about 5 mm to about 10 mm), for example about 0.3 inches (about 7.5 mm).

FIG. **1**H shown a bottom isometric view of adherent device **100** as in FIGS. **1**A to **1**G. Adherent device **100** comprises a width **174**, for example a maximum width along a width profile of adherent device **100**. Width **174** can be from about 2 to about 4 inches (from about 50 mm to 100 mm), for example about 3 inches (about 75 mm).

FIG. **2**A shows a method **200** of predicting an impending cardiac decompensation. A step **205** measures an ECG signal. The ECG signal may comprise a differential signal measured with at least two electrodes and may be measured in many known ways. A step **210** measures an hydration signal. The hydration signal may comprise an impedance signal, for example a four pole impedance signal, and may be measured in many known ways. A step **215** measures a respiration signal. The respiration signal may comprise an impedance signal, and may be measured in many known ways. A step **220** measures an activity signal. The activity signal may be measured in many known ways and may comprise a three dimensional accelerometer signal to determine a position of the patient, for example from a three dimensional accelerometer signal. A step **225** measures a temperature signal. The temperature signal may be measured in many ways, for example with a thermistor, a thermocouple, and known temperature measurement devices. A step **230** records a time of day of the signals, for example a local time of day such as morning, afternoon, evening, and/or nighttime.

A step **235** processes the signals. The signals may be processed in many known ways, for example to generate at least one of a derived signal, a time averaged signal, a filtered signal. In some embodiments, the signals may comprise raw signals. The ECG signal may comprise at least one of a heart rate signal, a heart rate variability signal, an average heart rate signal, a maximum heart rate signal or a minimum heart rate signal. The hydration signal may comprise an impedance measurement signal. The activity signal may comprise at least one of an accelerometer signal, a position signal indicating the orientation of the patient, such as standing, lying, or sitting. The respiration signal may comprise a least one of a respiration rate, a maximum respiration rate, a minimum respiration rate, an average respiration rate or respiration rate variability. The temperature may comprise an average temperature or a peak temperature.

A step **240** compares the signals with baseline values. In many embodiments, the baseline values may comprise measurements from the same patient at an earlier time. In some embodiments, the baseline values comprise values for a patient population. In some embodiments, the baseline values for a patient population may comprise empirical data from a suitable patient population size, for example at least about 144 patients, depending on the number of variables measured, statistical confidence and power used. The measured signals may comprise changes and/or deviations from the baseline values.

A step **245** transmits the signals. In many embodiments, the measurement signals, which may comprise derived and/or processed measurement signals, are transmitted to the remote site for comparison. In some embodiments, the signals may be transmitted to a processor supported with the patient for comparison.

A step **250** combines at least two of the ECG signal, the hydration signal, the respiration signal, the activity signal and the temperature signal to detect the impending decompensation. In many embodiments, at least three of the signals are combined. In some embodiments, at least four signals comprising ECG signal, the hydration signal, the respiration signal and the activity signal are combined to detect the impending decompensation. In specific embodiments, at least four signals comprising the ECG signal, the hydration signal, the respiration signal, the activity signal and the temperature signal are combined to detect the impending decompensation.

The signals can be combined in many ways. In some embodiments, the signals can be used simultaneously to determine the impending cardiac decompensation.

In some embodiments, the signals can be combined by using the at least two of the electrocardiogram signal, the hydration signal, the respiration signal or the activity signal to look up a value in a previously existing array.

TABLE 1

Lookup Table for ECG and Hydration Signals

	Heart Rate		
Hydration	0-49 bpm	50-69 bpm	70-90 bpm
>60 Ohms	N	N	Y
41-59 Ohms	N	Y	Y
0-40 Ohms	Y	Y	Y

Table 1 shows combination of the electrocardiogram signal with the hydration signal to look up a value in a pre-existing array. For example at a heart rate of 89 bpm and a hydration of 35 Ohms, the value in the table may comprise Y. In specific embodiments, the values of the look up table can be determined in response to empirical data measured for a patient population of at least about 100 patients, for example measurements on about 1000 to 10,000 patients.

In some embodiments, the table may comprise a three or more dimensional look up table.

In some embodiments, the signals may be combined with at least one of adding, subtracting, multiplying, scaling or dividing the at least two of the electrocardiogram signal, the hydration signal, the respiration signal or the activity signal. In specific embodiments, the measurement signals can be combined with positive and or negative coefficients determined in response to empirical data measured for a patient population of at least about 100 patients, for example data on about 1000 to 10,000 patients.

In some embodiments, a weighted combination may combine at least 3 measurement signals to generate an output value according to a formula of the general form

$$OUTPUT=aX+bY+cZ$$

where a, b and c comprise positive or negative coefficients determined from empirical data and X, Y and Z comprise measured signals for the patient, for example at least three of the electrocardiogram signal, the hydration signal, the respiration signal or the activity signal. While three coefficients and three variables are shown, the data may be combined with multiplication and/or division. One or more of the variables may be the inverse of a measured variable.

In some embodiments, the ECG signal comprises a heart rate signal that can be divided by the activity signal. Work in relation to embodiments of the present invention suggest that an increase in heart rate with a decrease in activity can indicate an impending decompensation. The signals can be combined to generate an output value with an equation of the general form

$$OUTPUT=aX/Y+bZ$$

where X comprise a heart rate signal, Y comprises a hydration rate signal and Z comprises a respiration signal, with each of the coefficients determined in response to empirical data as described above.

In some embodiments, the data may be combined with a tiered combination. While many tiered combinations can be used a tiered combination with three measurement signals can be expressed as

$$OUTPUT=(\Delta X)+(\Delta Y)+(\Delta Z)$$

where (ΔX), (ΔY), (ΔZ) may comprise change in heart rate signal from baseline, change in hydration signal from baseline and change in respiration signal from baseline, and each may have a value of zero or one, based on the values of the signals. For example if the heart rate increase by 10%, (ΔX) can be assigned a value of 1. If hydration increases by 5%, (ΔY) can be assigned a value of 1. If activity decreases below 10% of a baseline value (ΔZ) can be assigned a value of 1. When the output signal is three, a flag may be set to trigger an alarm.

In some embodiments, the data may be combined with a logic gated combination. While many logic gated combinations can be used a logic gated combination with three measurement signals can be expressed as

$$OUTPUT=(\Delta X)AND(\Delta Y)AND(\Delta Z)$$

where (ΔX), (ΔY), (ΔZ) may comprise change in heart rate signal from baseline, change in hydration signal from baseline and change in respiration signal from baseline, and each may have a value of zero or one, based on the values of the signals. For example if the heart rate increase by 10%, (ΔX) can be assigned a value of 1. If hydration increases by 5%, (ΔY) can be assigned a value of 1. If activity decreases below 10% of a baseline value (ΔZ) can be assigned a value of 1. When each of (ΔX), (ΔY), (ΔZ) is one, the output signal is one, and a flag may be set to trigger an alarm. If any one of (ΔX), (ΔY) or (ΔZ) is zero, the output signal is zero and a flag may be set so as not to trigger an alarm. While a specific example with AND gates has been shown the data can be combined in may ways with known gates for example NAND, NOR, OR, NOT, XOR, XNOR gates. In some embodiments, the gated logic may be embodied in a truth table.

A step **255** sets a flag. The flag can be set in response to the output of the combined signals. In some embodiments, the flag may comprise a binary parameter in which a value of zero does not triggers an alarm and a value of one triggers an alarm.

A step **260** communicates with the patient and/or a health care provider. In some embodiments, the remote site may contact the patient to determine if he or she is okay and communicate the impending decompensation such that the patient can receive needed medical care. In some embodiments, the remote site contacts the health care provider to warn the provider of the impending decompensation and the need for the patient to receive medical care.

A step **265** collects additional measurements. Additional measurements may comprise additional measurements with the at least two signals, for example with greater sampling rates and or frequency of the measurements. Additional measurements may comprise measurements with a additional sensors, for example an onboard microphone to detect at least one of rales, S**1** heart sounds, S**2** heart sounds, S**3** heart sounds, or arrhythmias. In some embodiments, the additional measurements, for example sounds, can be transmitted to the health care provider to diagnose the patient in real time.

The processor system, as described above, can be configured to perform the method **200**, including many of the steps described above. It should be appreciated that the specific steps illustrated in FIG. **2**A provide a particular method of predicting an impending cardiac decompensation, according to an embodiment of the present invention. Other sequences of steps may also be performed according to alternative embodiments. For example, alternative embodiments of the present invention may perform the steps outlined above in a different order. Moreover, the individual steps illustrated in FIG. **2**A may include multiple sub-steps that may be performed in various sequences as appropriate to the individual step. Furthermore, additional steps may be added or removed depending on the particular applications. One of ordinary skill in the art would recognize many variations, modifications, and alternatives.

Experimental Clinical Study

The protocol below has been used to measure signals from actual patients with an adherent device. These data show that an adherent patch as described above can be continuously adhered for at least one week. These data also show that 90 day continuous in home monitoring can be achieved with a set of 13 patches in which one of the patches is replaced each week. The clinical testing device used an adherent device with modifications, as described more fully below and referred to as the MS system (multi-sensor). Although the clinical device did not include wireless circuitry and processor circuitry supported with the patch adhered to the skin of the patient, these data do show that such a device, as described above, can be made by one of ordinary skill in the art based on the teachings described herein. Additional empirical studies can be conducted on a suitable number of patients.

MS Clinical System Description

The MS clinical system includes many of the structure components described above. There is a flexible connection between the electrodes and the flex PCB, for example wires or polyurethane with silver ink. The cover can stretch with the breathable tape on both the clinical device and the above described wireless device. There is generally a gap between the flex PCB and breathable tape in both clinical and above described wireless devices. The tested device used weights to at least partially simulate the weight of wireless and processor circuitry. The adherent device of the MS clinical system comprises four electrodes to measure bioimpedance and ECG signals and a 3-axis accelerometer, as described above. Bioimpedance signals were used to determine patient respiration and patient hydration, and accelerometer signals were used to determine patient activity and posture. The MS clinical adherent patch device comprising the sensors and at least some sensor circuitry were connected to a processor to record data. The processor was connected to the tested adherent device with wires and supported away from the tested adherent patch device, for example around the patient's waist. Data were collected at regular intervals and uploaded to a remote site, as described above.

Clinical testing of the MS clinical system shows the effectiveness of the structures for continuous adherence of at least one week and data collection, and that patches can be successively removed and replaced by the patient for in-home monitoring. This effectiveness has been shown without requiring fully functional electronics circuitry such as a battery, wireless circuitry and process circuitry on the adherent device. For example, the MS system includes an insert with about 20 g of additional weight. Although an insert with a 20 gram weight was used for the MS clinical device, greater amounts of weight and circuitry can be used, for example about 30-50 g. The patch device may be modified to accommodate additional weight, for example by increasing the size of the adherent surface. The shape of the MS clinical patch is generally elongate, similar to the elongate shape shown above.

Study Design and Rationale

The MS System is used in a clinical study of heart failure patients to gather data that can be used to develop an algorithm for diagnosing and predicting impending heart failure decompensation events. Events typically manifest as heart failure-related hospitalization, emergency room or urgent care visits leading to a change in oral or IV diuretic treatment.

The purpose of the clinical study is to correlate physiological signals recorded by the system to clinical events of acute heart failure decompensation (AHFD). Signals from the patch can be weighted and combined to determine an index that associates physiologic parameters to impending events of decompensation. Patients who have been classified as New York Heart Association class III and IV within the last 12 months and have had a recent AHFD event can be enrolled into the study and are monitored with the MS system for approximately 90 days.

AHFD events are defined as any of the following:

1) Any heart failure related ER, Urgent Care, in-office visit or hospitalization requiring administration of IV diuretics, administration of IV inotropes, or ultrafiltration for fluid removal.

2) A change in diuretic, defined as a change in diuretic directed by the health care provider occurring inside a hospital, emergency room, or urgent care setting (i.e. no patient self-directed changes to medications not approved by a health care provider would be included), that satisfies one or more of the following: a) a change in the type of diuretic the patient is taking, b) a dose increase of an existing diuretic, or c) the addition of another diuretic.

3) A heart failure decompensation event for which death is the outcome.

Patients enrolled in the study were asked to replace the patch weekly. The study can enroll at least about 550 patients. The patient was provided with a kit comprising 13 patches for replacement. The patches were placed on alternating left and right sides of the patient's thorax, as described above, to minimize progressive irritation.

The data collected in the study can be used to develop an algorithm to at least one of detect, diagnose or predict an impending cardiac decompensation. The algorithm can be implemented on a processor system as described above. Known methods can be used to analyze the data, for example splitting the patients into two groups, one to develop parameters for the algorithm and a second group to test the algorithm developed with the first group. In many embodiments, the signal of the algorithm may comprise a simple binary output for impending cardiac decompensation of the patient. The logic output, yes or no, can be determined in response to patient data combined as described above. The logic output may comprise a signal, such as a binary Y or N signal.

The developed algorithm can be evaluated with composite sensitivity and false positive patient signal status rates. The sensitivity may be defined as the percent of true positive events out of all condition present events, and the false positive patient status signal status rate can be defined as the number of false positive patient status signals per patient-years of follow up. For example, the sensitivity can be at least 50%, for example at least 60%, at least 70%, or even at least 80%. The false positive patient signal status rate may be limited to no more than about 1.1 false positive patient status signals per patient year, for example no more than about 1.0 false positive patient status signals per patient year, no more than about 0.9 false positive patient status signals per patient year, and even no more than about 0.8 false positive patient status signals per patient year.

Clinical Results

Clinical data are available for the first 180 patients enrolled in the study.

FIGS. **3**A and **3**B show clinical data measured with an adherent patch device, in accordance with the above protocol. FIG. **3**A shows data from a patient with the MS patch adhered to a first patient, and the data was acquired over the 90 day period with the series of 13 patches. The signals measured included Heart Rate (beats per minute), Heart Rate Variability (ms), Respiratory Rate (breaths per minute), Activity (m-G's) and Body Fluid (Ohms). FIG. **3**B shows data from a second patient similar to FIG. **3**A.

Of the 180 patients who have completed the study with the MS adherent patch, as described above, all patches in all

patients adhered continuously without patch failure. In all patients, the first patch adhered continuously for the first week. With the exception of a handful of patient deaths and early withdrawals that were unrelated to device failure, all patients reached the end of 90-day follow-up period having used 13 weekly patches without incident. None of the 180 patients showed skin irritation or damage that required withdrawal from the study.

The above data show that the wireless adherent patch device can be constructed for in home wireless patient monitoring for an extended period of at least 90 day, in which each patch of a set is continuously adhered to a patient for at least one week and each patch is configured to support the measurement circuitry, the processor, the wireless communication circuitry and the battery with the skin of the patient.

While the exemplary embodiments have been described in some detail, by way of example and for clarity of understanding, those of skill in the art will recognize that a variety of modifications, adaptations, and changes may be employed. Hence, the scope of the present invention should be limited solely by the appended claims.

The invention claimed is:

1. A system to detect impending acute cardiac decompensation of a patient, the system comprising:

impedance circuitry to measure a hydration signal of the patient, wherein the hydration signal corresponds to a tissue hydration of the patient;

an activity sensor to measure an activity signal associated with the patient; and

a processor system comprising a computer readable memory in communication with the impedance circuitry and the activity sensor, wherein the computer readable memory of the processor system embodies instructions to combine the hydration signal and the activity level of the patient to detect the impending acute cardiac decompensation.

2. The system of claim **1**, wherein the activity signal comprises an accelerometer signal to determine at least one of inclination, position, orientation, and acceleration of the patient.

3. The system of claim **1**, further including:

additional sensing circuitry to measure additional physiological parameters in response to a detected impending acute cardiac decompensation.

4. The system of claim **3**, wherein the additional sensing circuitry includes an onboard microphone to detect at least one of rales, heart sounds, or arrhythmias.

5. The system of claim **1**, further including:

electrocardiogram circuitry coupled to at least two electrodes and configured to measure an electrocardiogram signal of the patient, wherein the processor system utilizes the electrocardiogram signal in combination with the calculated hydration measurement and activity level of the patient to detect the impending acute cardiac decompensation of the patient.

6. The system of claim **1**, wherein the impedance circuitry is utilized to measure a respiration signal of the patient, wherein the processor system further utilizes the measured respiration signal in combination with the measured hydration signal and the activity level of the patient to detect the impending acute cardiac decompensation.

7. A method of detecting decompensation in a patient, the method comprising:

measuring a hydration signal of the patient with impedance circuitry and a plurality of electrodes affixed to the patient, wherein the hydration signal corresponds to a tissue hydration of the patient;

measuring an activity signal associated with the patient with an activity sensor; and

combining via a processing system the hydration signal and the activity level of the patient to detect an impending acute cardiac decompensation.

8. The method of claim **7**, wherein the activity signal comprises an accelerometer signal that is used to determine at least one of inclination, position, orientation, and acceleration of the patient.

9. The method of claim **7**, wherein in response to a detected impending acute cardiac decompensation, the method further includes measuring additional physiological parameters.

10. The method of claim **9**, wherein the additional physiological parameters includes one or more of rales, heart sounds, or arrhythmias.

11. The method of claim **7**, further including:

measuring electrocardiogram signals of the patient with electrocardiogram circuitry coupled to at least two of the plurality of electrodes, wherein the electrocardiogram signals are combined with the measured hydration signal and activity signal to detect the impending acute cardiac decompensation of the patient.

12. The method of claim **7**, further including:

measuring a respiration signal of the patient with the impedance circuitry, wherein the respiration signal is combined with the measured hydration signal and activity signal to detect the impending acute cardiac decompensation of the patient.

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