



US008112148B2

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

(10) **Patent No.:** **US 8,112,148 B2**
(45) **Date of Patent:** **Feb. 7, 2012**

(54) **SYSTEM AND METHOD FOR MONITORING
CARDIAC SIGNAL ACTIVITY IN PATIENTS
WITH NERVOUS SYSTEM DISORDERS**

(58) **Field of Classification Search** 600/513;
607/45
See application file for complete search history.

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3 pgs.

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(*) Notice: Subject to any disclaimer, the term of this
patent is extended or adjusted under 35
U.S.C. 154(b) by 1232 days.

(21) Appl. No.: **11/767,054**

(Continued)

(22) Filed: **Jun. 22, 2007**

Primary Examiner — Eric D. Bertram

(65) **Prior Publication Data**

US 2007/0260147 A1 Nov. 8, 2007

(74) *Attorney, Agent, or Firm* — Fredrikson & Byron, PA

(57) **ABSTRACT**

A medical device system and method for monitoring cardiac signal activity in patients with nervous system disorders. In some embodiments, a brain signal and a cardiac signal are received by a processor, brain events are identified in the brain signal, and the brain events are used to identify portions of the cardiac signal. In some embodiments, Event portions of the cardiac signal are identified corresponding to brain event time periods, and Inter-event portions are identified corresponding to time periods between brain events. An Inter-event heart-rate variability (HRV) calculation is performed using Inter-event portions of the cardiac signal, and an output of the medical device system is modified based upon the calculated Inter-event HRV according to certain embodiments of the invention. An Event HRV may also be calculated according to certain embodiments, and an output modified based on comparisons of the Event HRV to the Inter-event HRV, for example.

Related U.S. Application Data

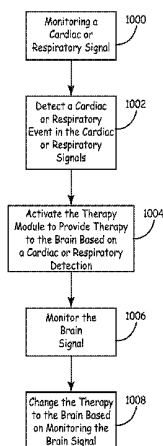
(63) Continuation-in-part of application No. 11/380,462, filed on Apr. 27, 2006, which is a continuation-in-part of application No. 11/311,043, filed on Dec. 19, 2005, now Pat. No. 7,865,244, and a continuation-in-part of application No. 11/311,200, filed on Dec. 19, 2005, now Pat. No. 8,041,418, and a continuation-in-part of application No. 11/311,393, filed on Dec. 19, 2005, now Pat. No. 8,041,419, and a continuation-in-part of application No. 11/311,456, filed on Dec. 19, 2005, now Pat. No. 7,945,316.

(60) Provisional application No. 60/636,929, filed on Dec. 17, 2004.

(51) **Int. Cl.**
A61B 5/00 (2006.01)

(52) **U.S. Cl.** 600/513

58 Claims, 57 Drawing Sheets



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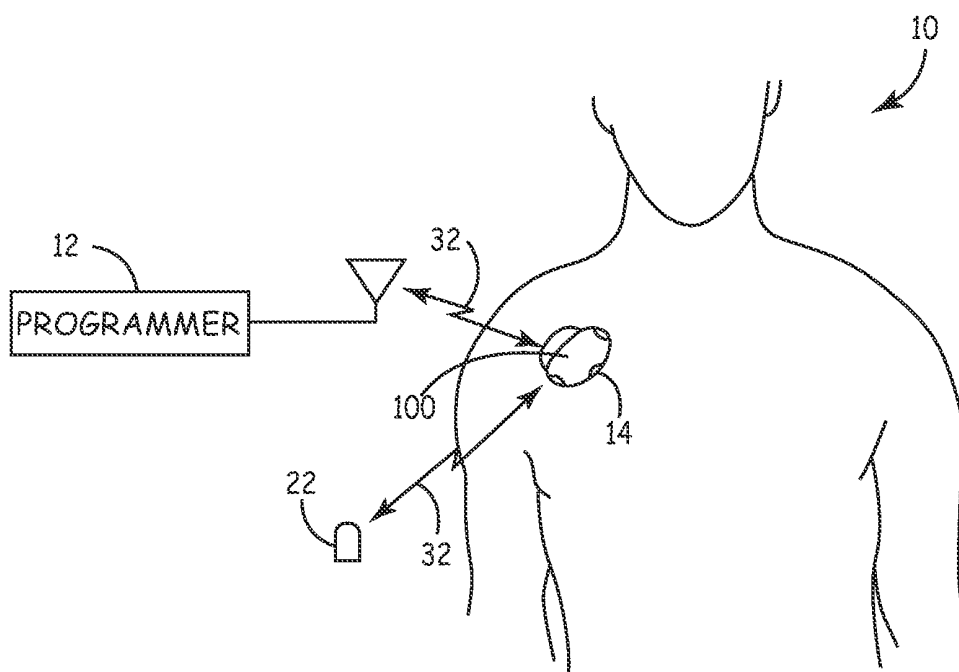


FIG. 1

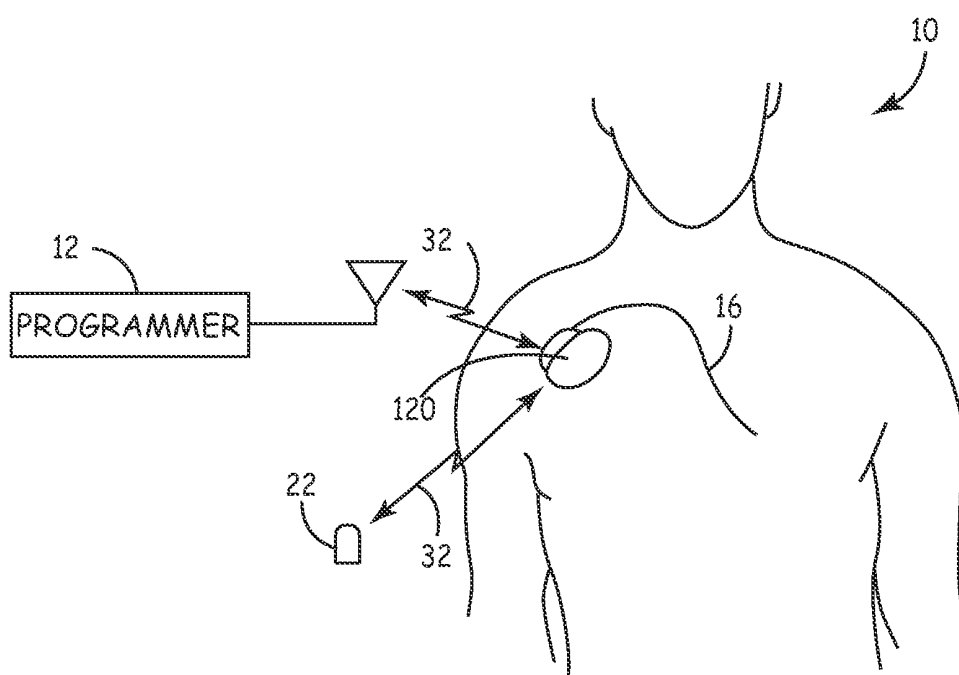


FIG. 2

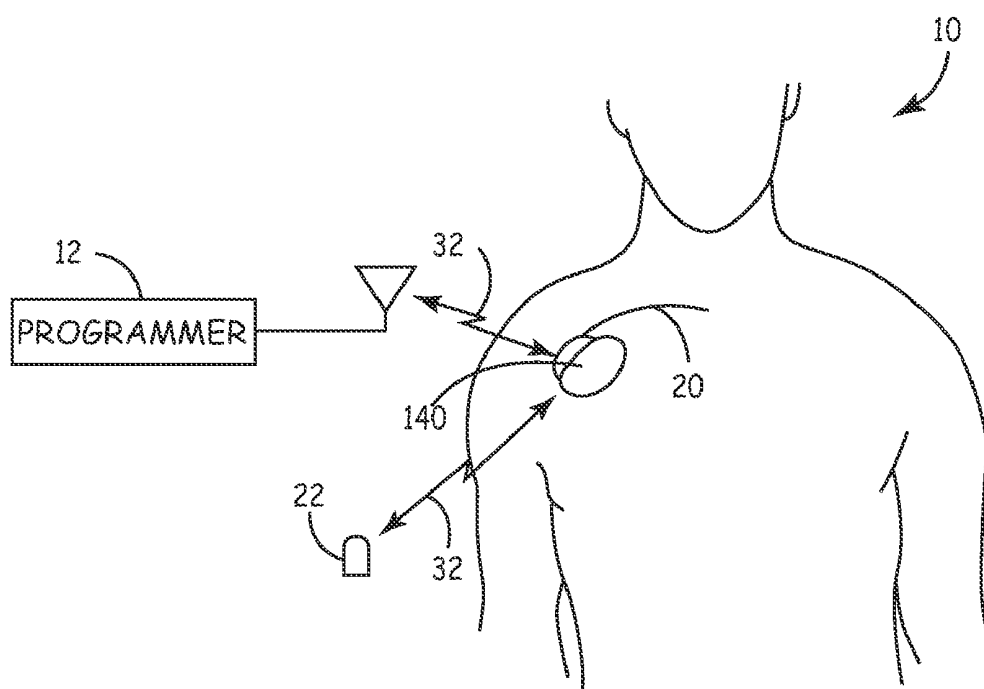


FIG. 3

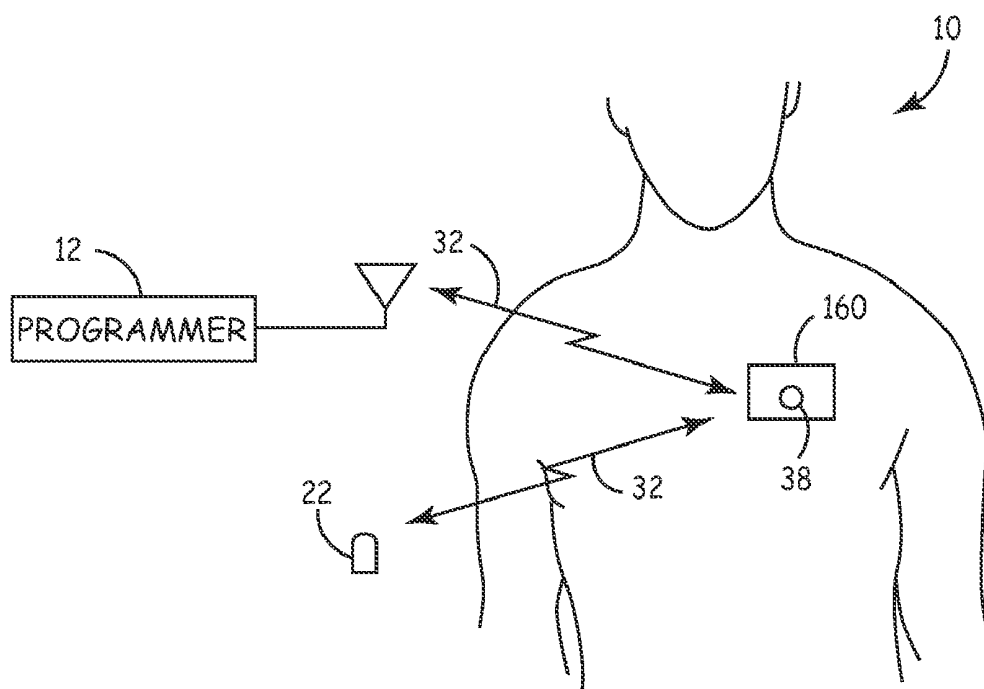


FIG. 4

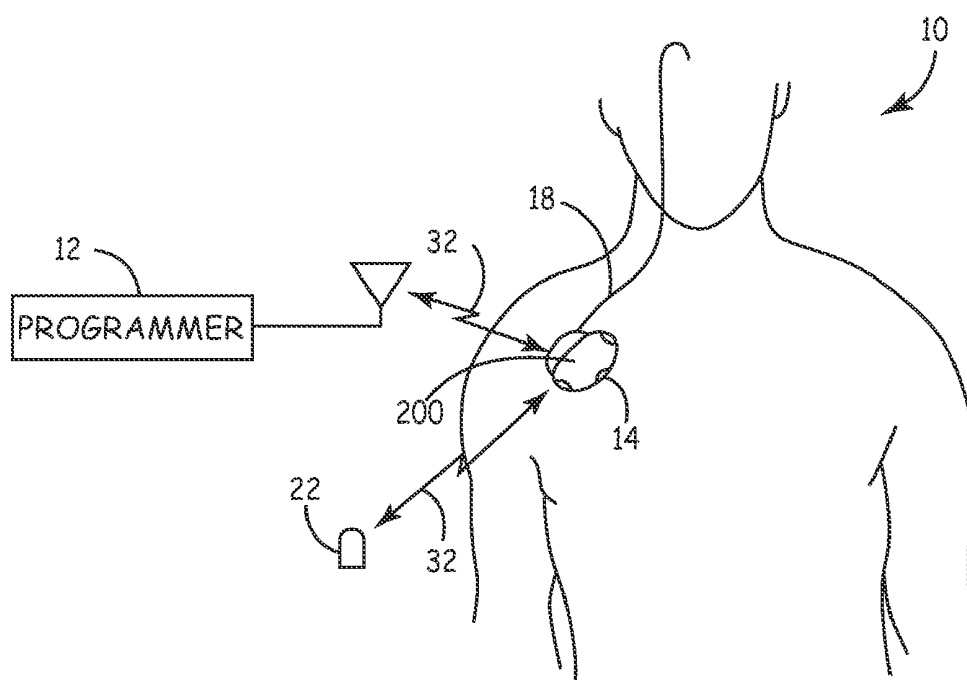


FIG. 5

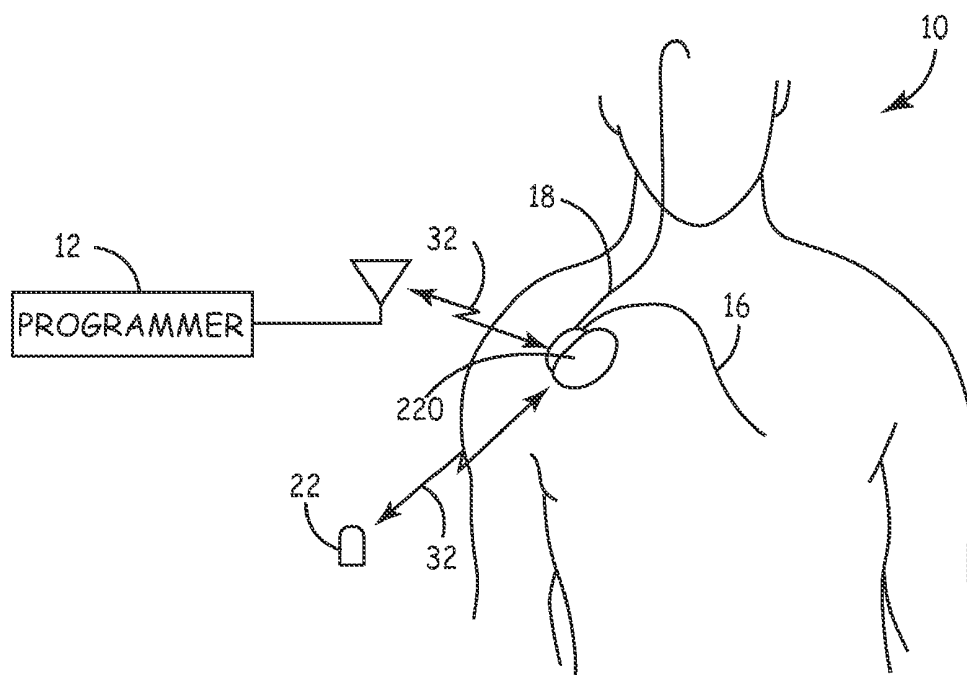


FIG. 6

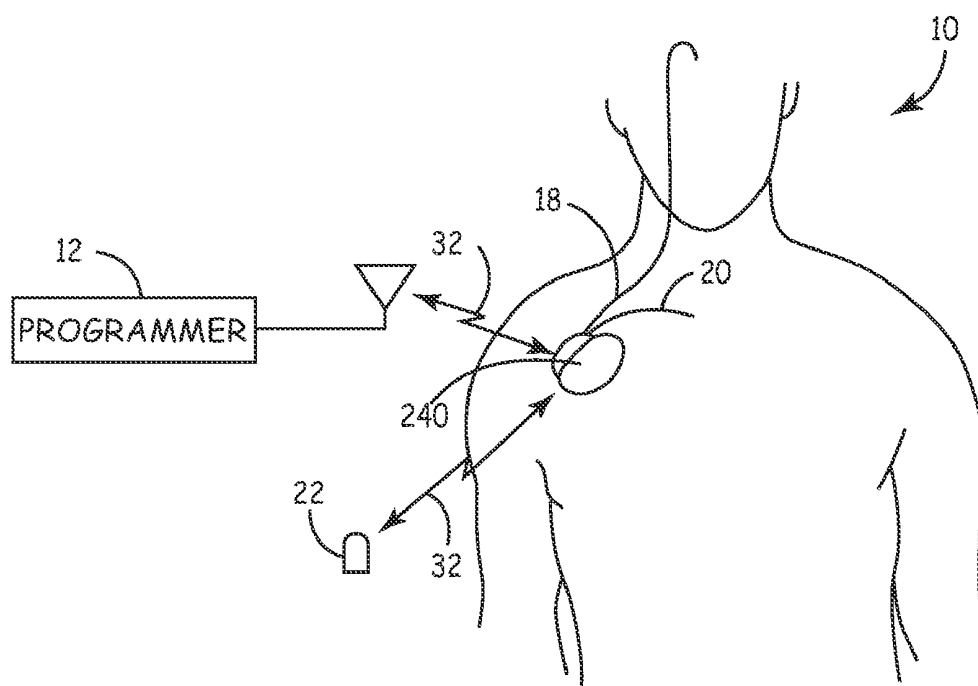


FIG. 7

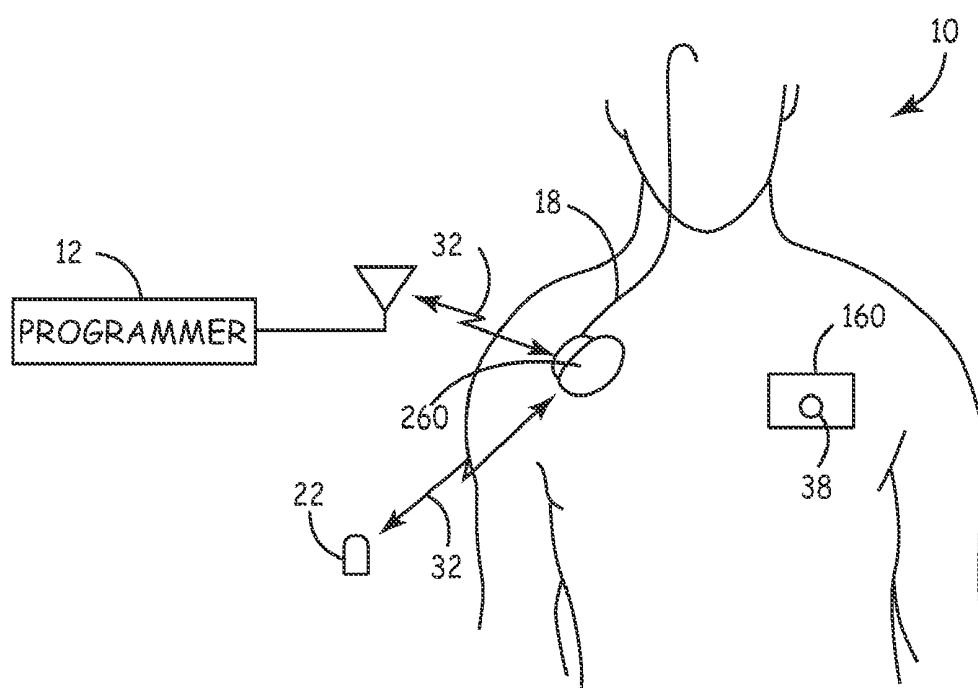


FIG. 8

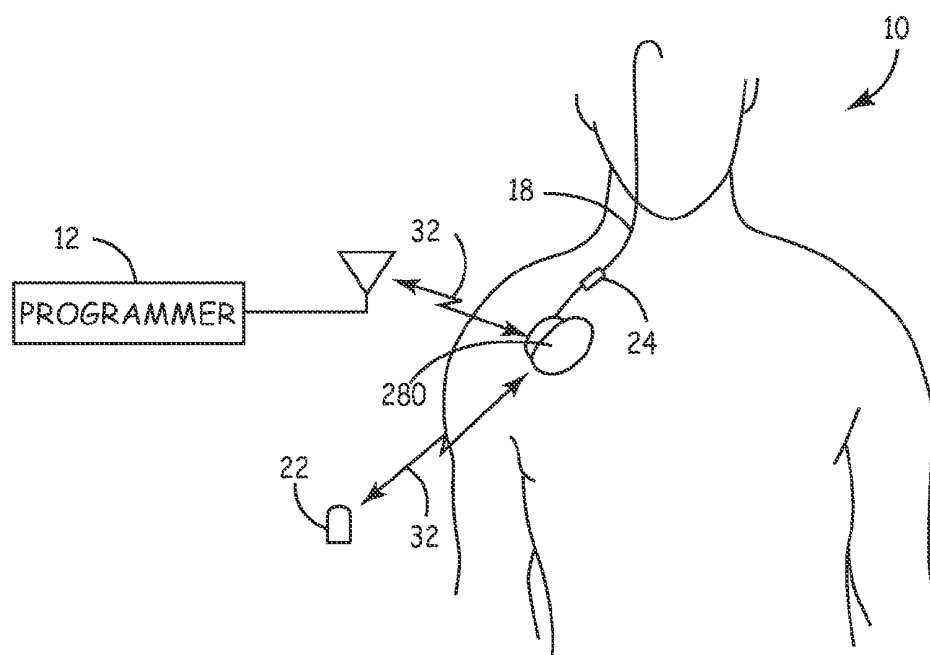


FIG. 9

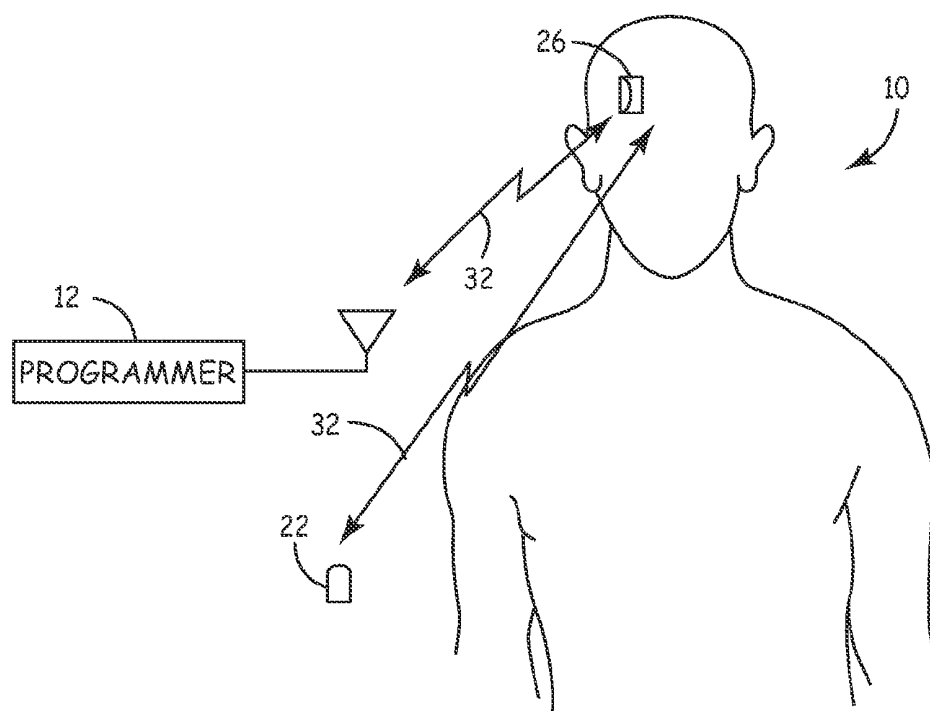


FIG. 10

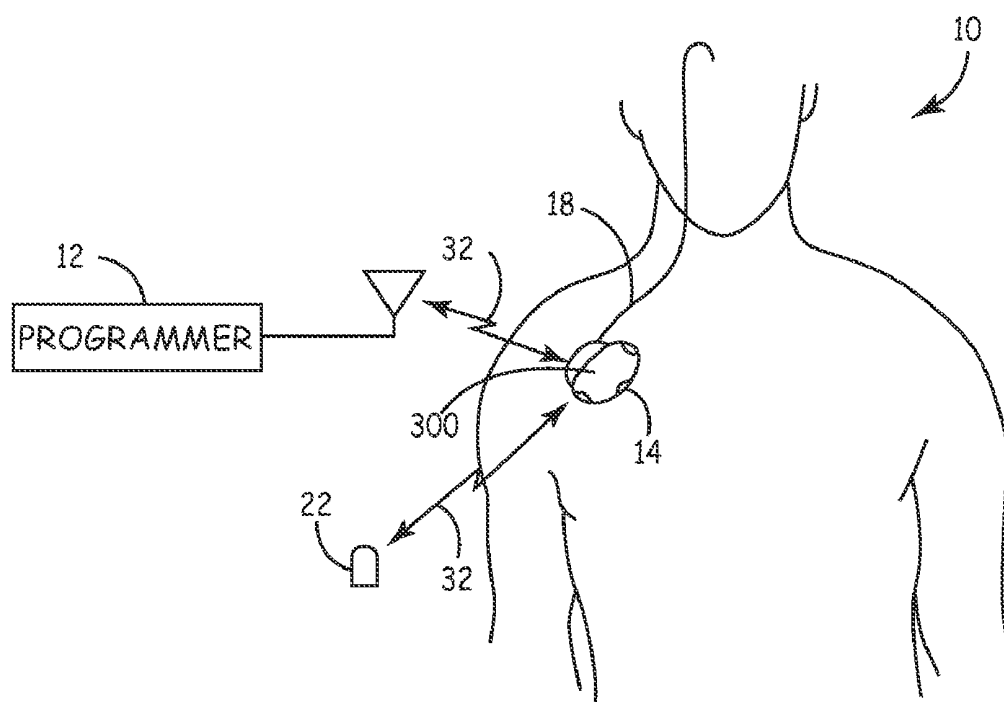


FIG. 11

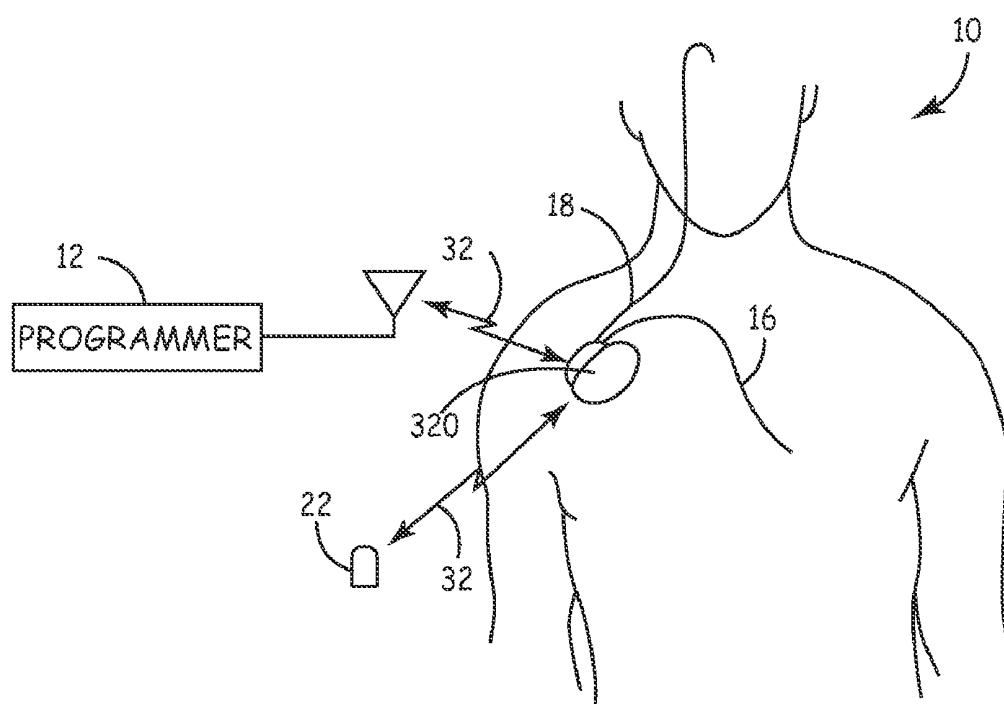


FIG. 12A

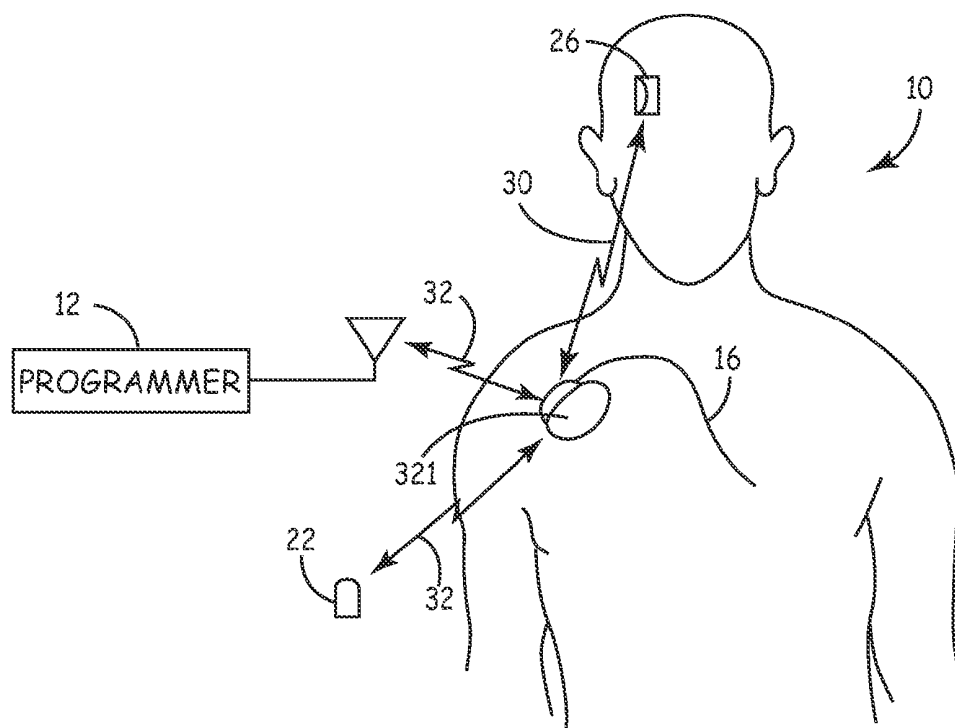


FIG. 12B

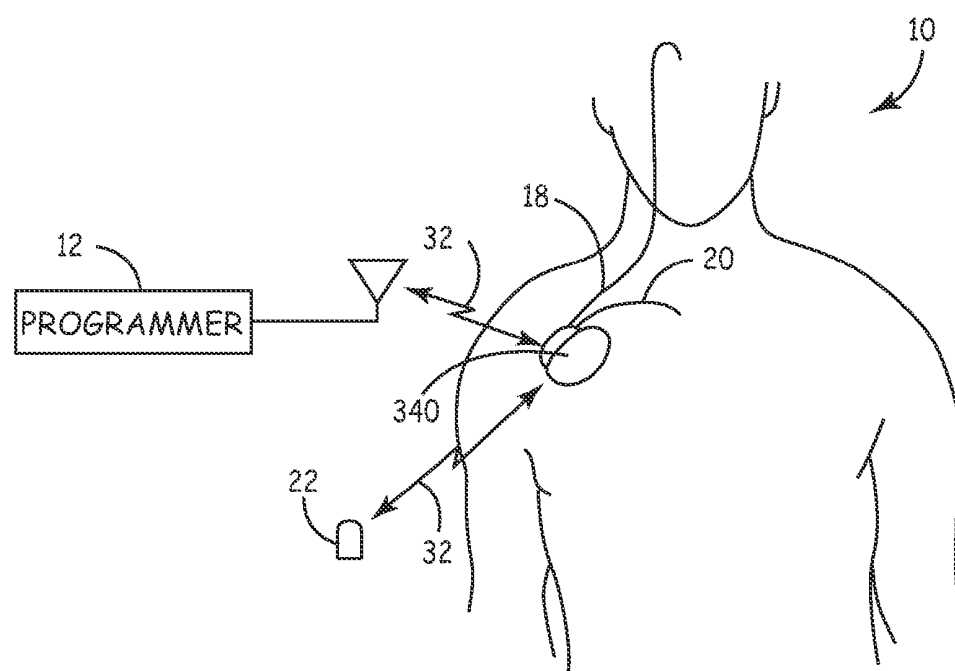


FIG. 13

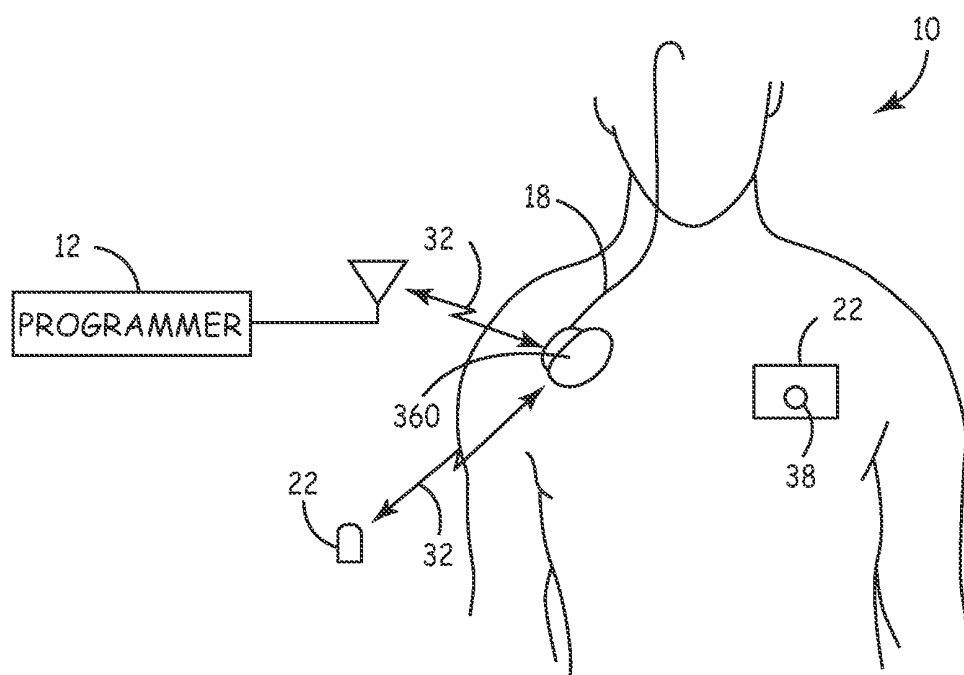


FIG. 14

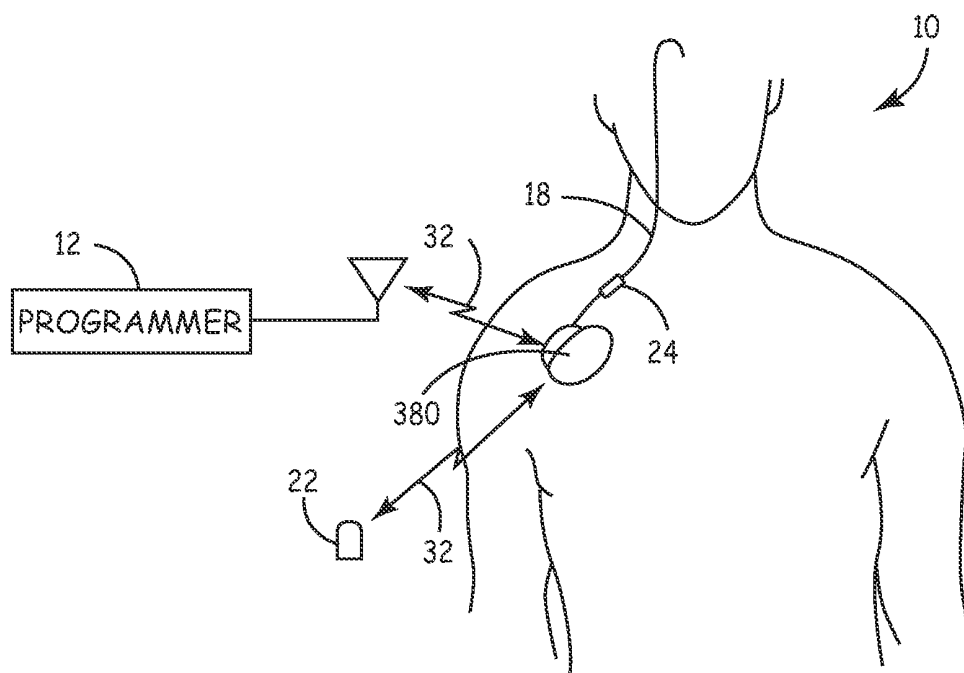


FIG. 15

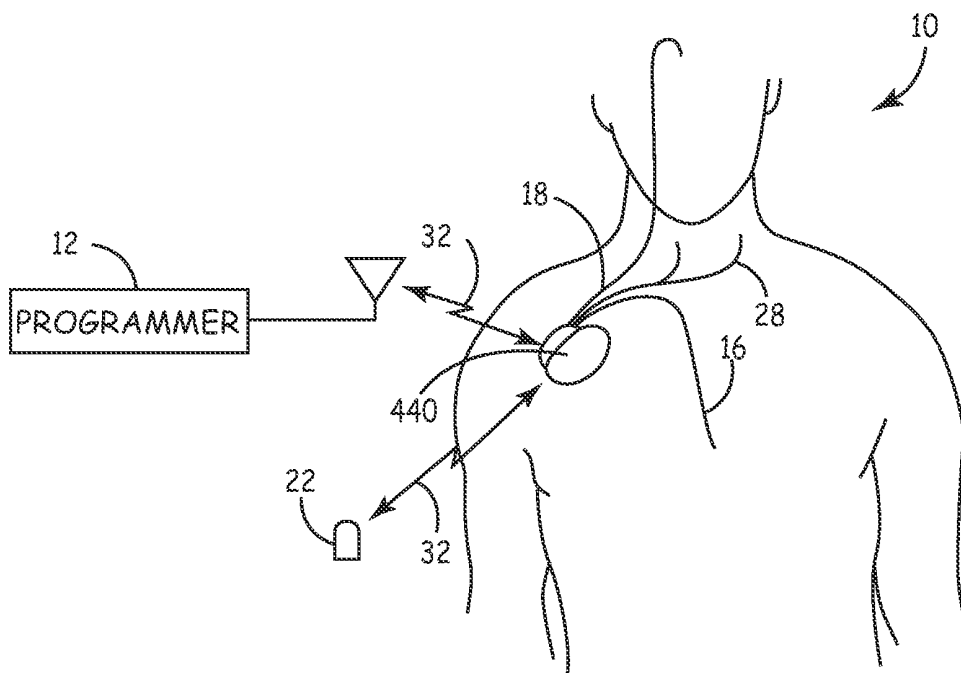


FIG. 16A

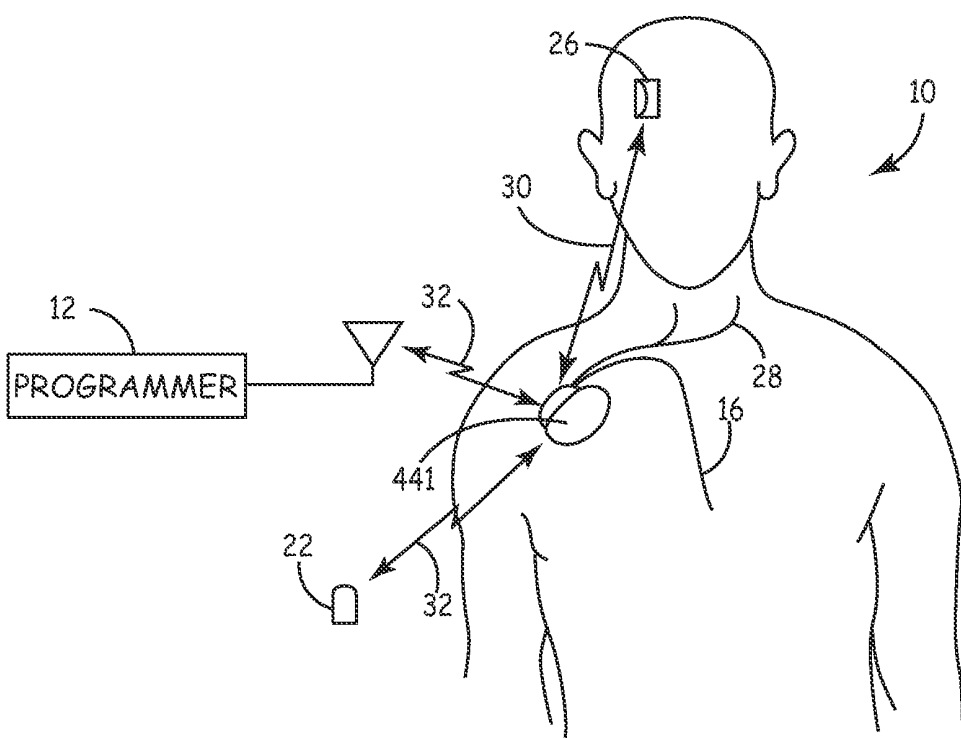


FIG. 16B

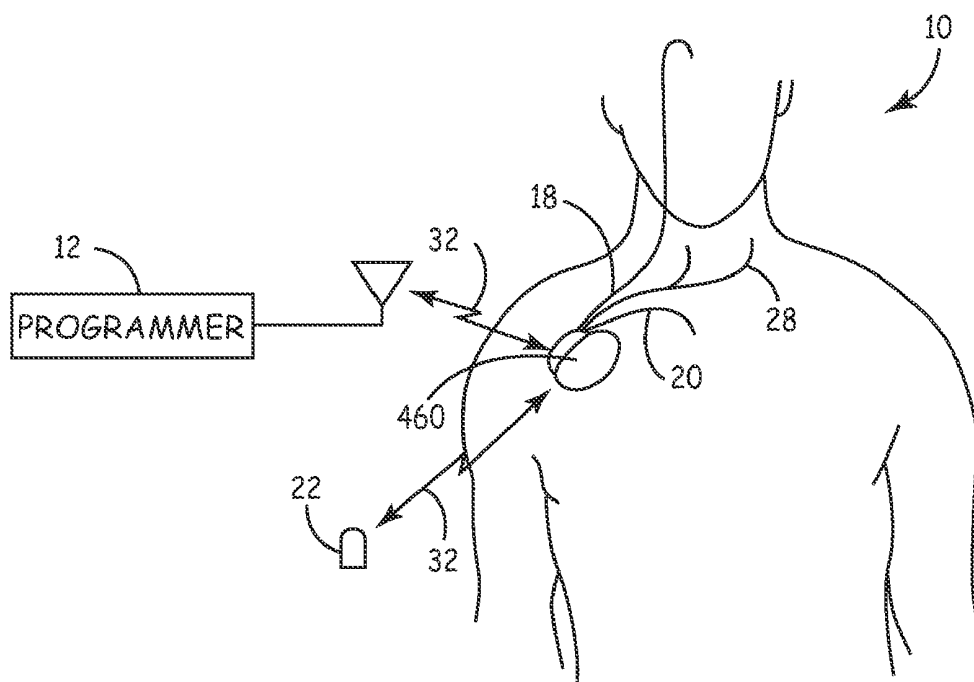


FIG. 17

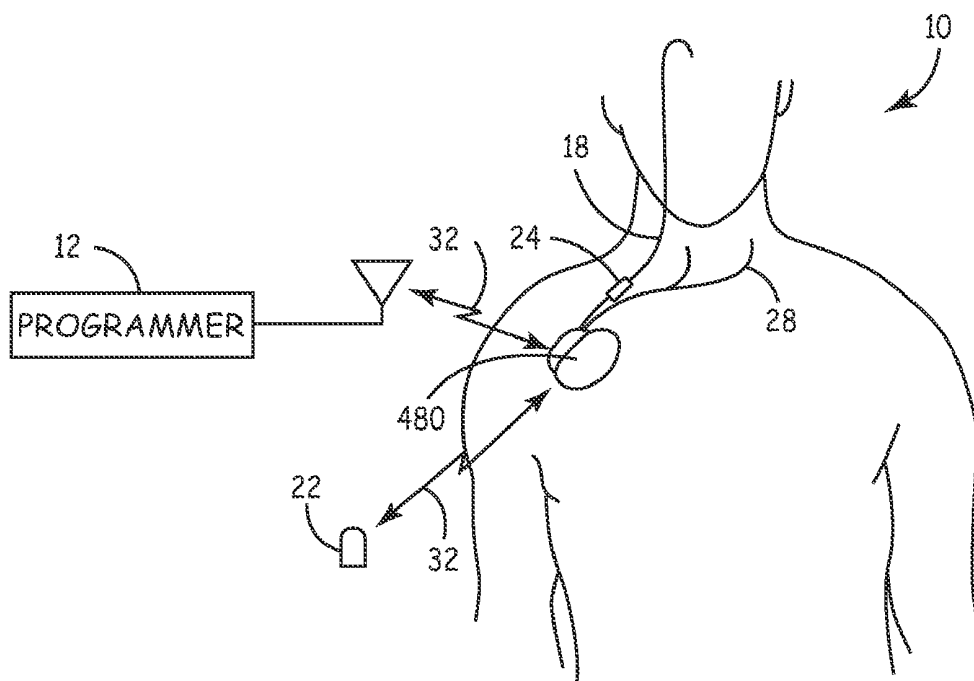


FIG. 18

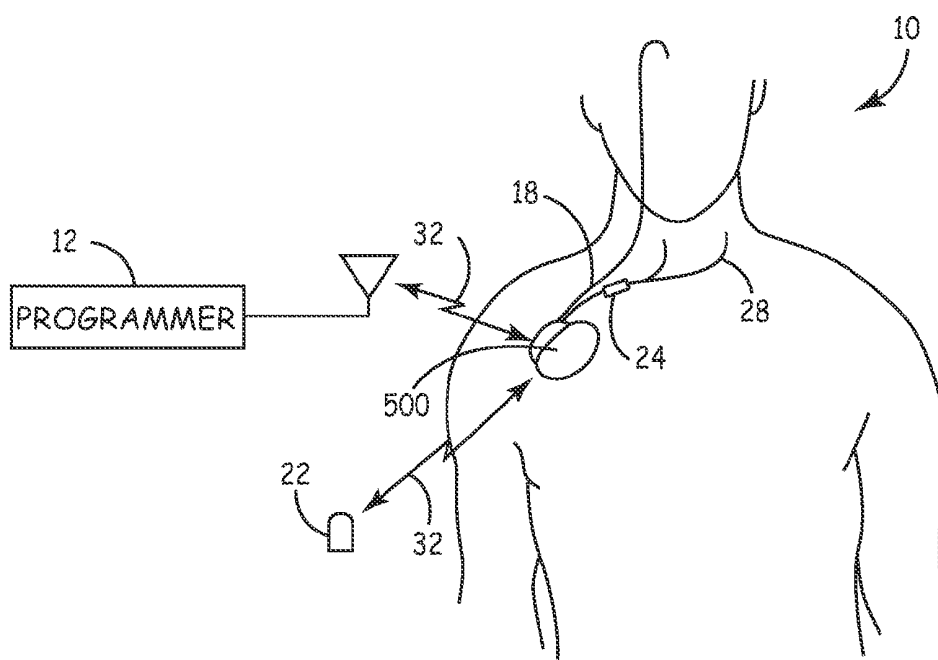


FIG. 19

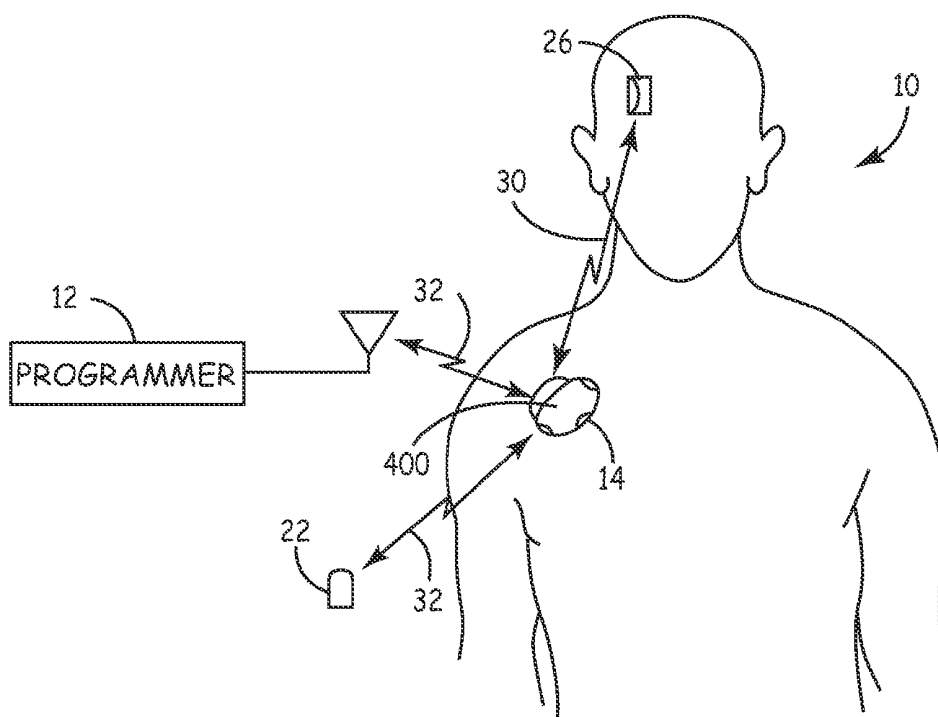


FIG. 20

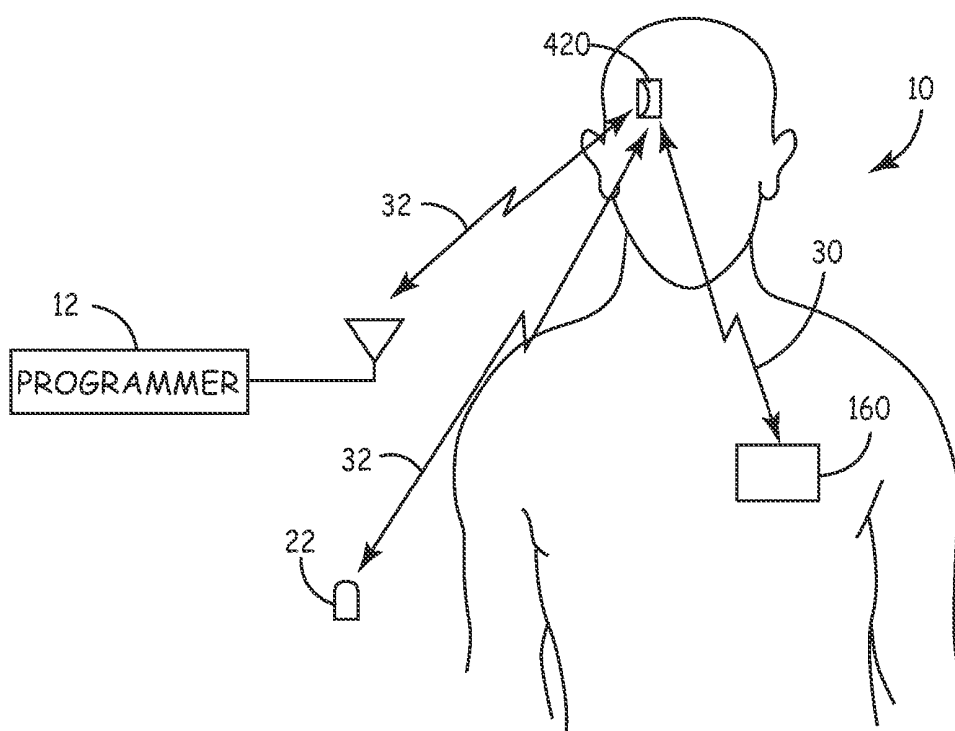


FIG. 21

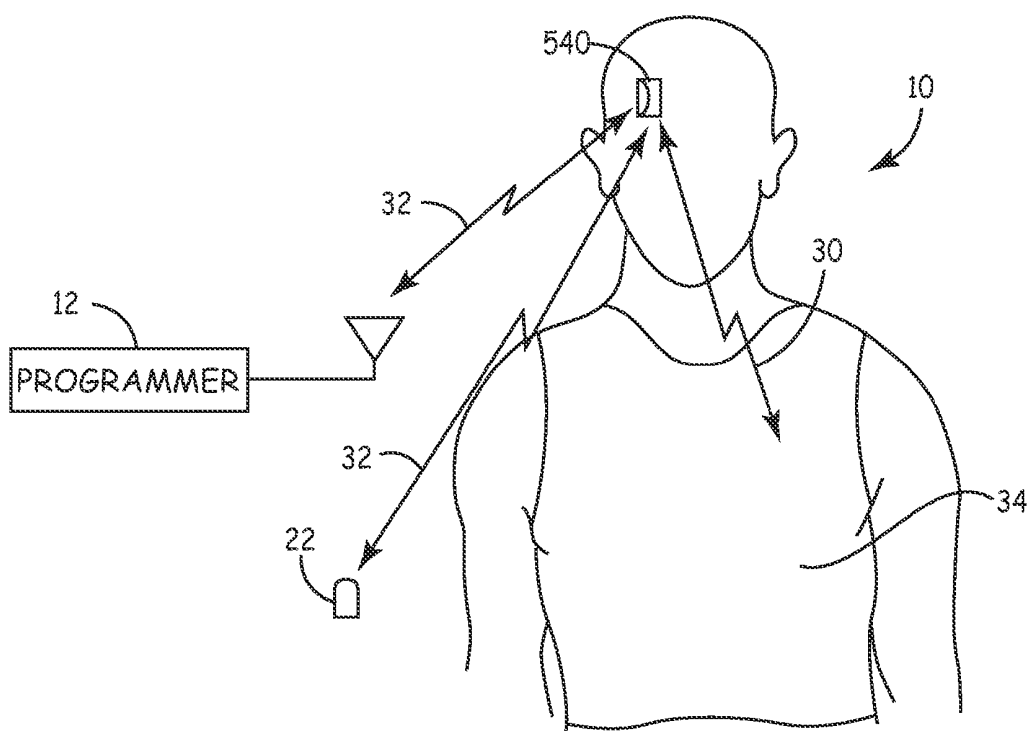


FIG. 22

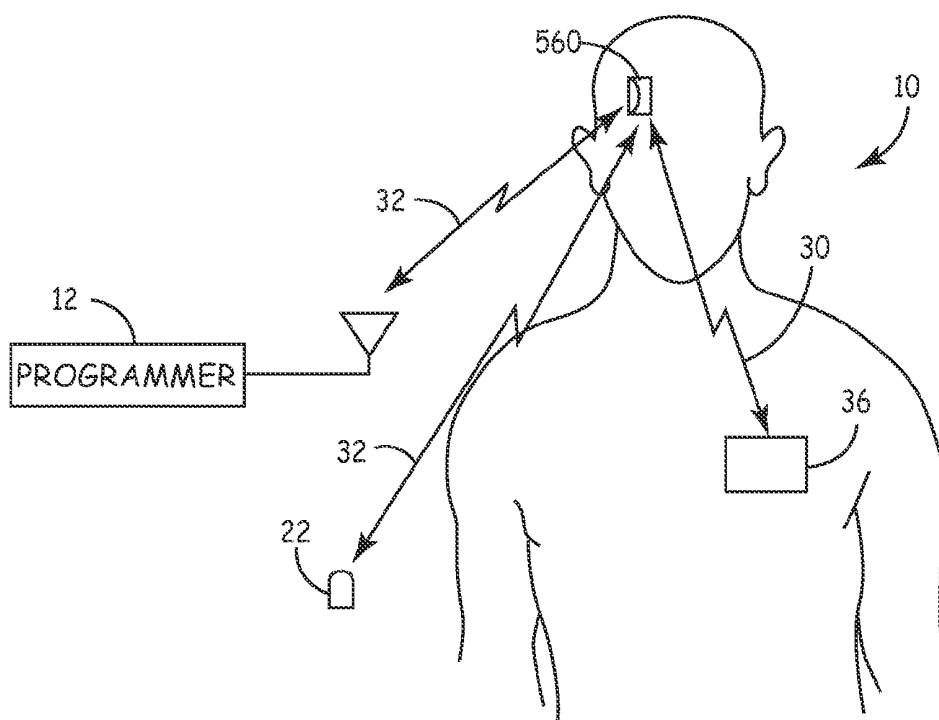


FIG. 23

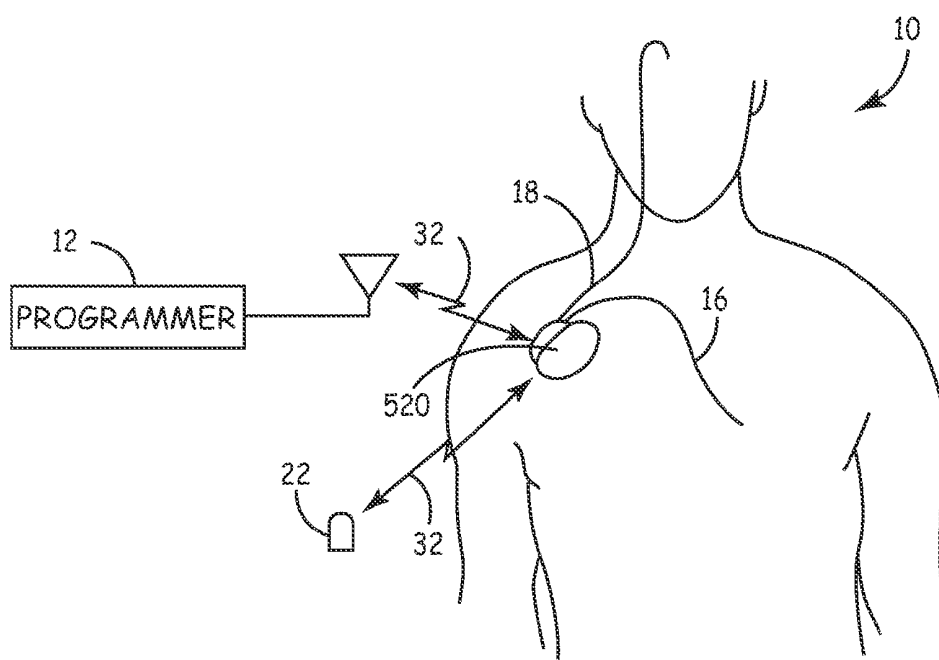


FIG. 24A

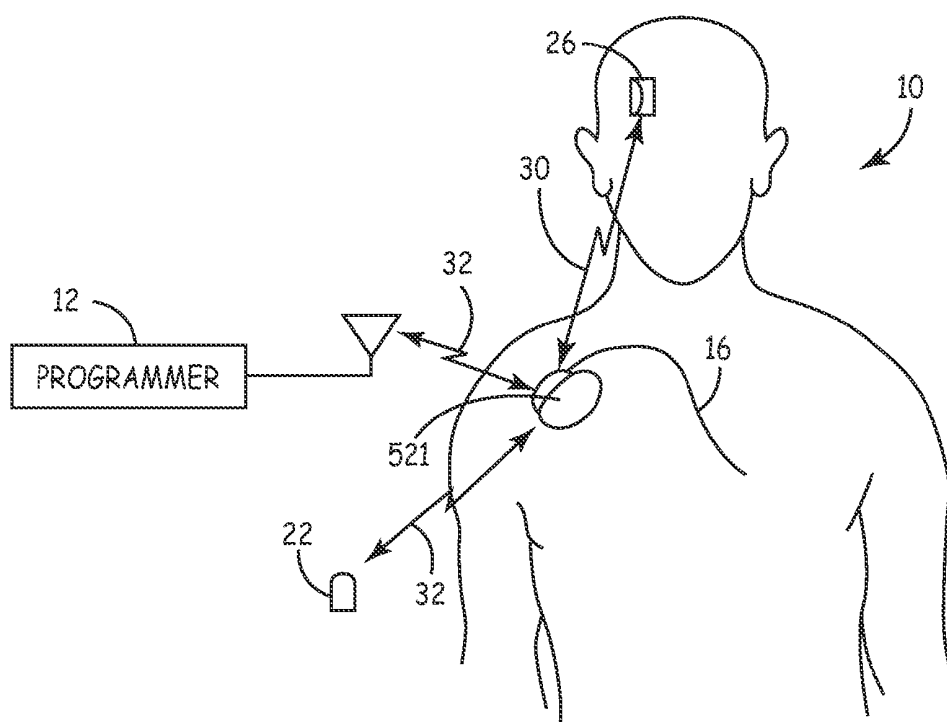


FIG. 24B

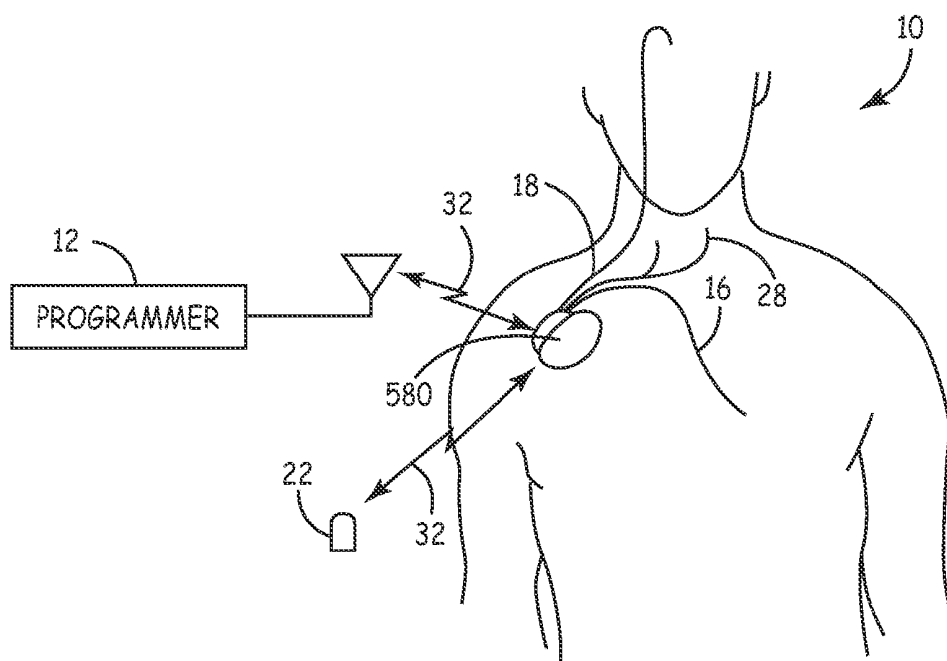


FIG. 25A

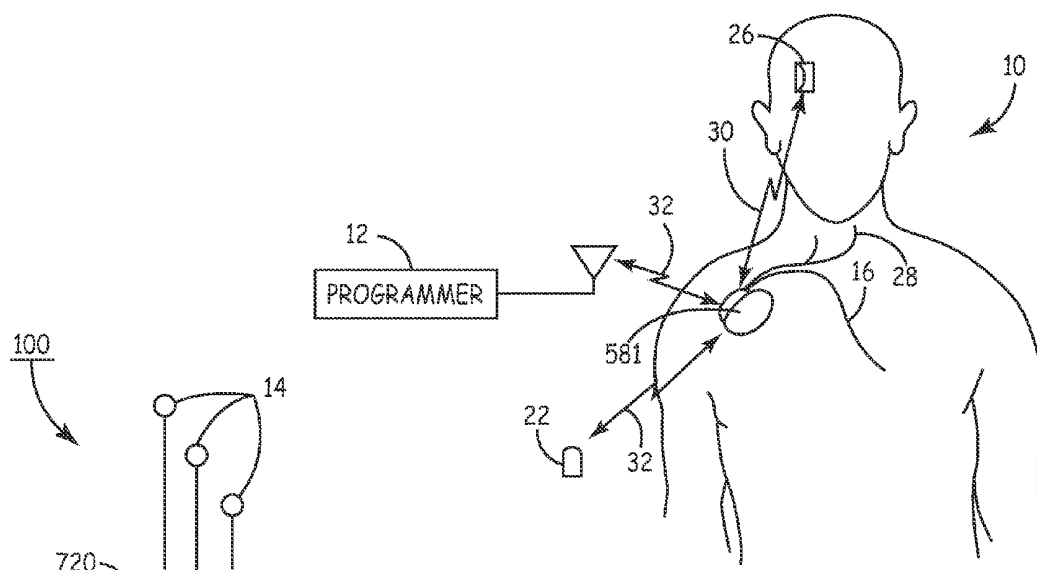


FIG. 25B

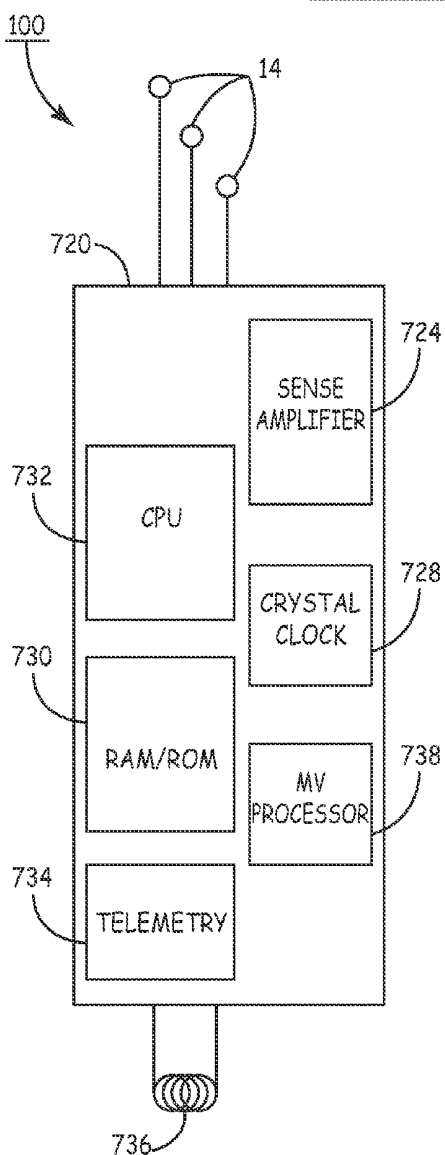


FIG. 26

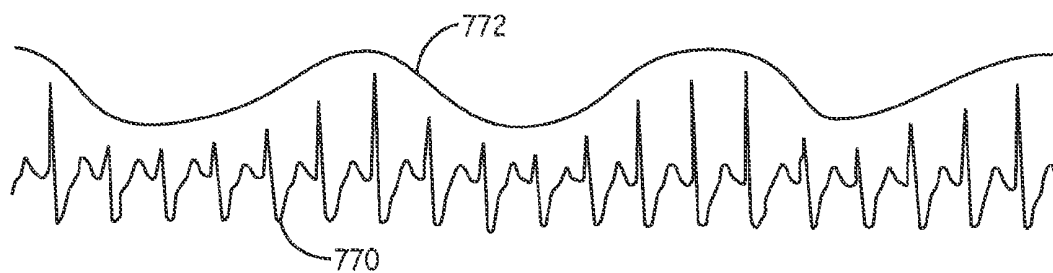


FIG. 27

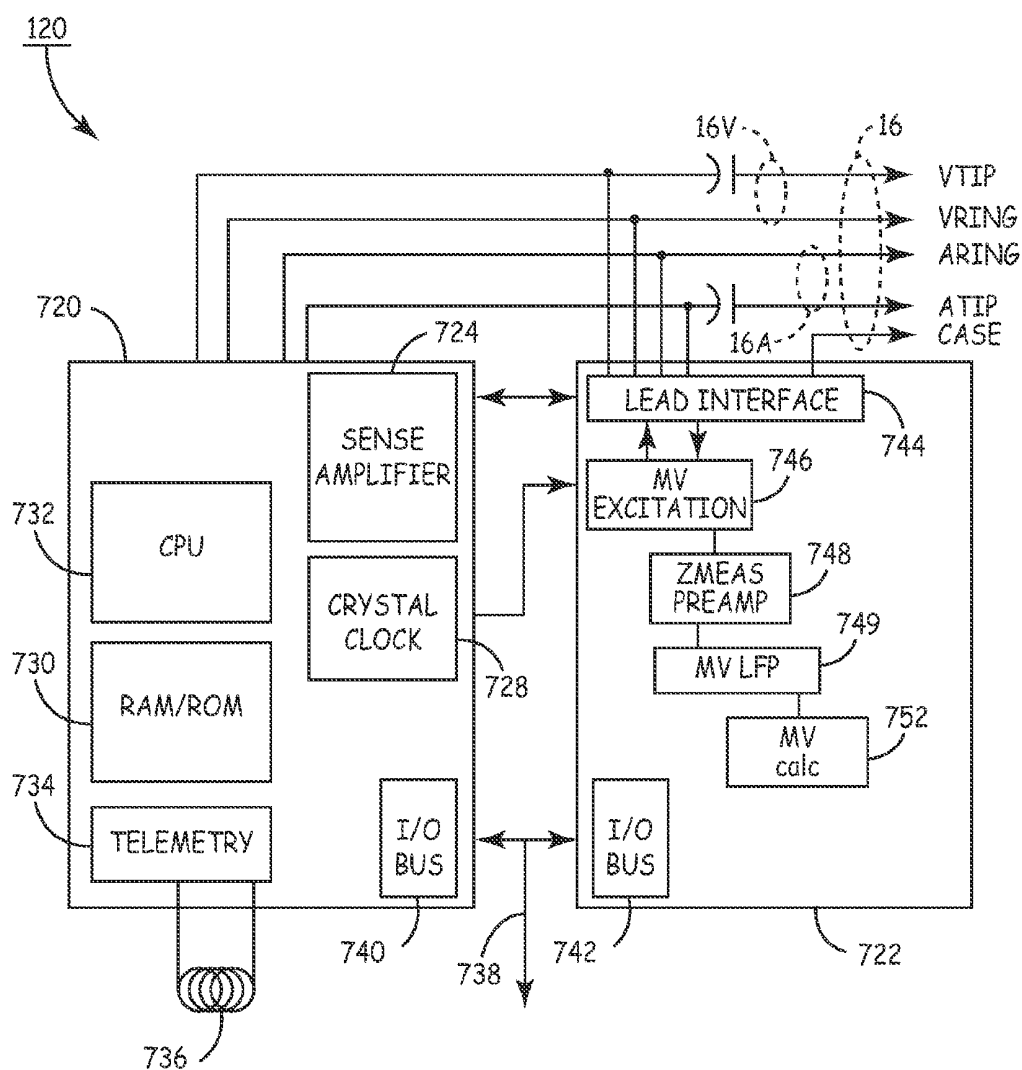


FIG. 28

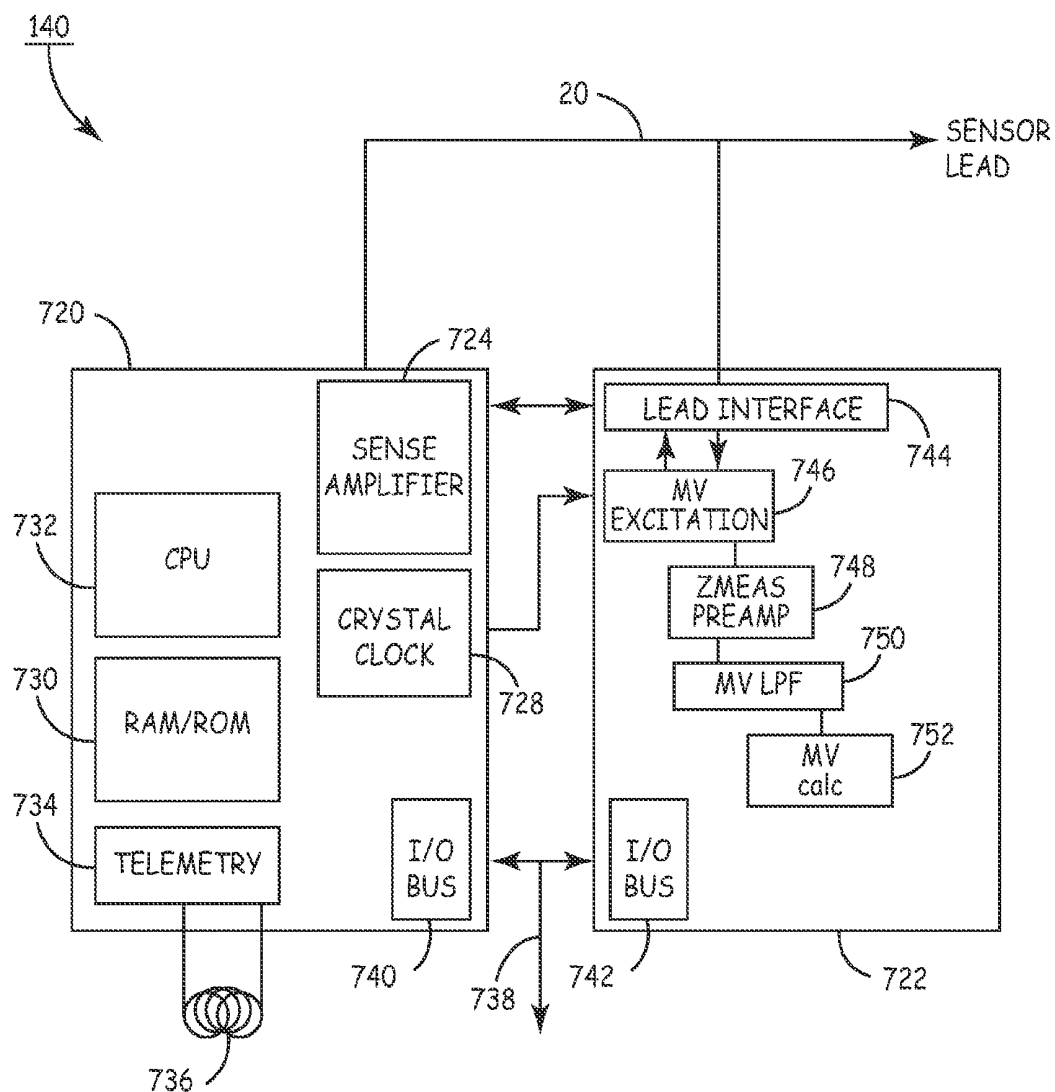


FIG. 29

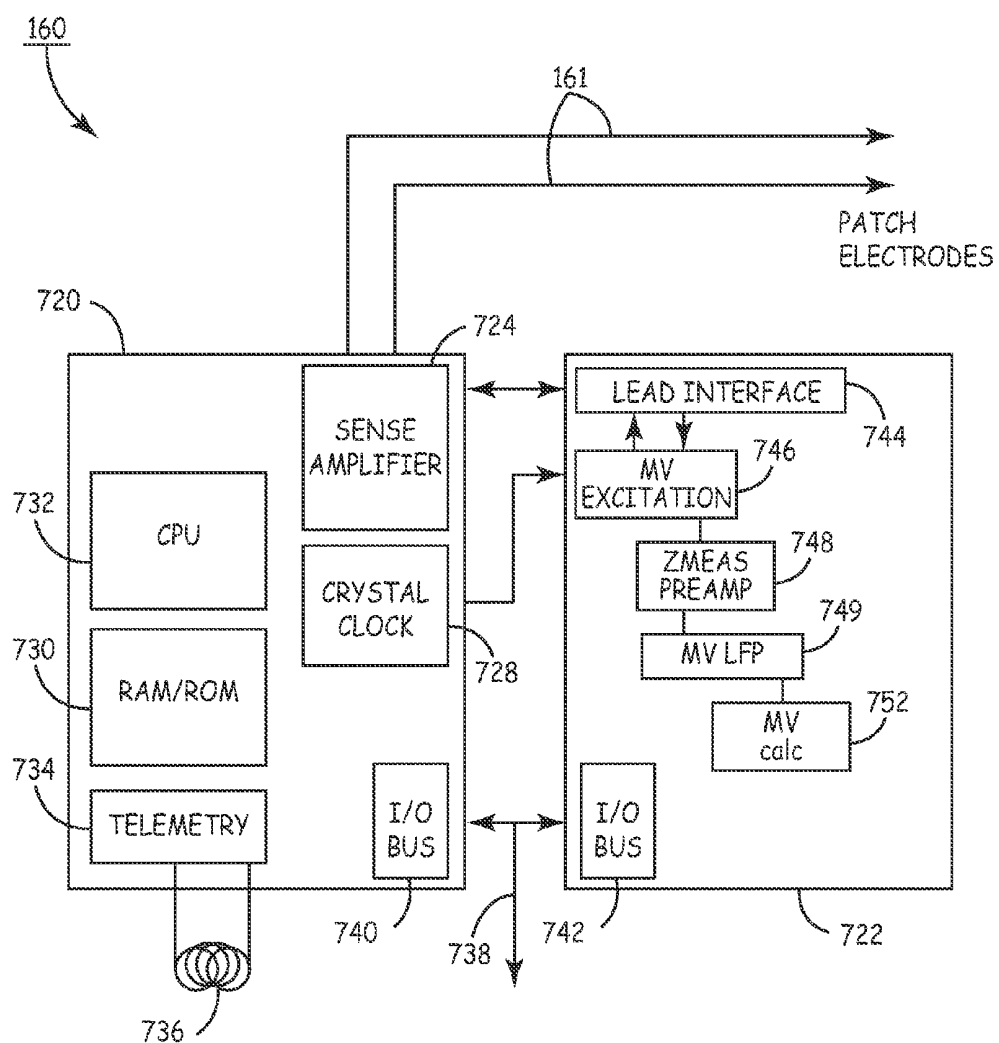


FIG. 30

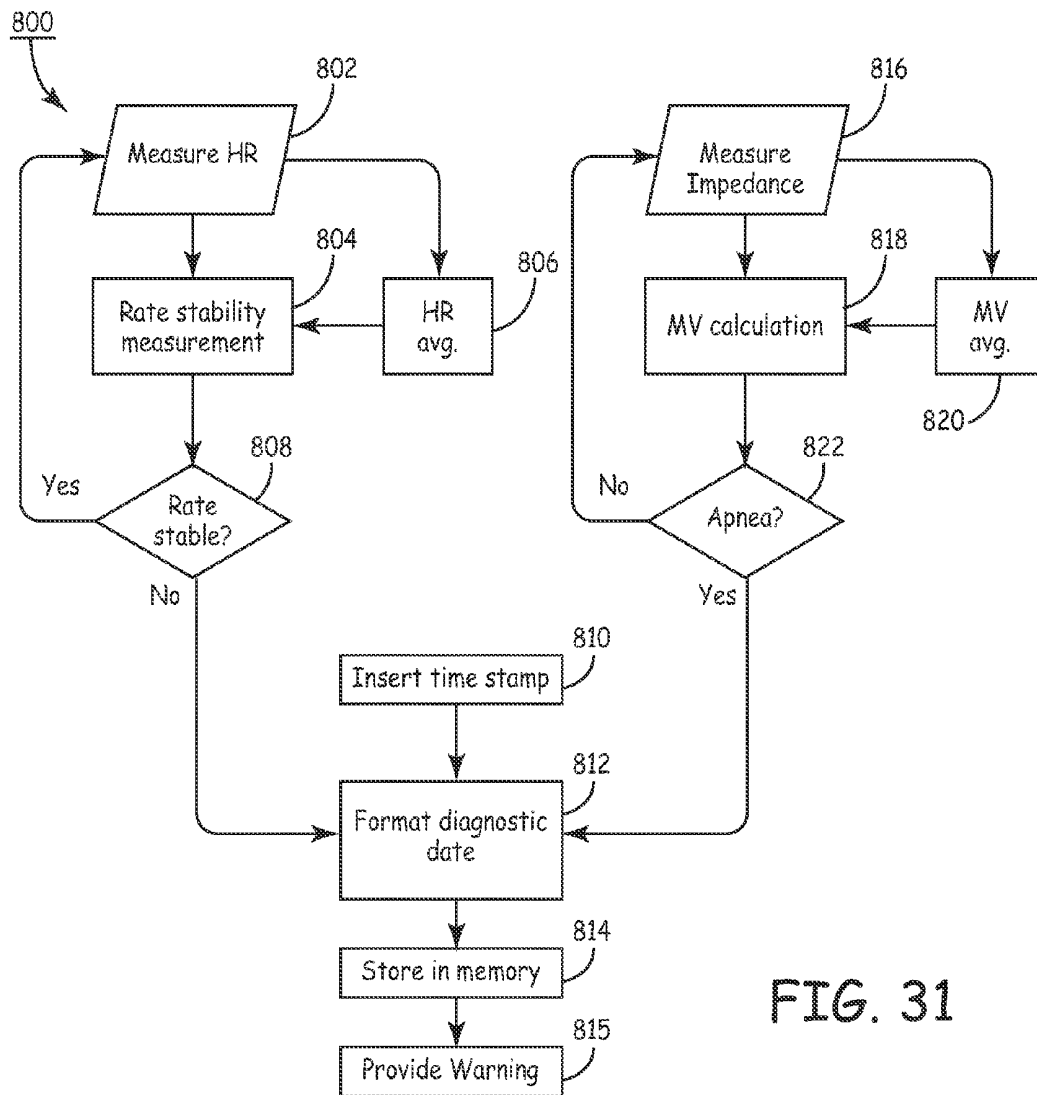


FIG. 31

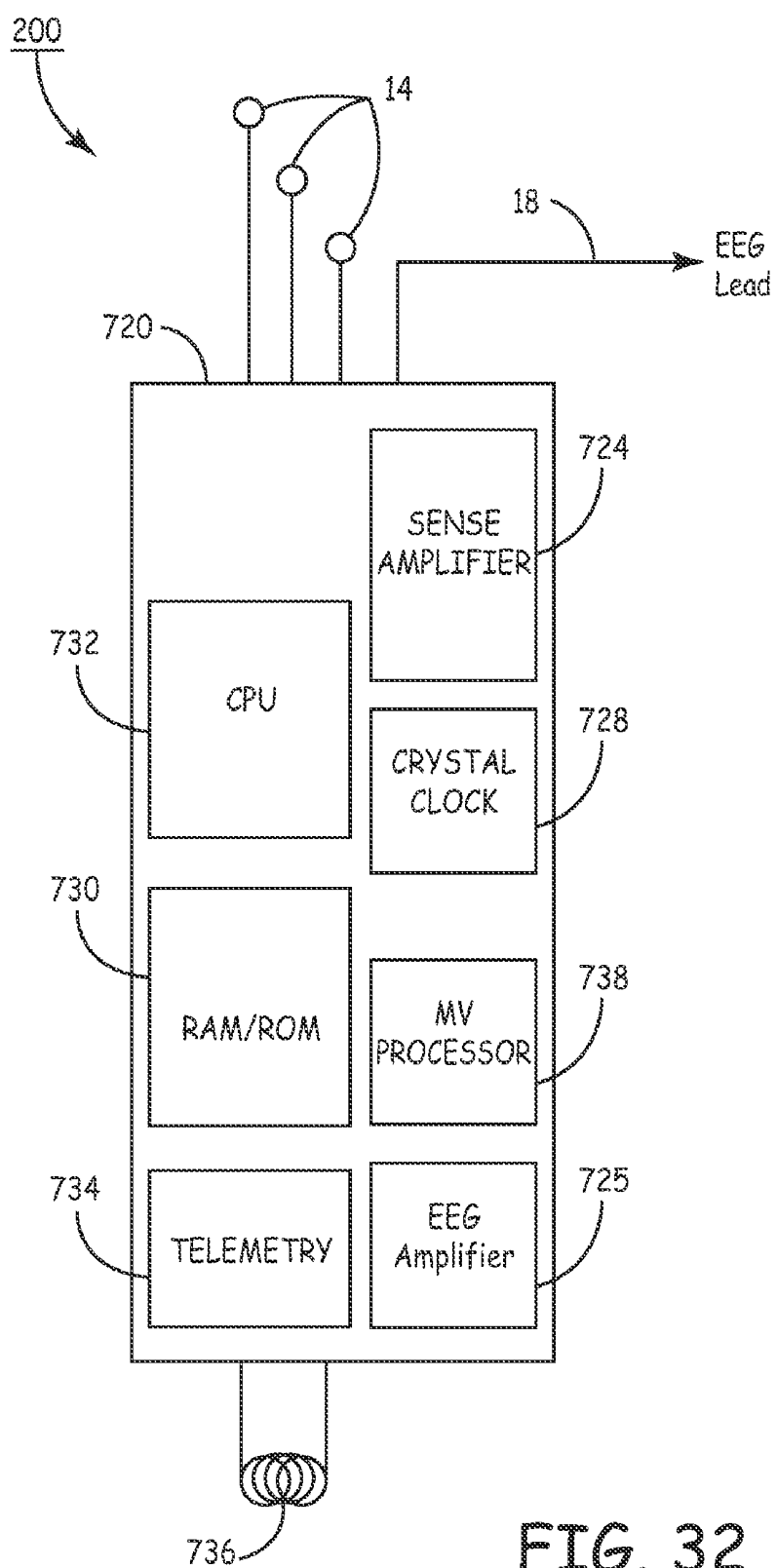


FIG. 32

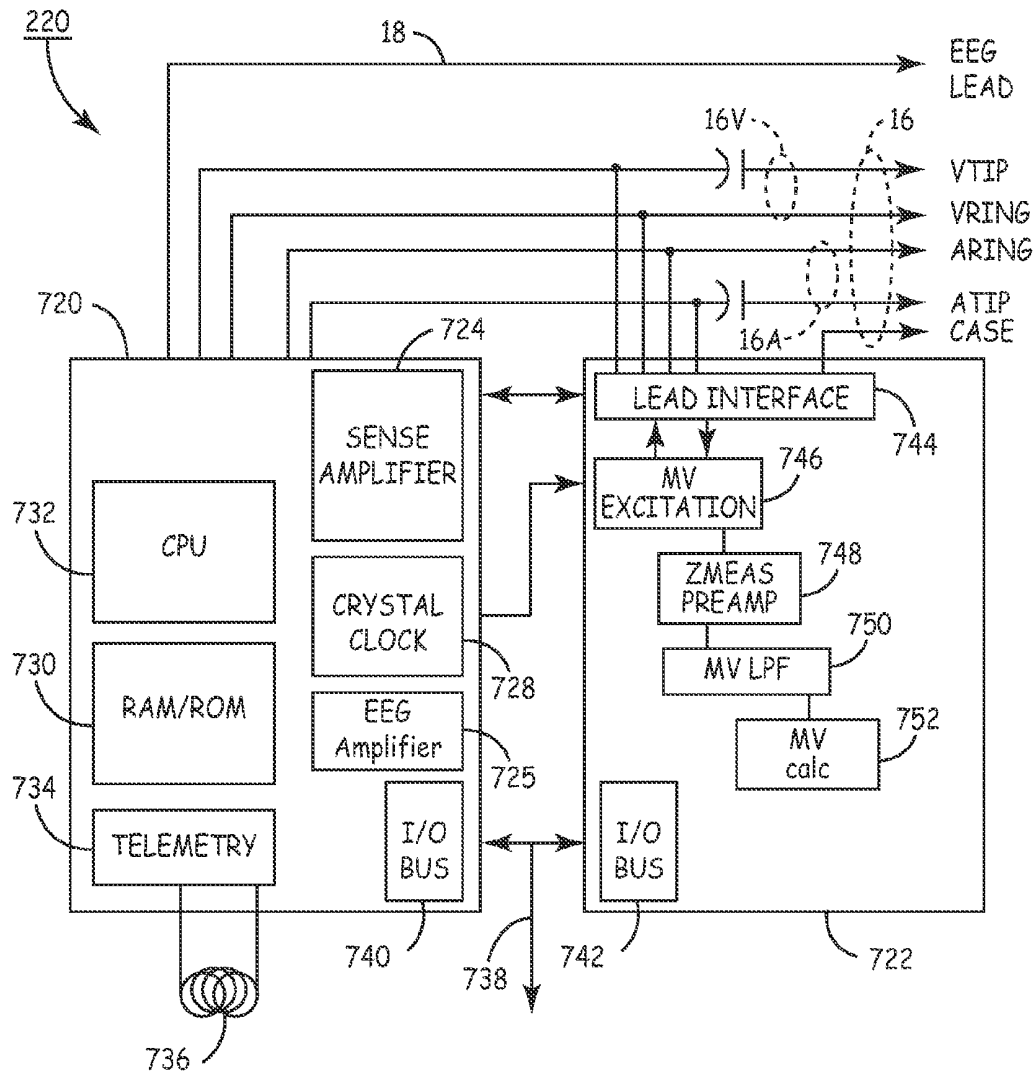


FIG. 33

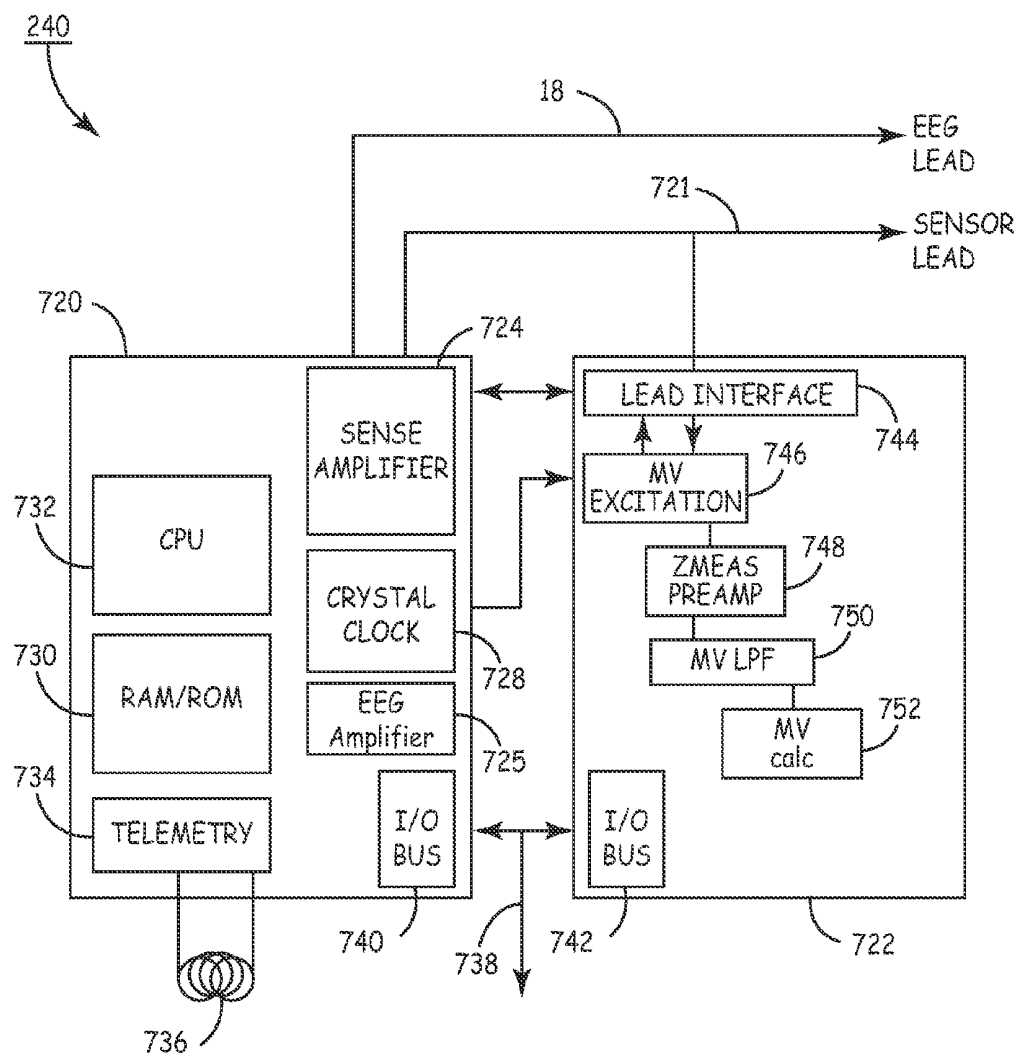


FIG. 34

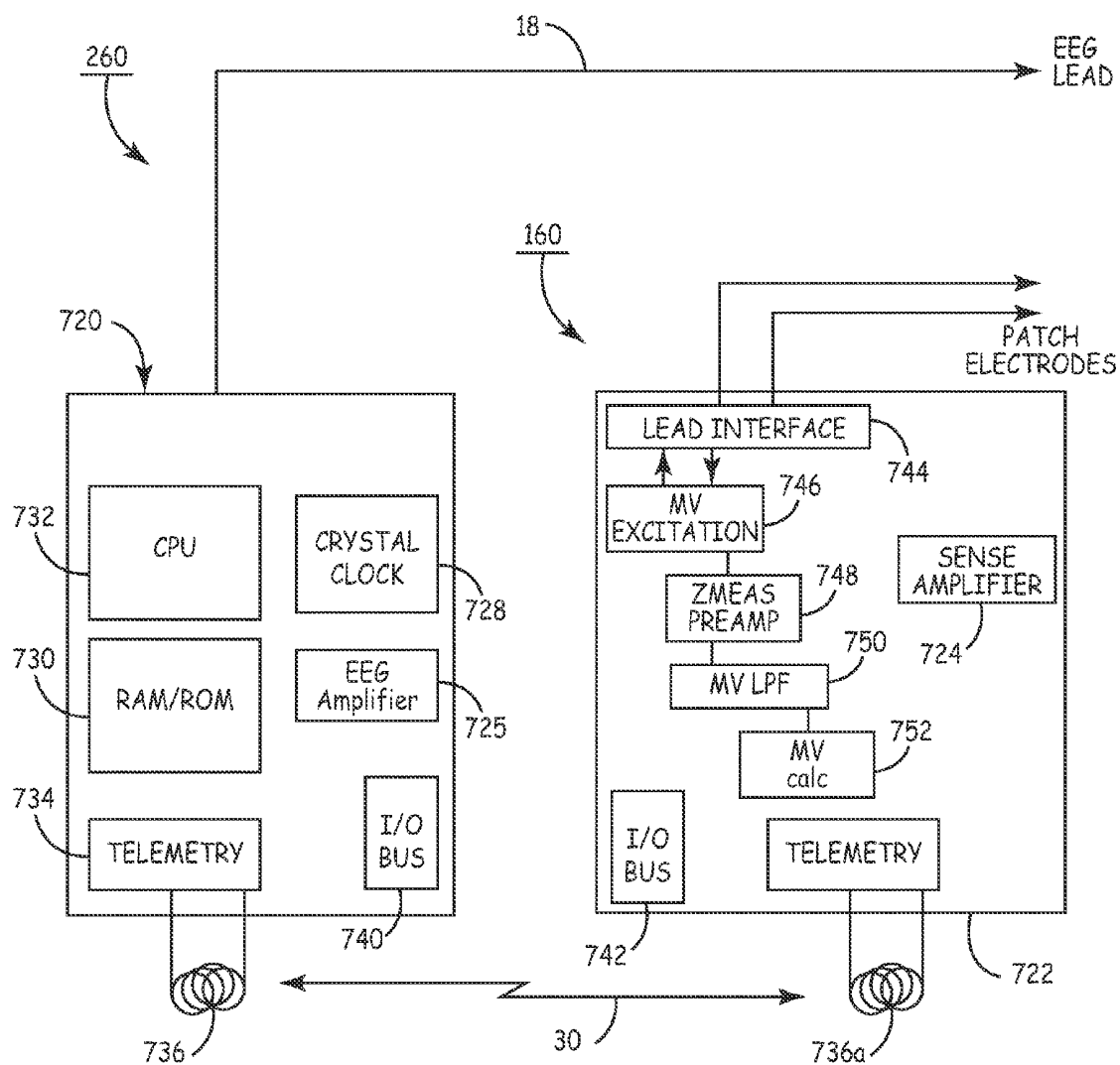


FIG. 35

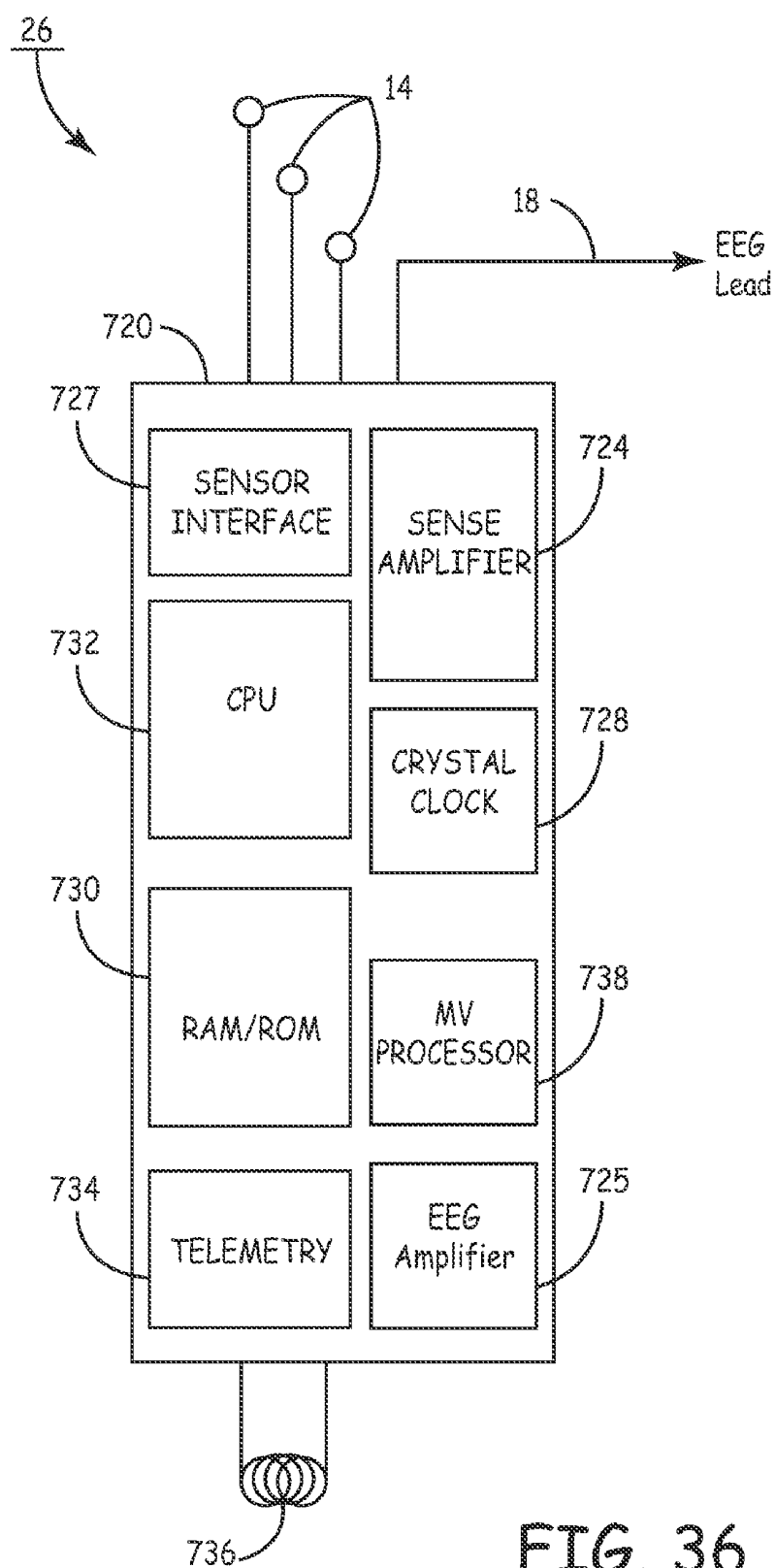


FIG. 36

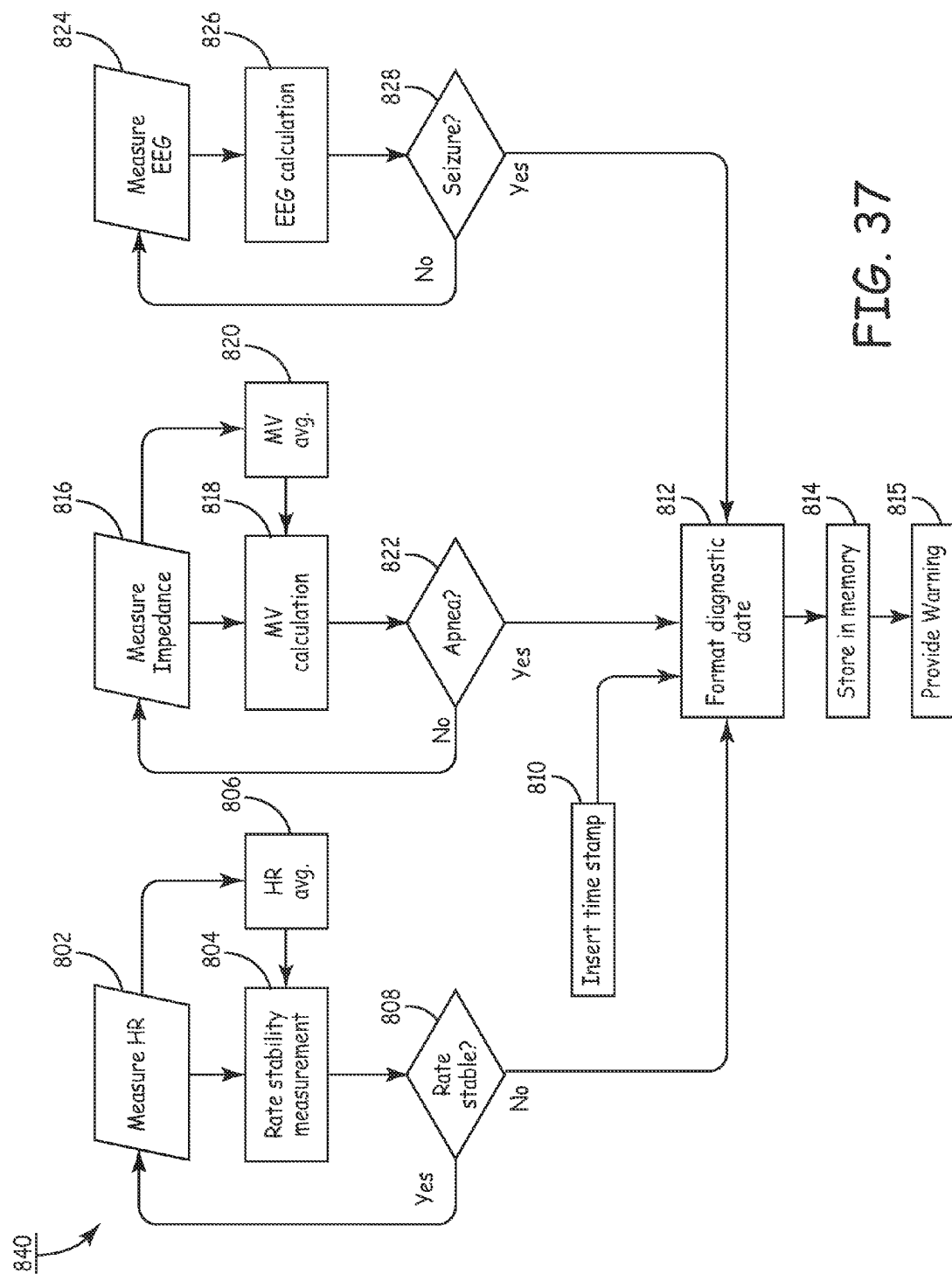


FIG. 37

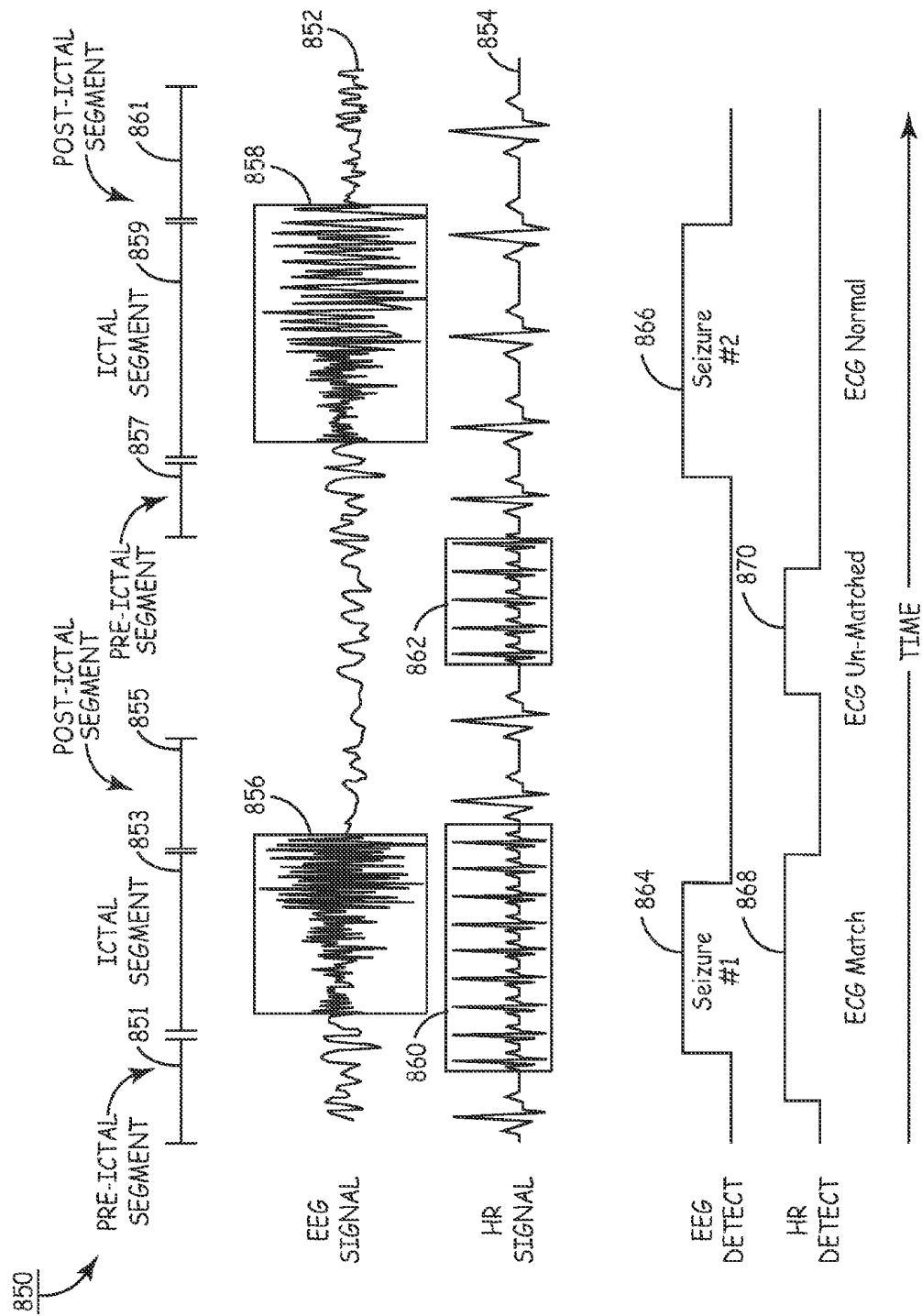


FIG. 38

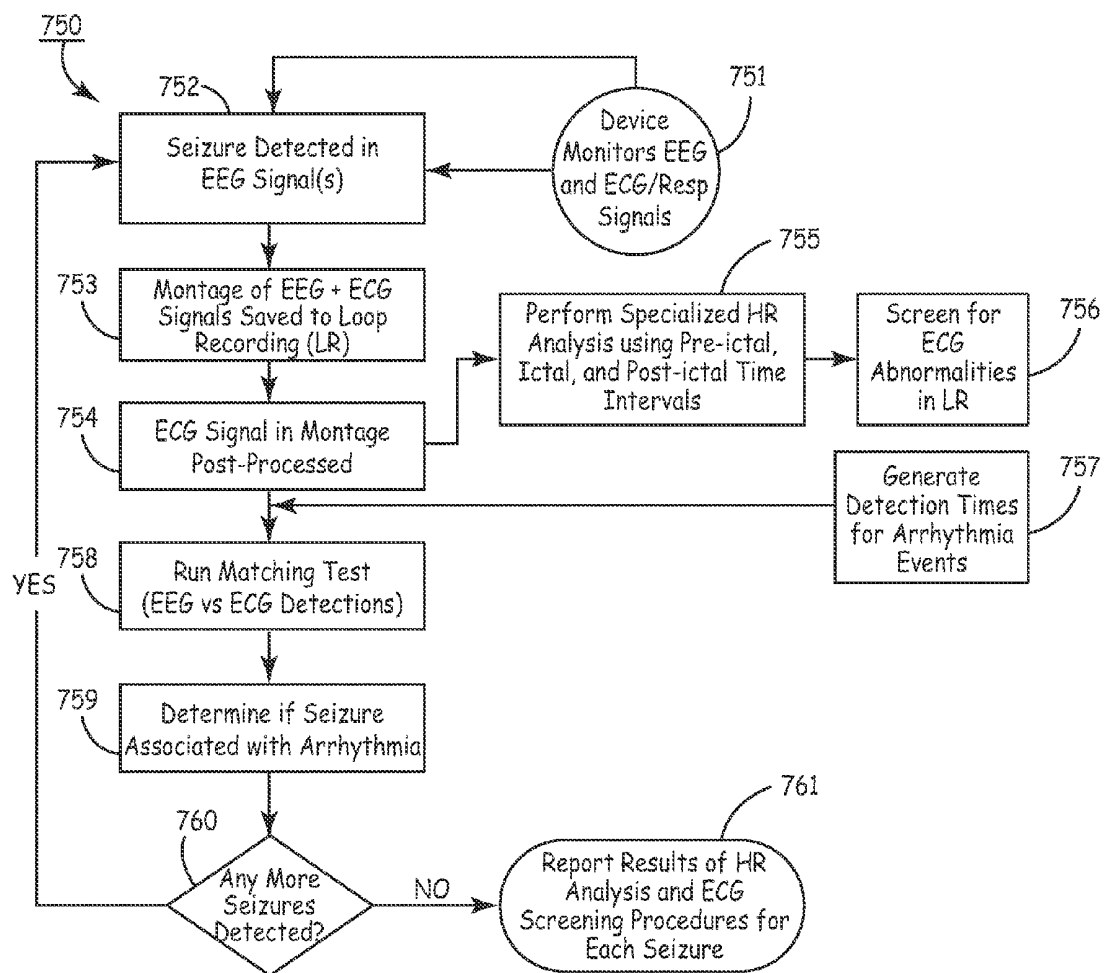
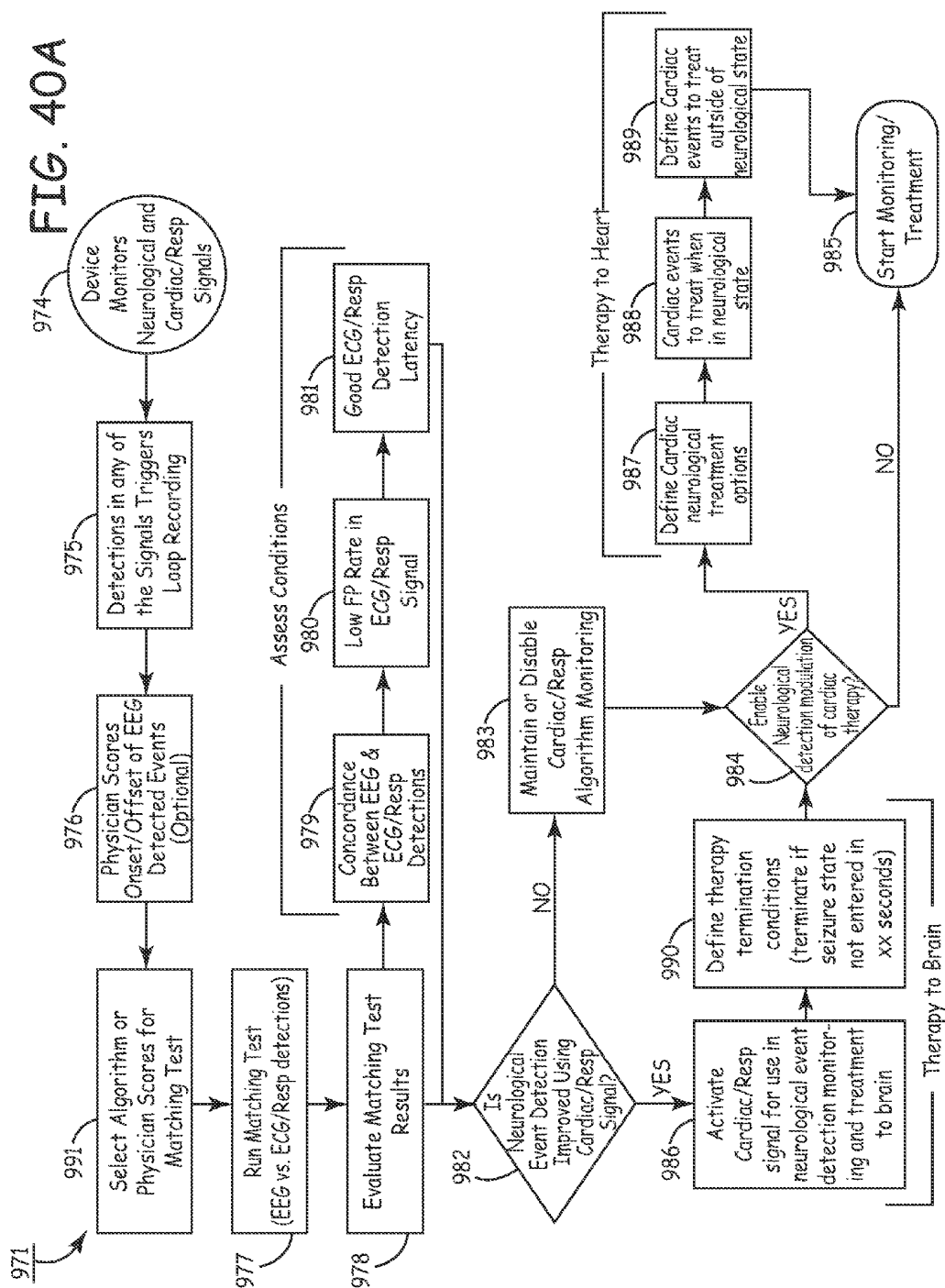
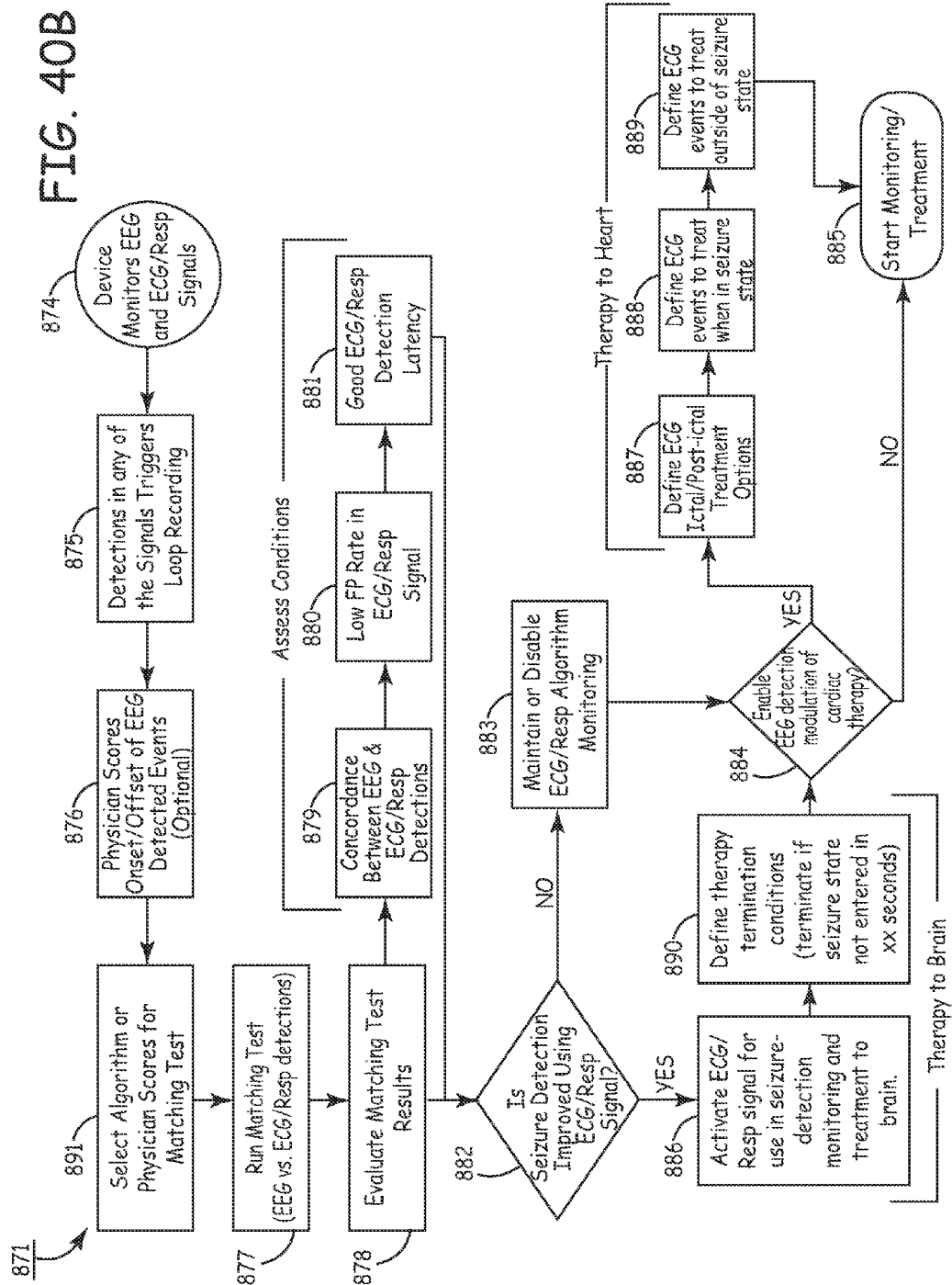


FIG. 39





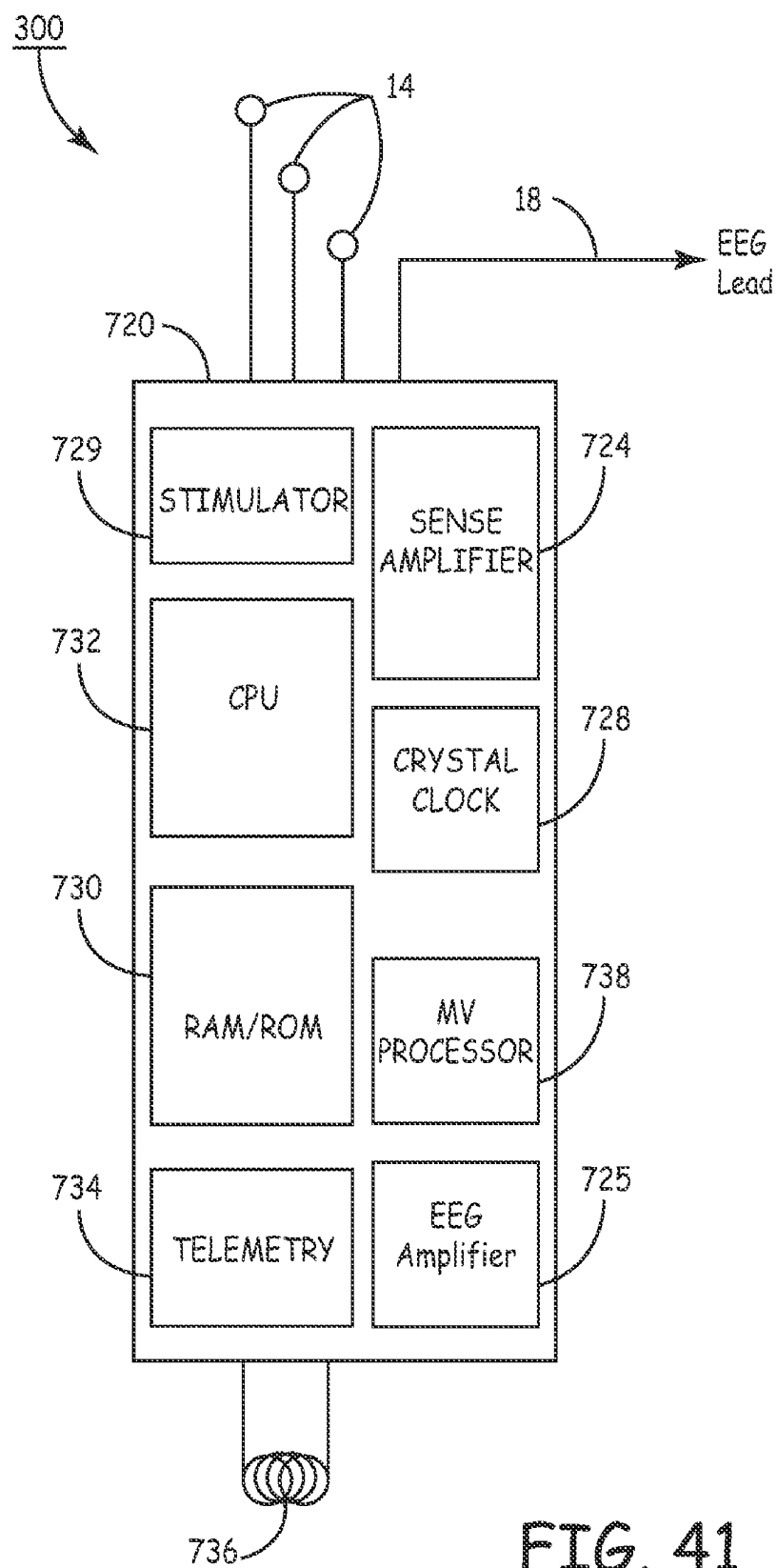


FIG. 41

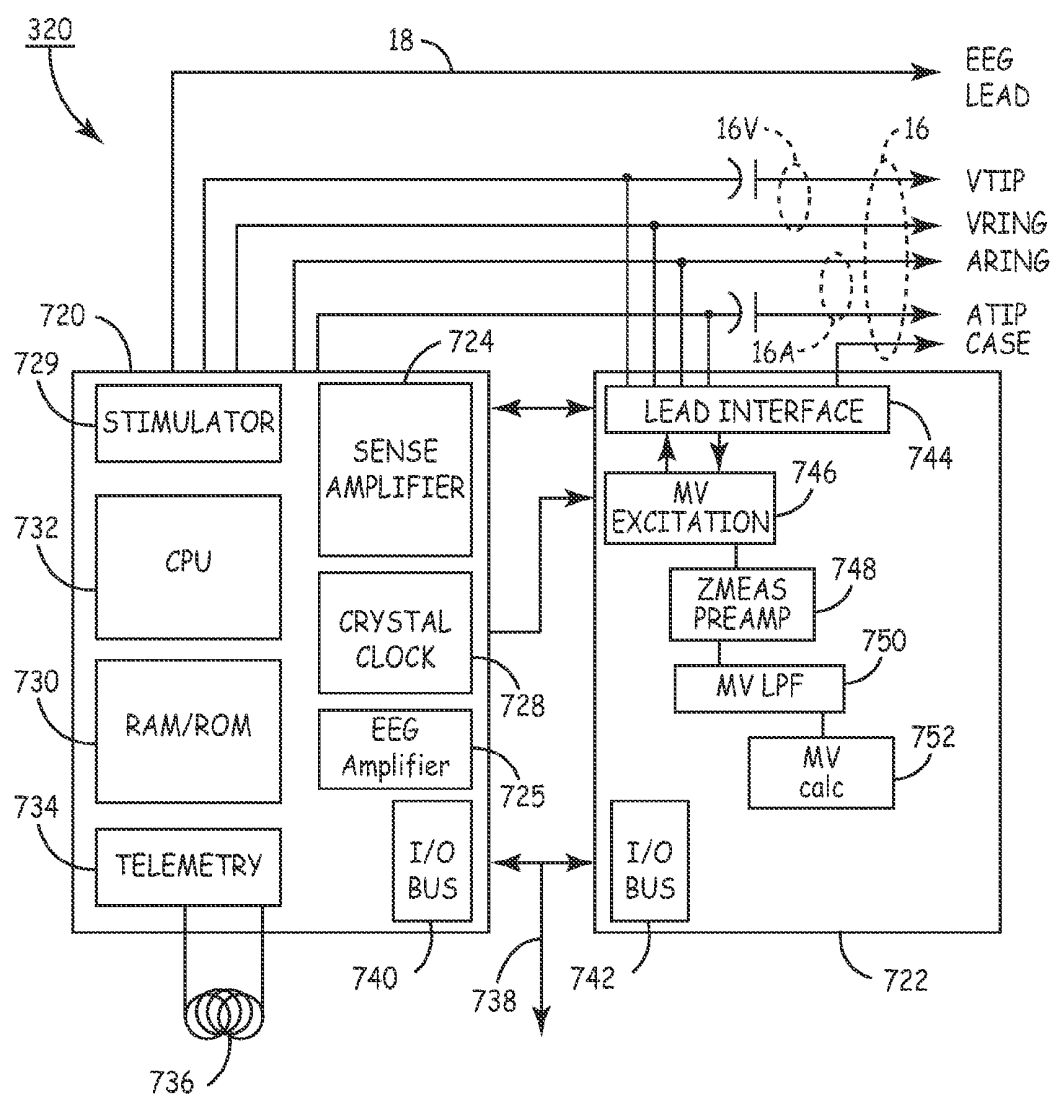


FIG. 42

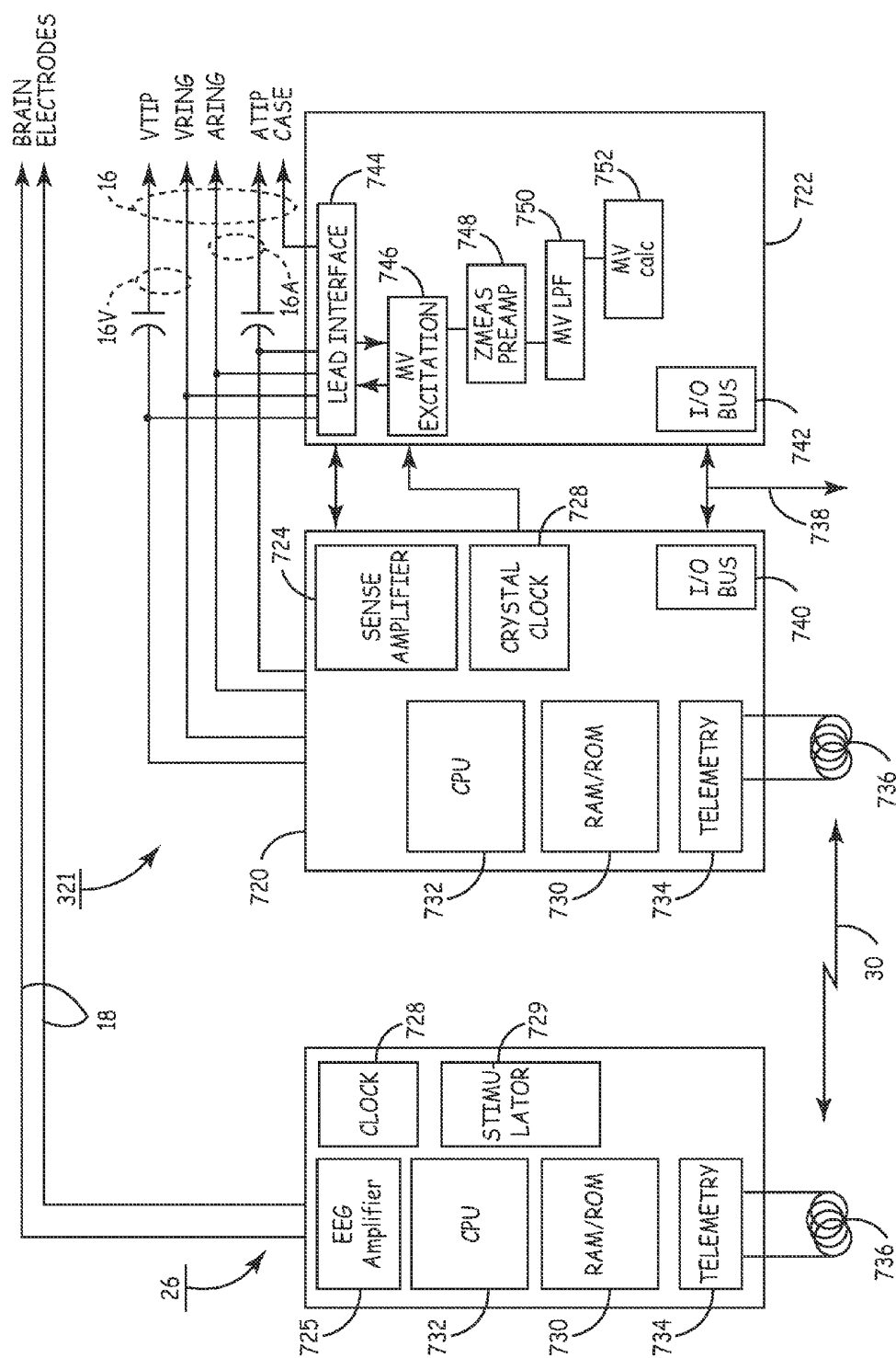


FIG. 43

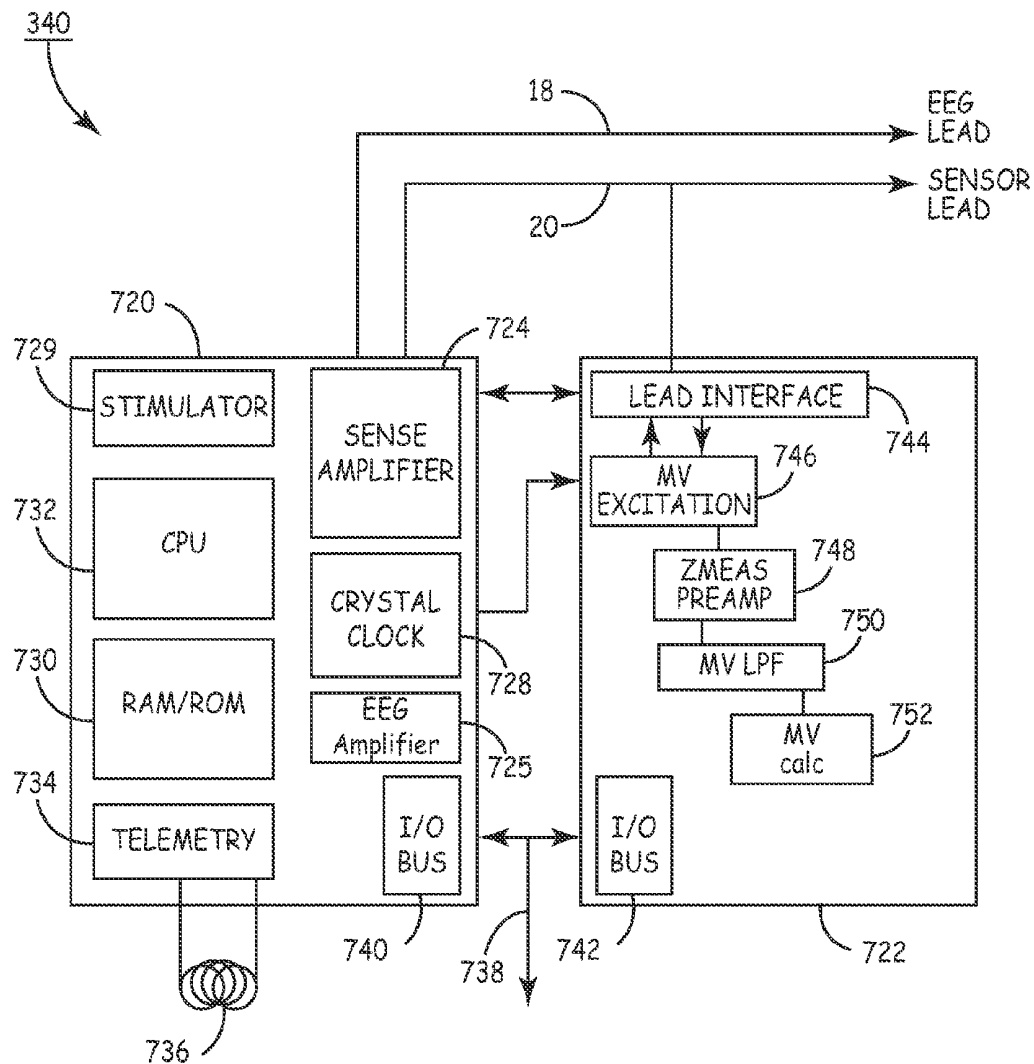


FIG. 44

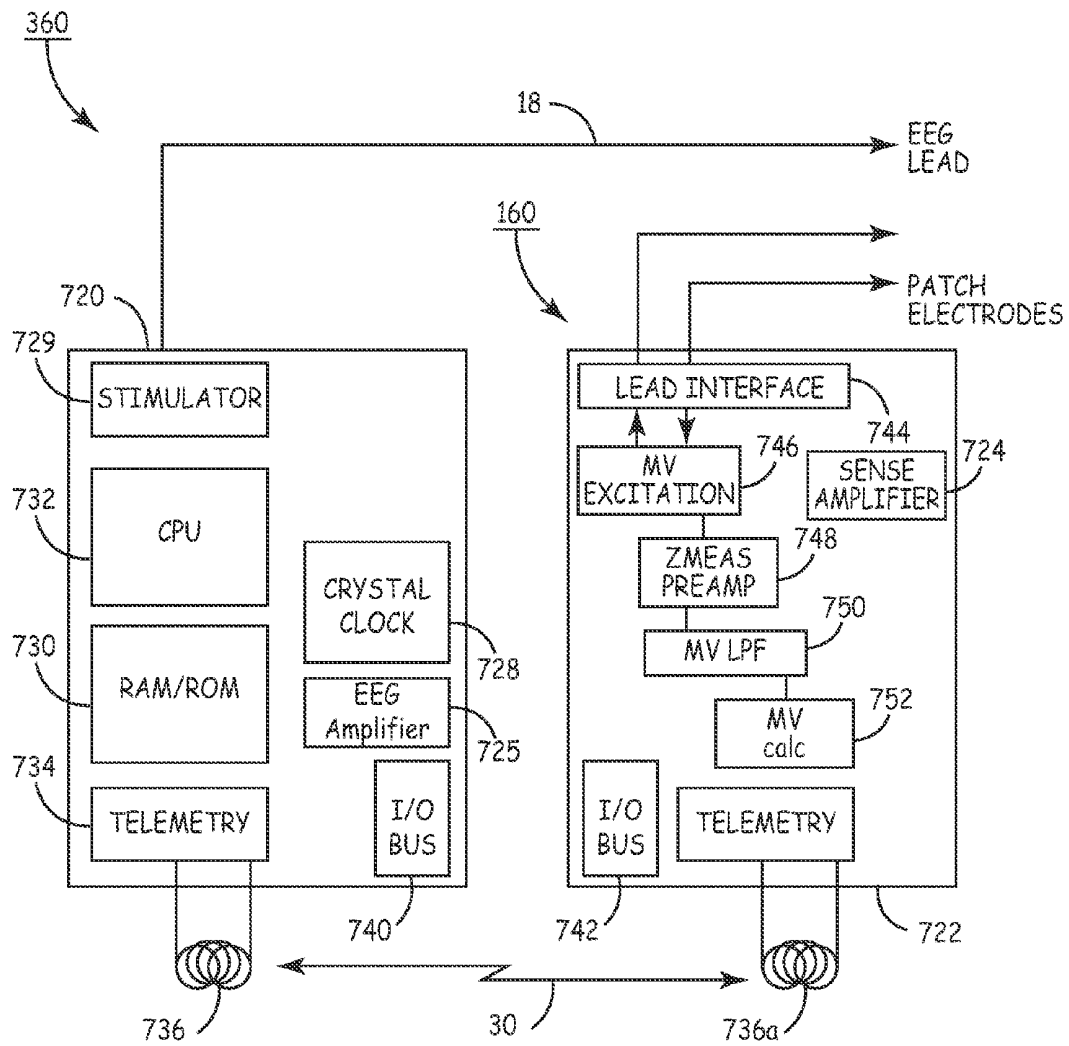


FIG. 45

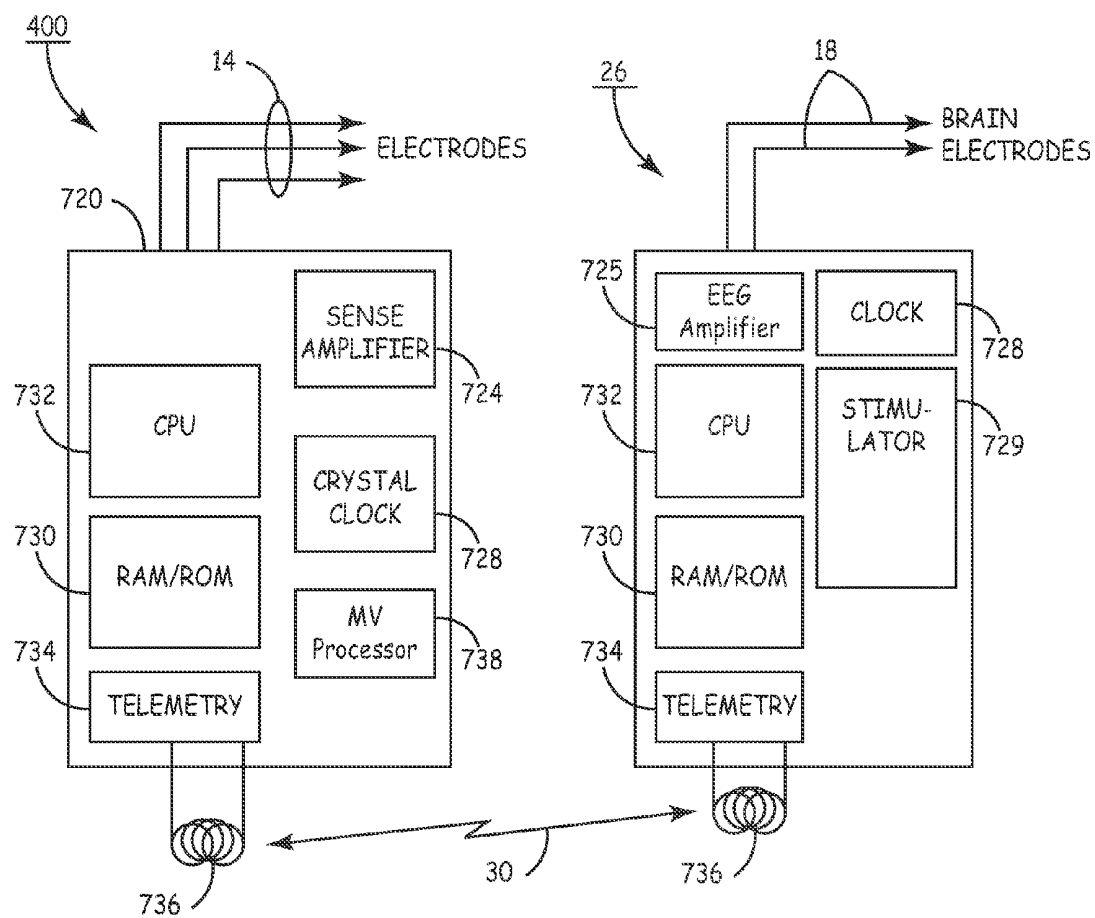


FIG. 46

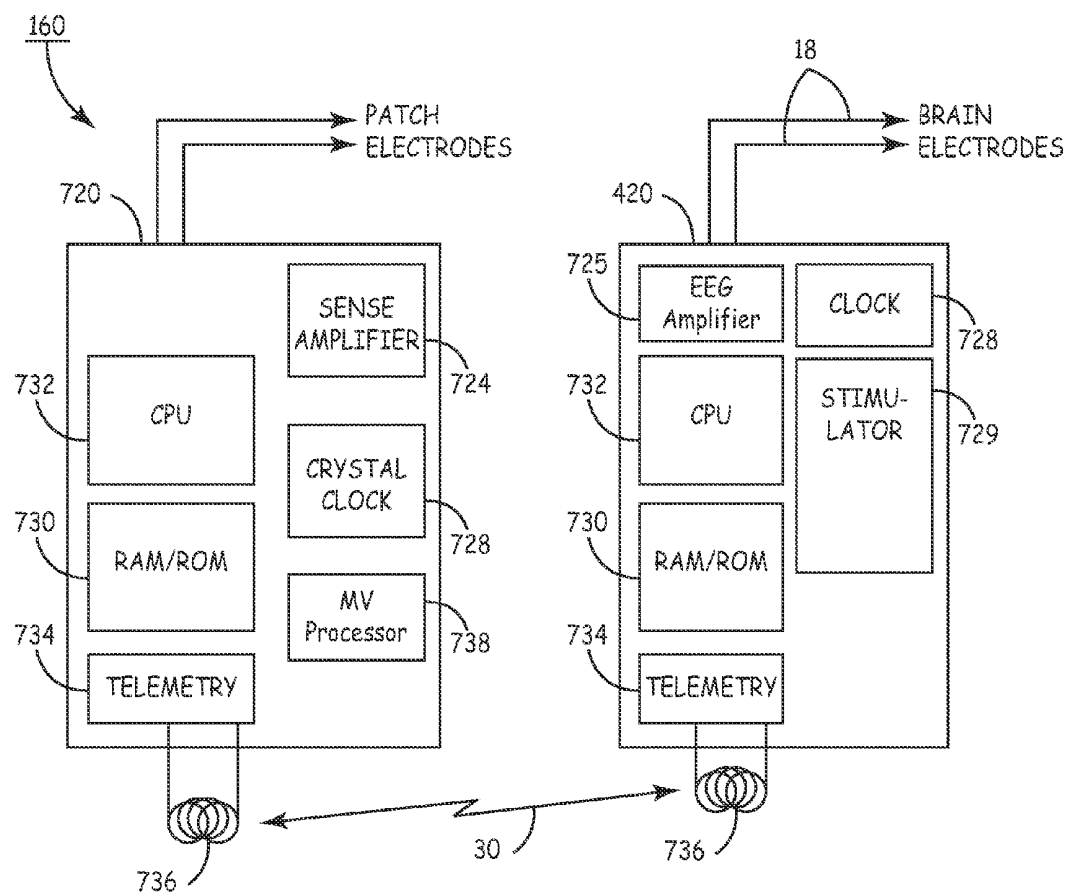


FIG. 47

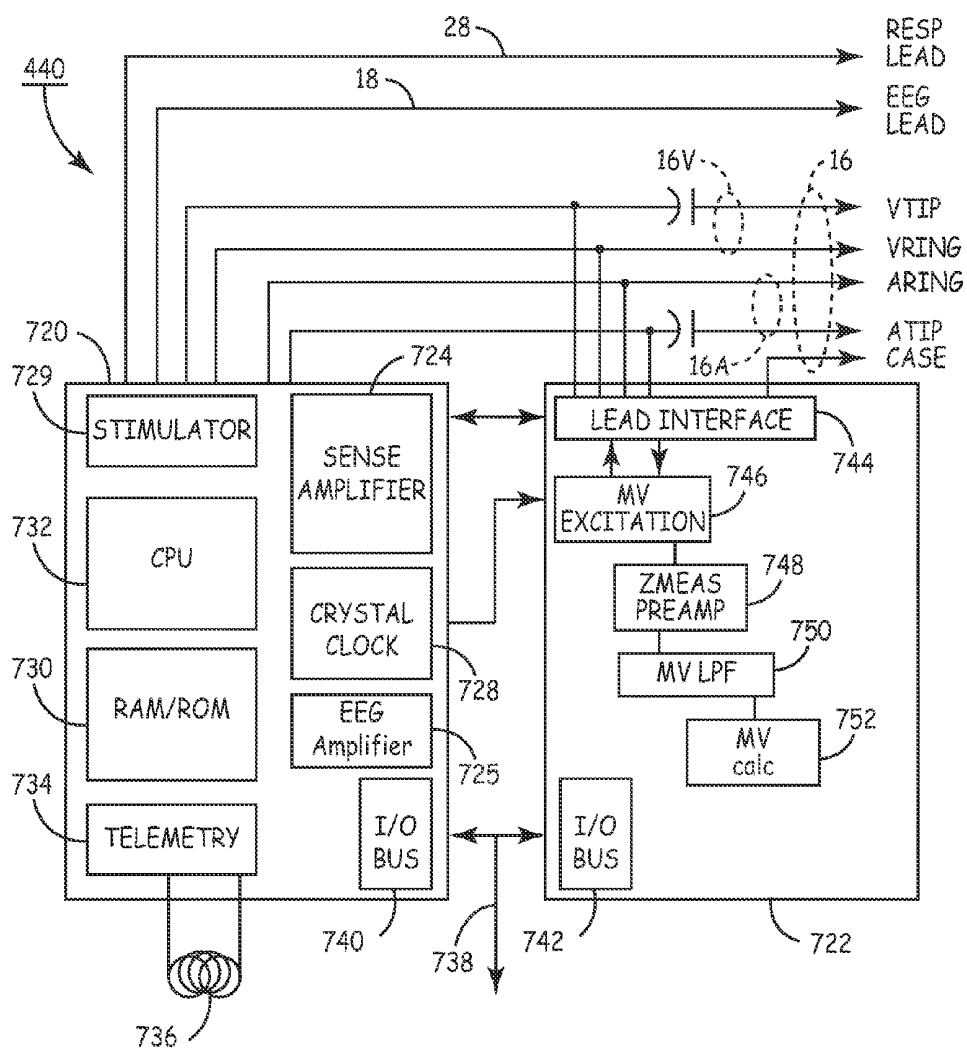


FIG. 48

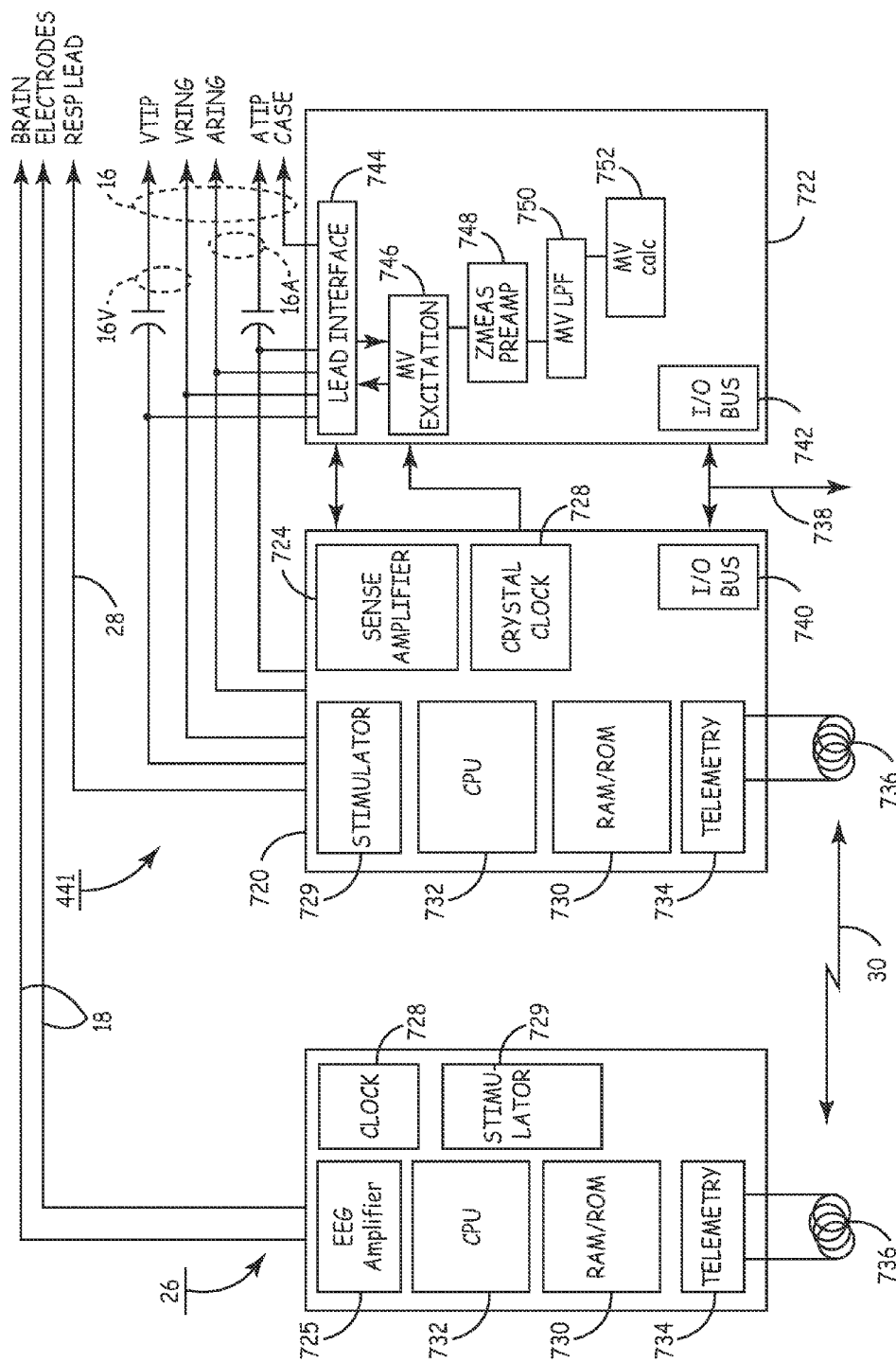


FIG. 49

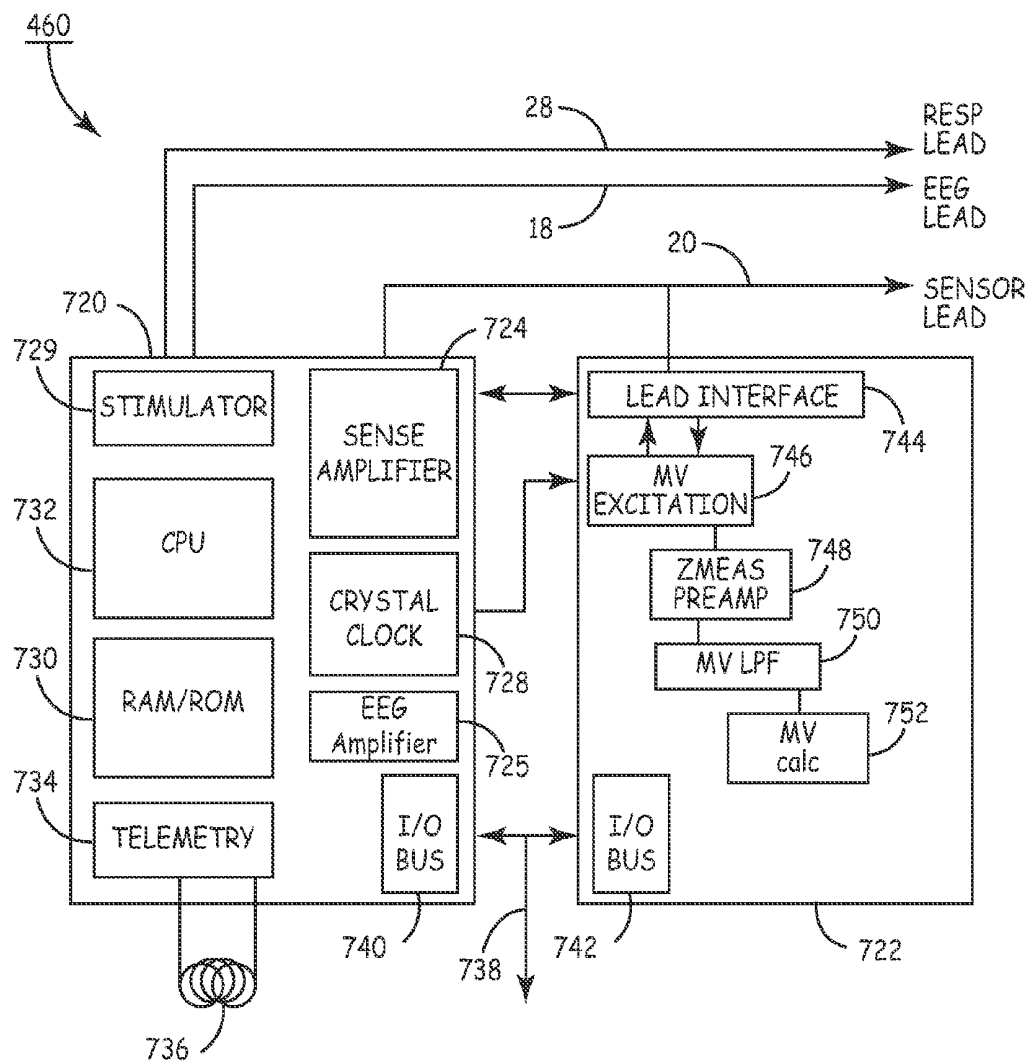


FIG. 50

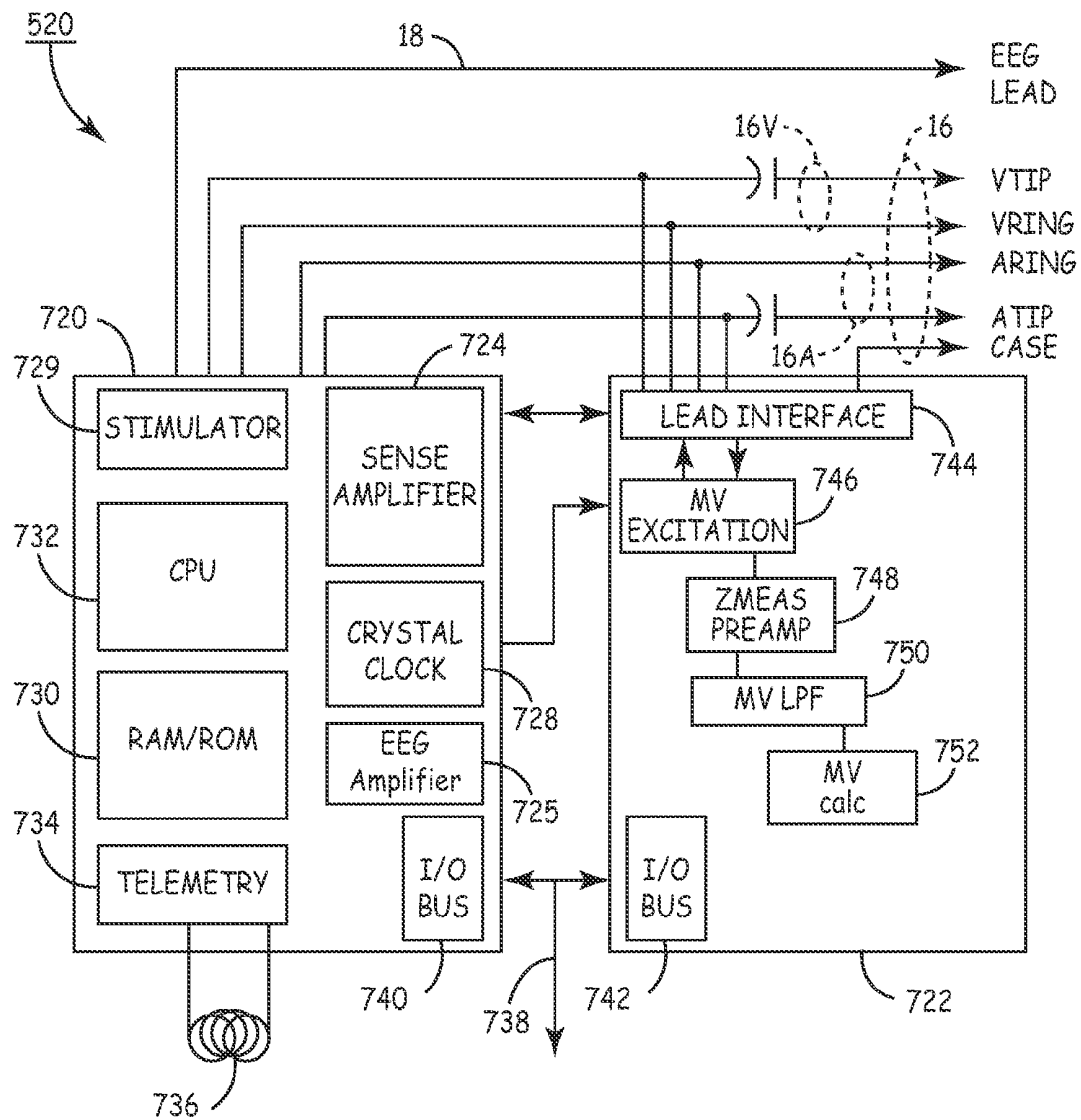


FIG. 51

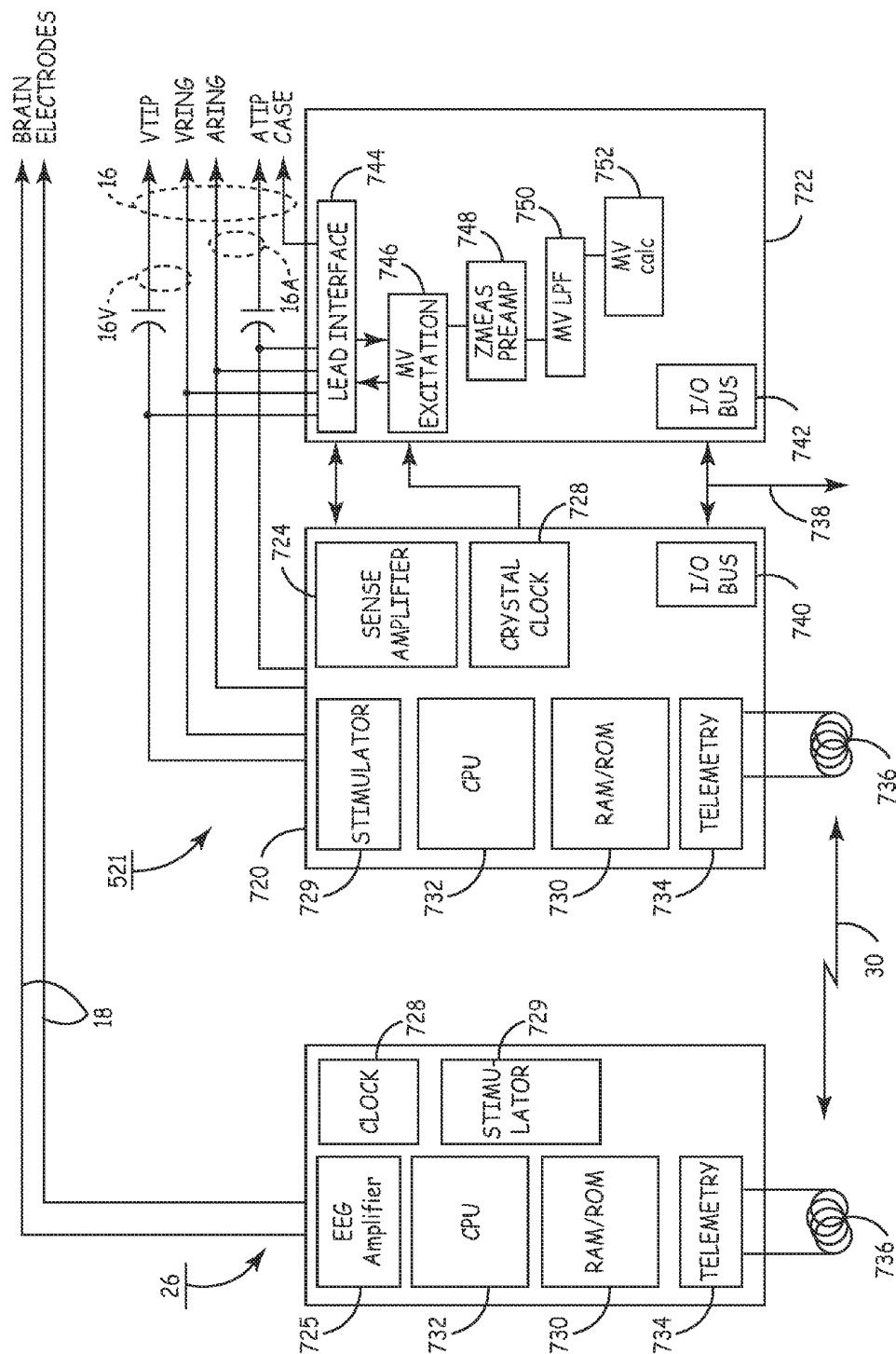


FIG. 52

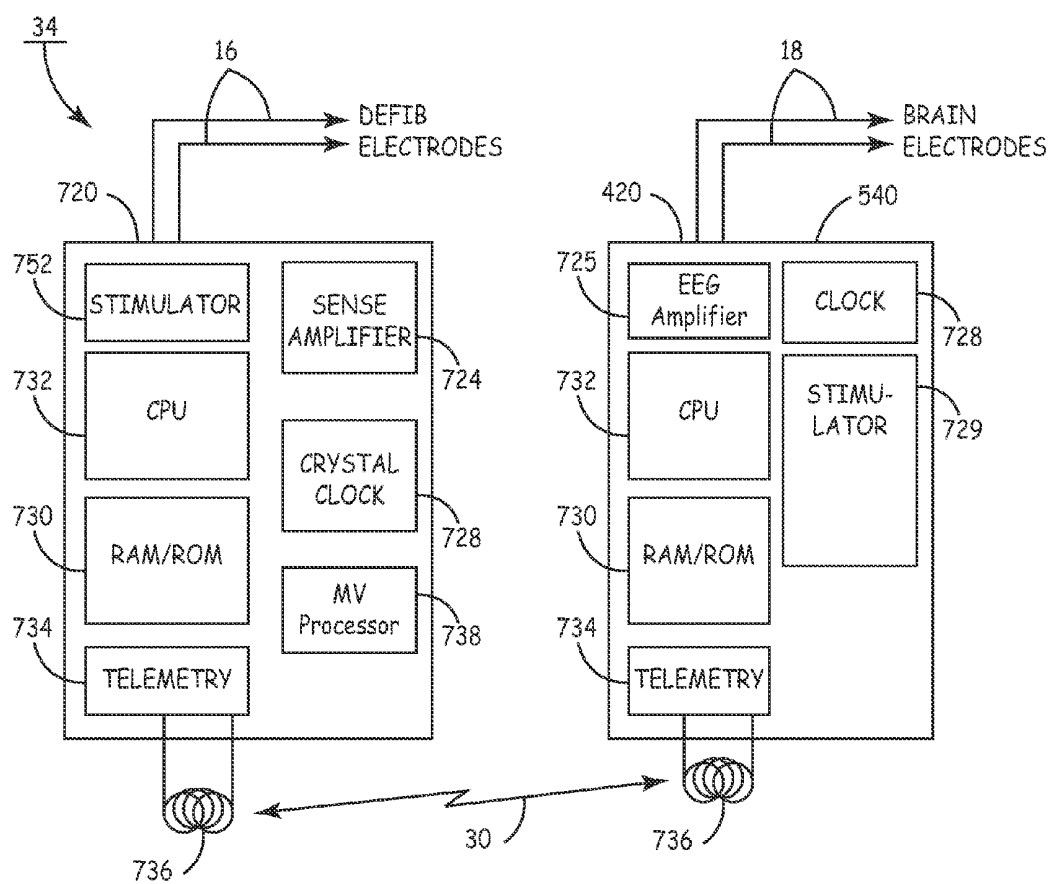


FIG. 53

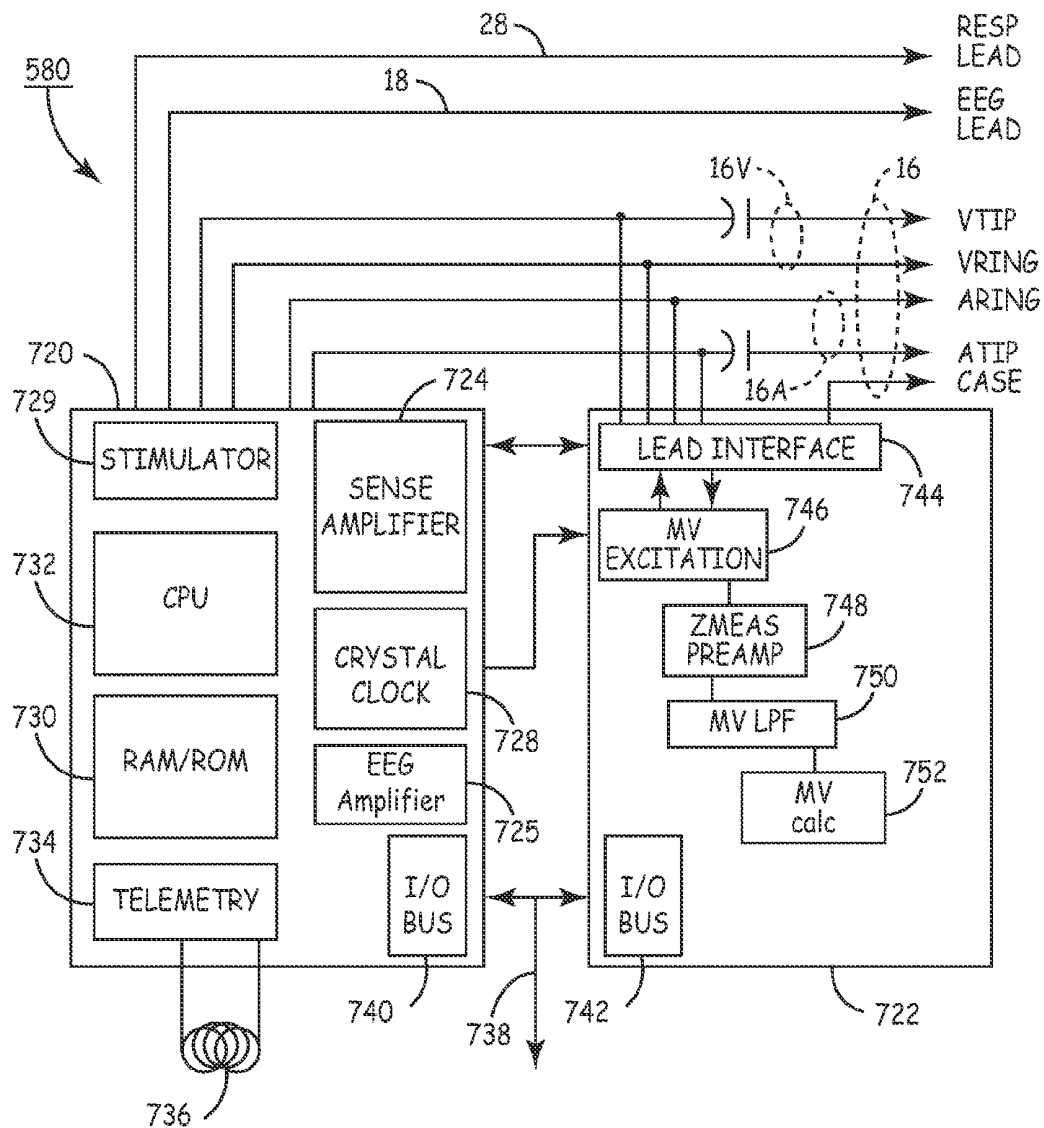


FIG. 54

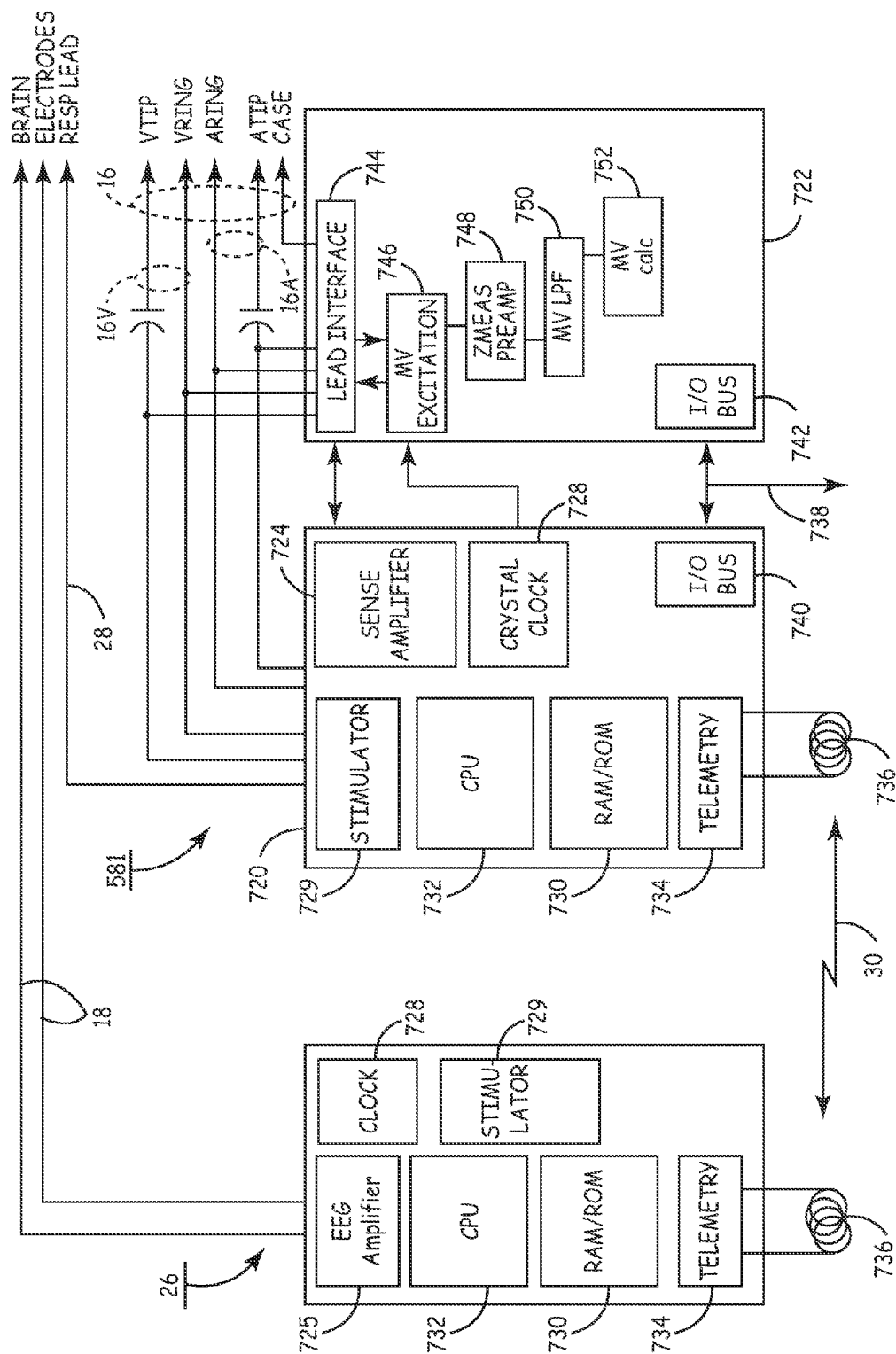
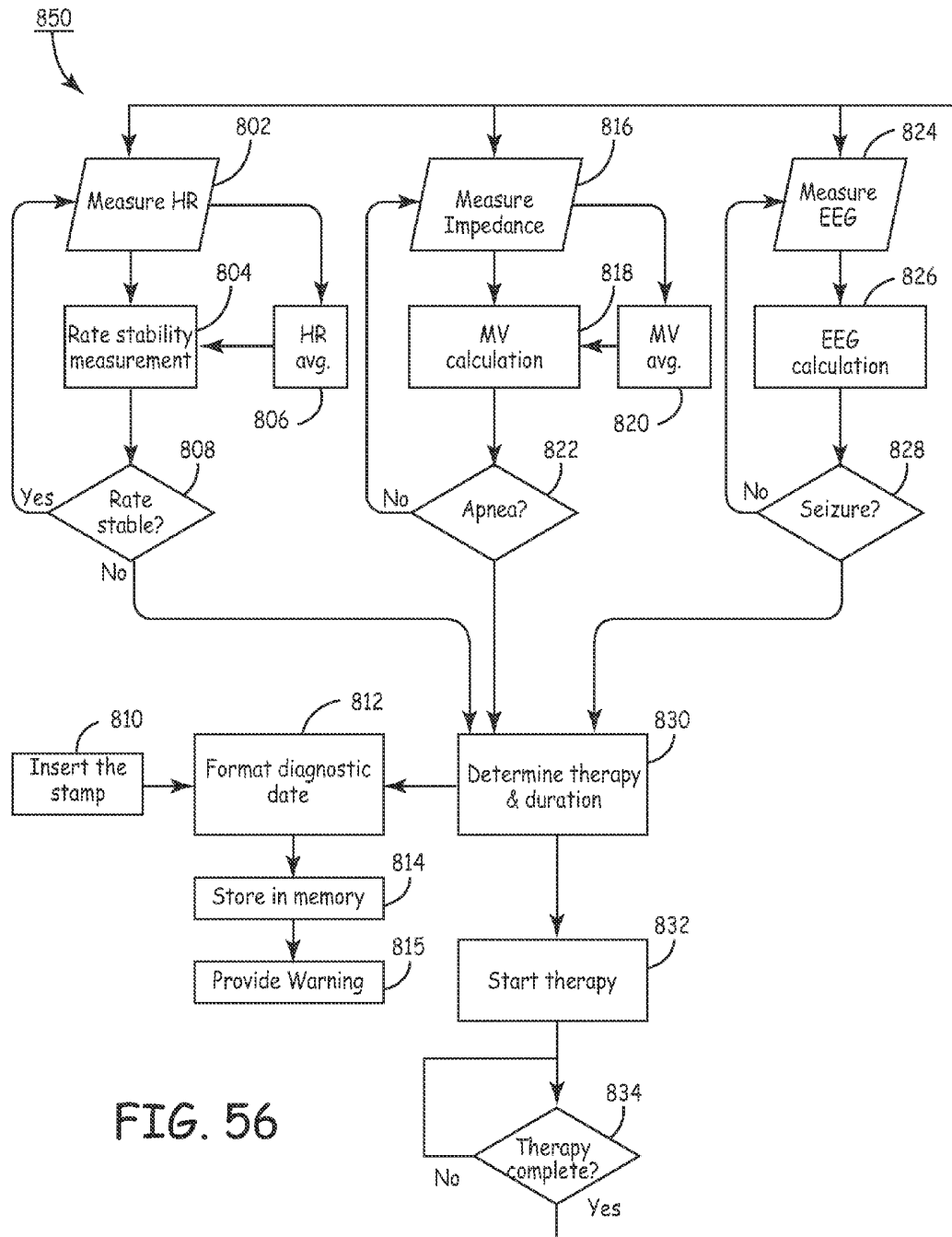


FIG. 55



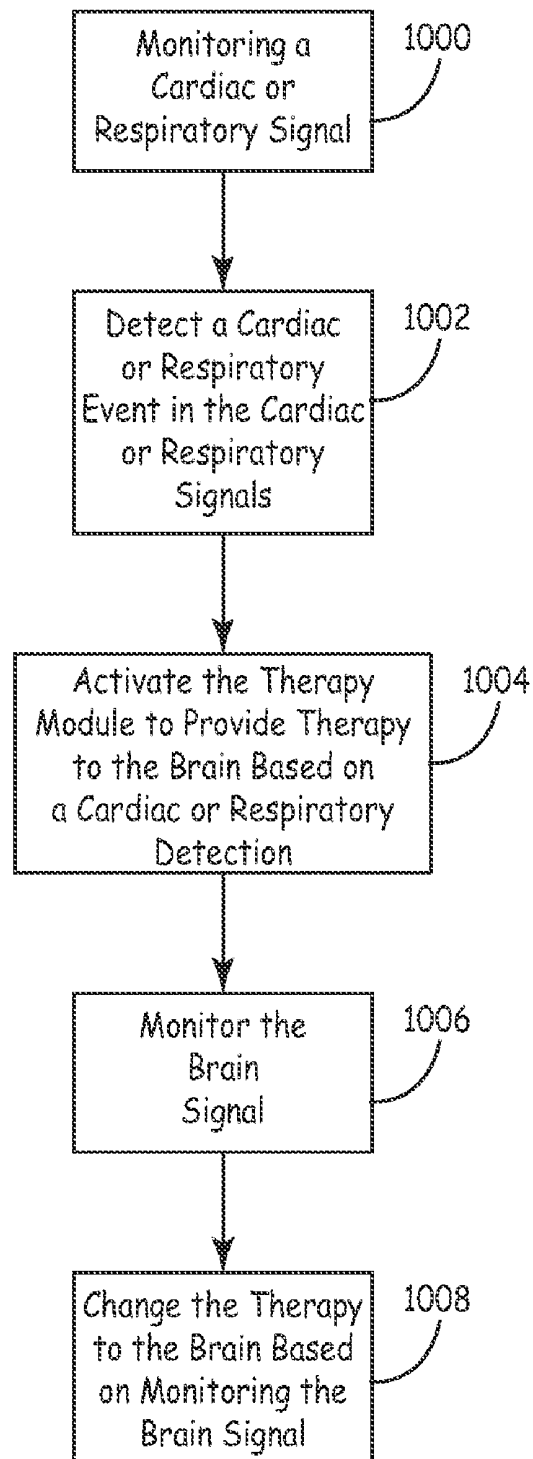


FIG. 57A

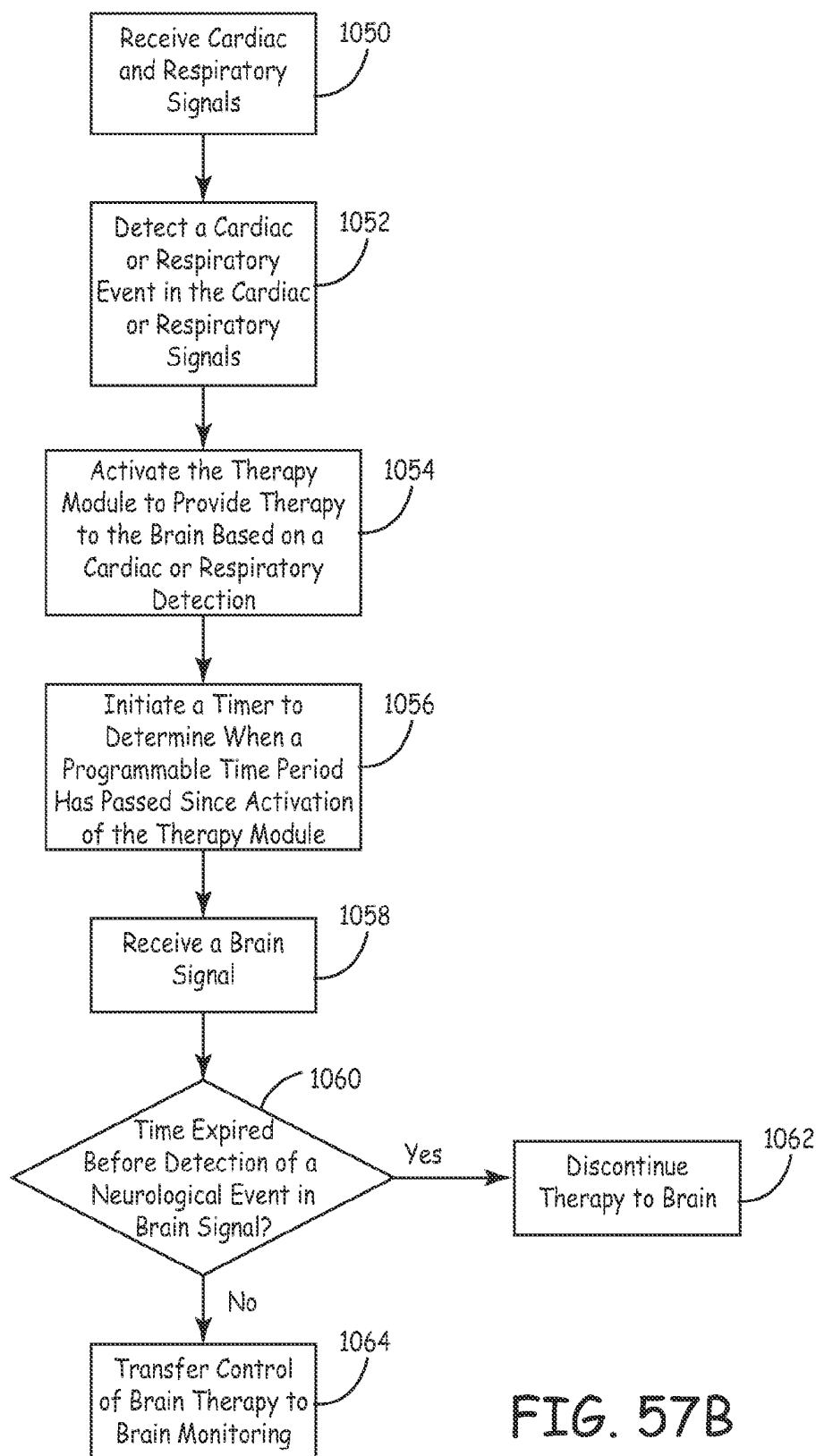


FIG. 57B

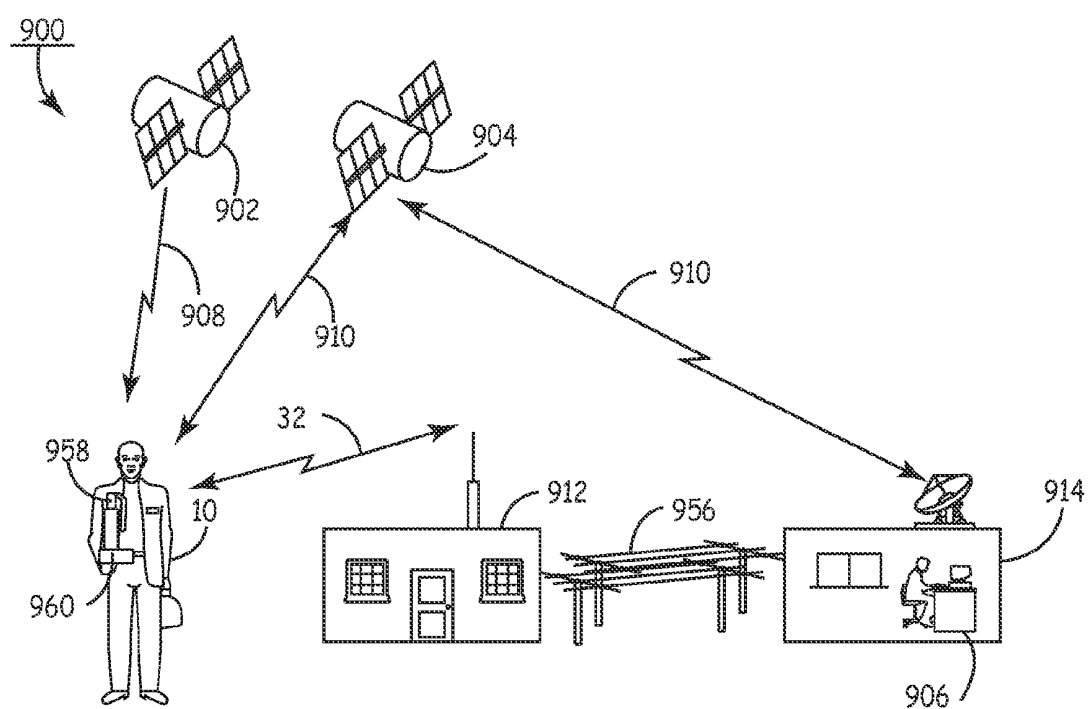


FIG. 58

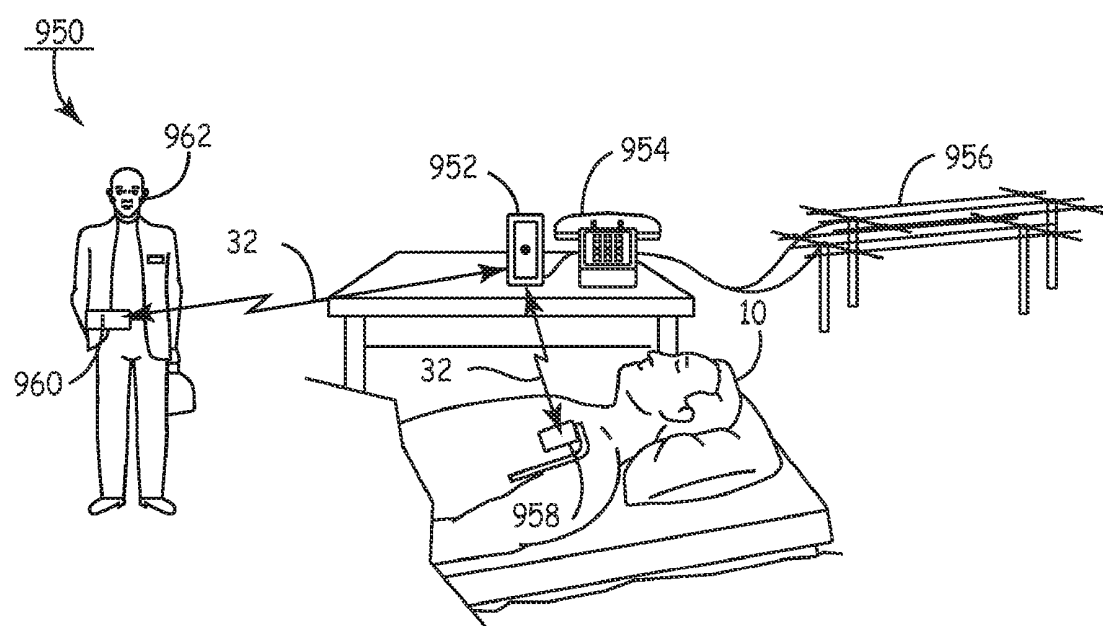
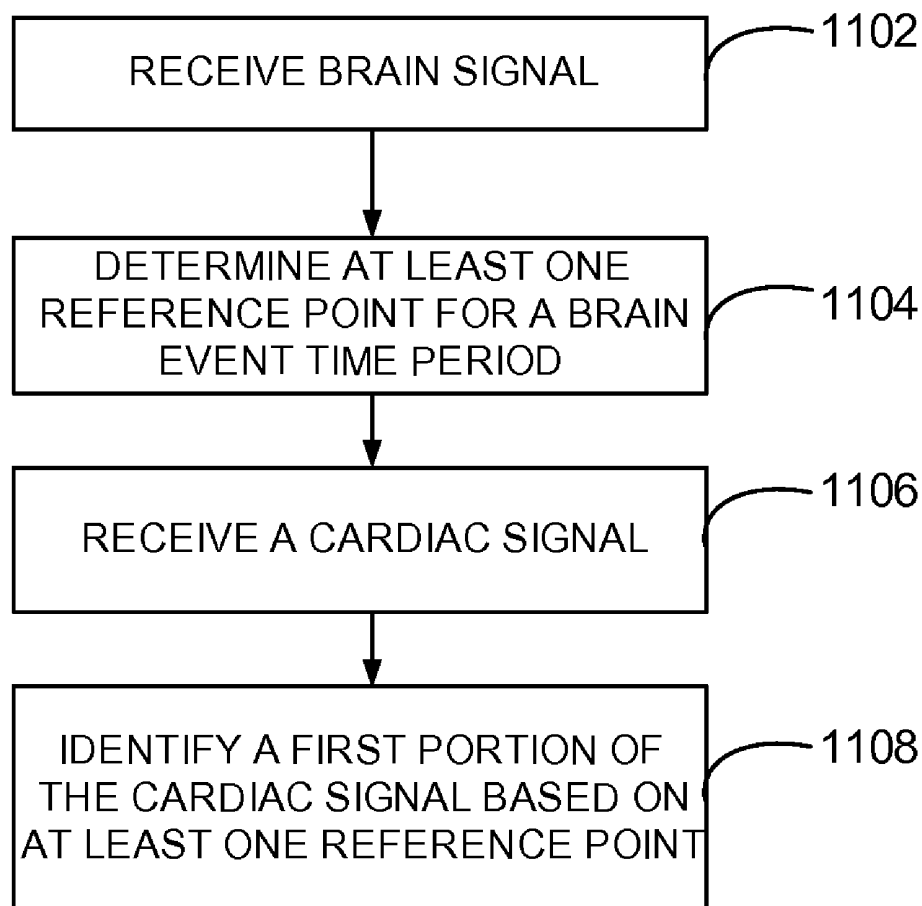


FIG. 59

**FIG. 60**

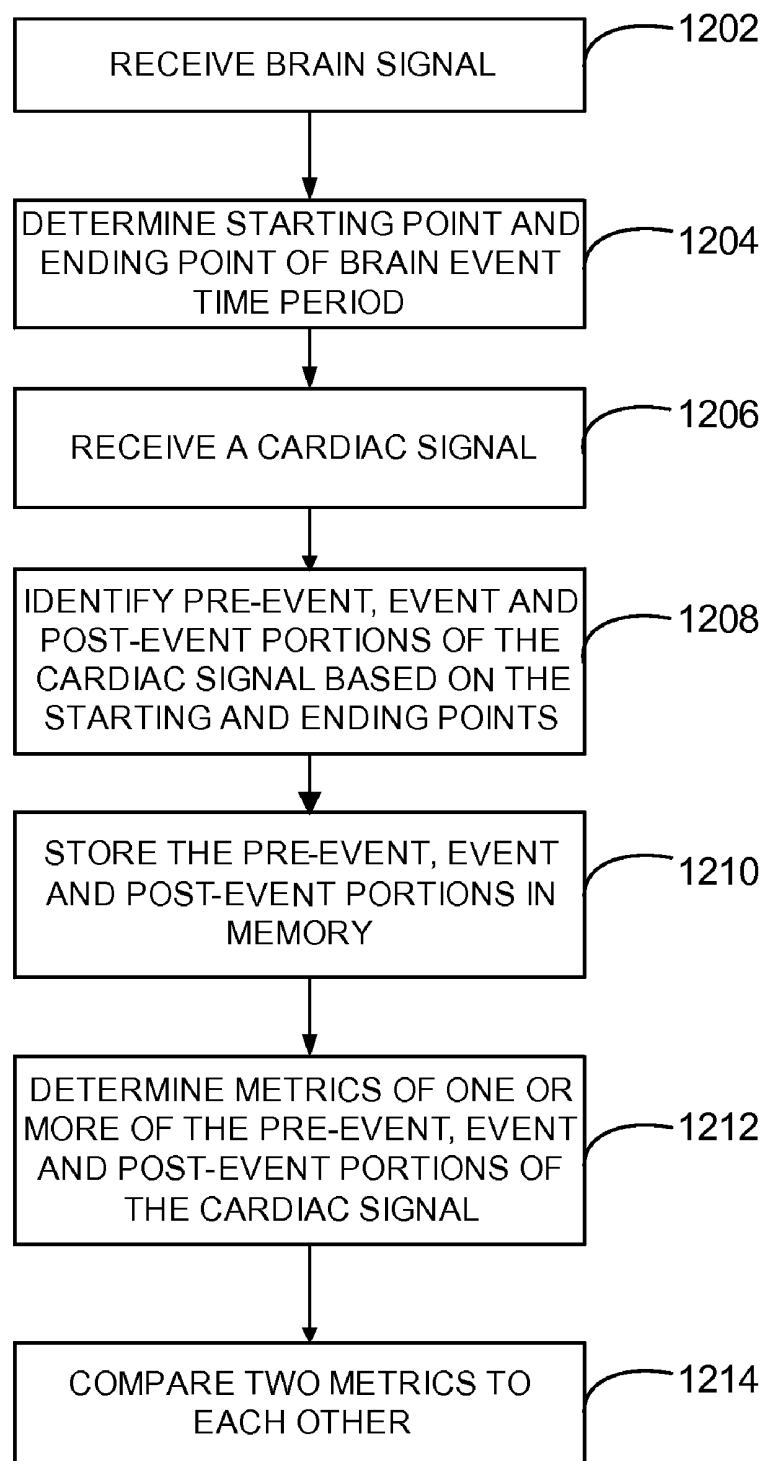


FIG. 61

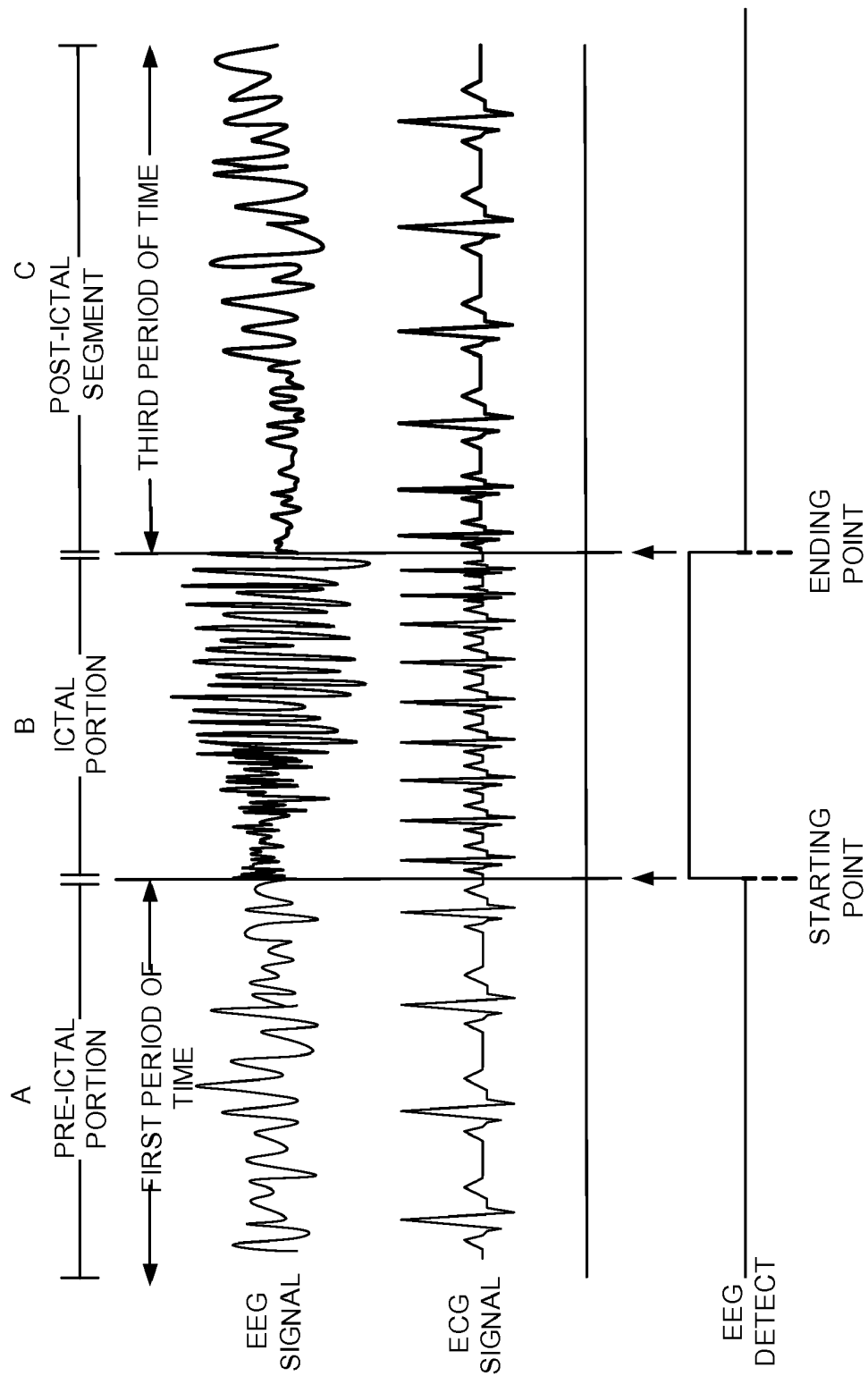


FIG. 62

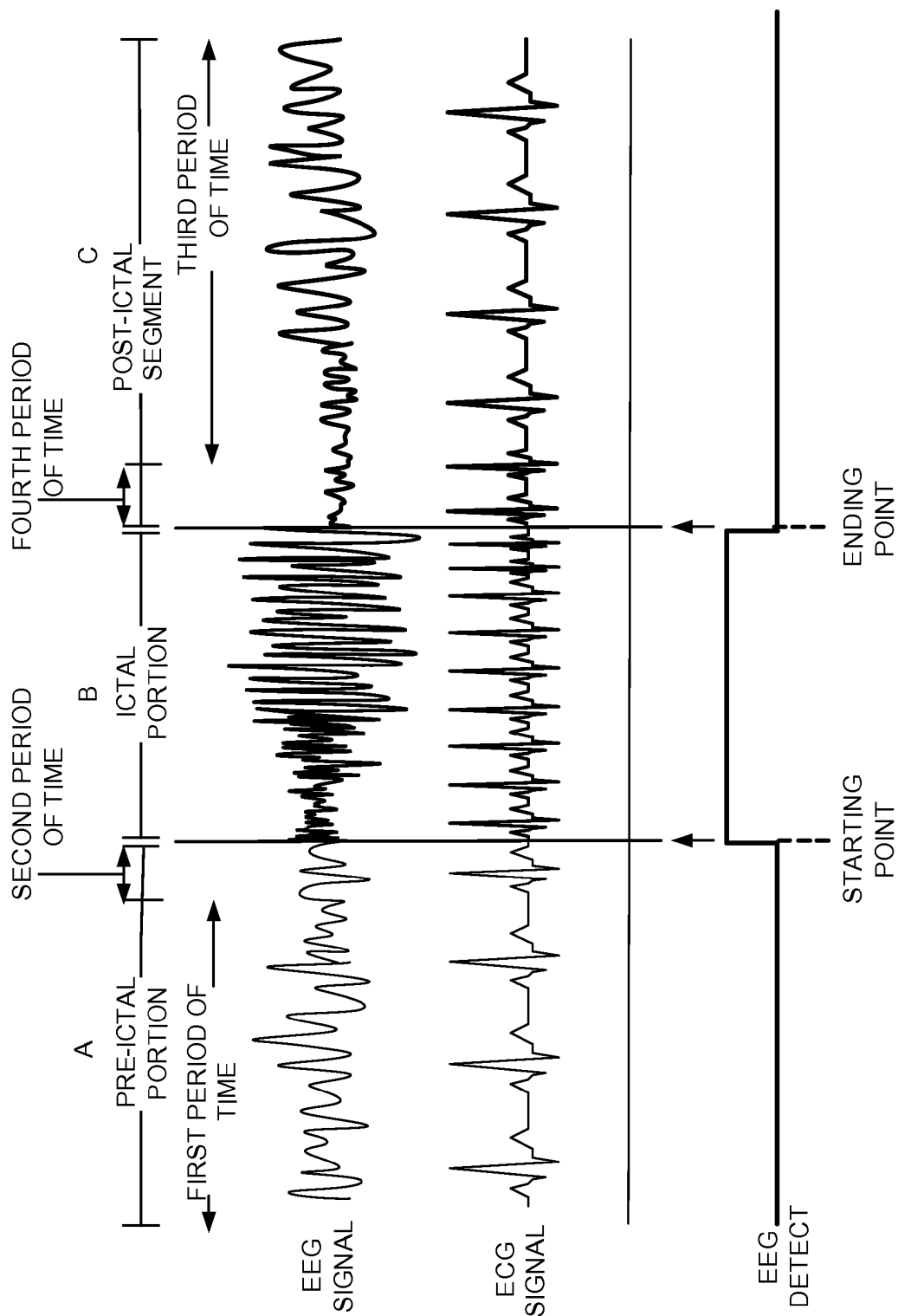


FIG. 63

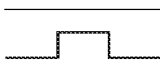
Top = Neurological Event Detection Bottom = Cardiac Event Detection	Category Code	Cardiac Event Timing	CRITERIA
	TP1	EQUAL- EQUAL	$((\text{Beg}_{\text{card}} = \text{START}_N) \ \& \ (\text{Term}_{\text{card}} = \text{END}_N))$
	TP2	OUT-IN	$((\text{Beg}_{\text{card}} \leq \text{START}_N) \ \& \ (\text{Term}_{\text{card}} > \text{START}_N) \ \& \ (\text{Term}_{\text{card}} \leq \text{END}_N))$
	TP3	OUT- OUT	$((\text{Beg}_{\text{card}} \leq \text{START}_N) \ \& \ (\text{Term}_{\text{card}} \geq \text{END}_N))$
	TP4	IN-OUT	$((\text{Beg}_{\text{card}} \geq \text{START}_N) \ \& \ (\text{Beg}_{\text{card}} < \text{END}_N) \ \& \ (\text{Term}_{\text{card}} \geq \text{END}_N))$
	TP5	IN-IN	$((\text{Beg}_{\text{card}} \geq \text{START}_N) \ \& \ (\text{Beg}_{\text{card}} < \text{END}_N) \ \& \ (\text{Term}_{\text{card}} > \text{START}_N) \ \& \ (\text{Term}_{\text{card}} \leq \text{END}_N))$
	TP6	OUT- EQUAL	$((\text{Beg}_{\text{card}} < \text{START}_N) \ \& \ (\text{Term}_{\text{card}} = \text{START}_N))$
	TP7	EQUAL- OUT	$((\text{Beg}_{\text{card}} = \text{END}_N) \ \& \ (\text{Term}_{\text{card}} > \text{END}_N))$
	TP8	OUT- OUT AFTER DETECT	$((\text{Beg}_{\text{card}} > \text{END}_N) \ \& \ (\text{Beg}_{\text{card}} - \text{WinSize} \leq \text{END}_N))$ Beg _{card} within window after neuro event end.
	TP9	OUT- OUT BEFORE DETECT	$((\text{Term}_{\text{card}} < \text{START}_N) \ \& \ (\text{Term}_{\text{card}} + \text{WinSize} \geq \text{START}_N))$ Term _{card} within window prior to neuro event start.
	FN	OUT- OUT	FALSE NEGATIVE (UN-MATCHED NEURO EVENT DETECTION)
	FP	-----	FALSE POSITIVE (UN-MATCHED CARDIAC EVENT DETECTION)

FIG. 64

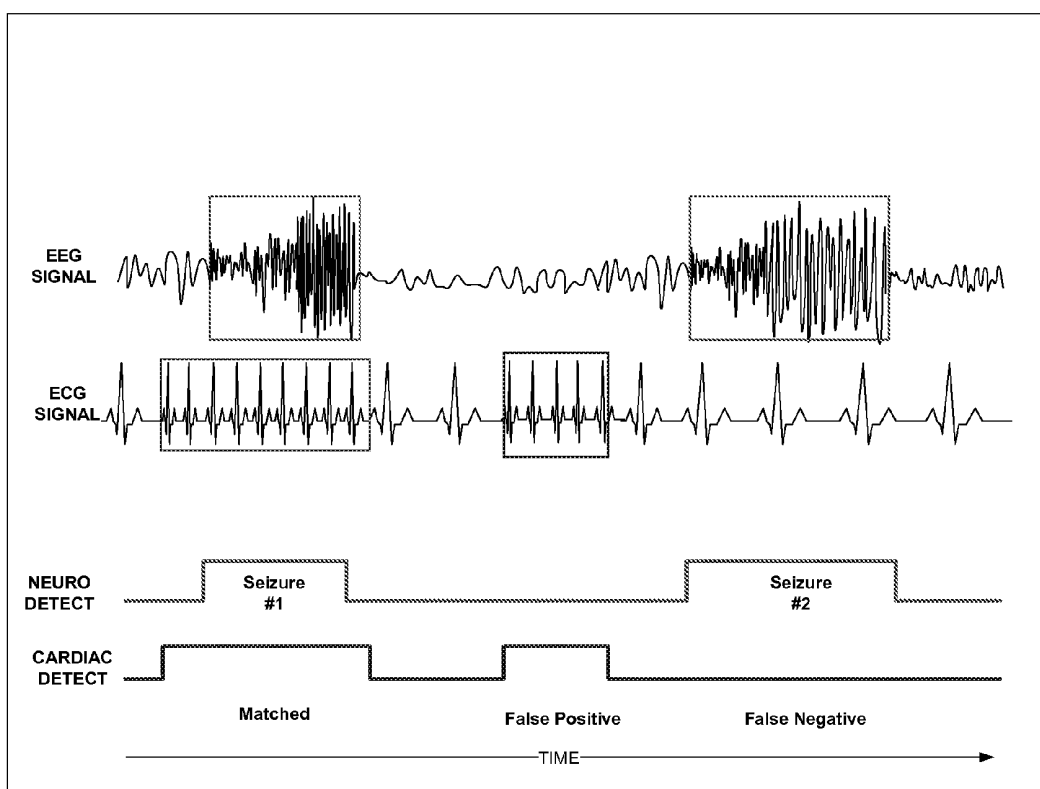


FIG. 65

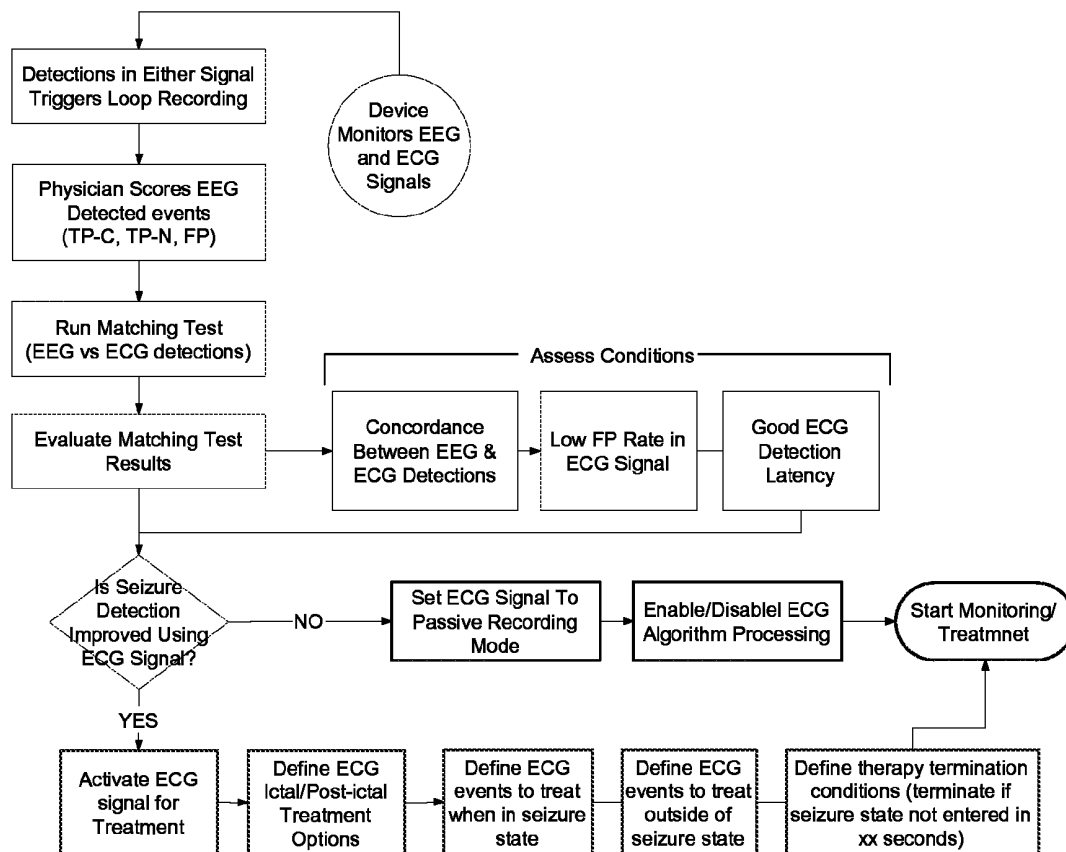


FIG. 66

SYSTEM AND METHOD FOR MONITORING CARDIAC SIGNAL ACTIVITY IN PATIENTS WITH NERVOUS SYSTEM DISORDERS

RELATED APPLICATIONS

This application is a continuation-in-part of U.S. application Ser. No. 11/380,462, filed Apr. 27, 2006, which is a continuation-in-part of U.S. application Ser. No. 11/311,043, filed Dec. 19, 2005, now U.S. Pat. No. 7,865,244; a continuation-in-part of U.S. application Ser. No. 11/311,200, filed Dec. 19, 2005 now U.S. Pat. No. 8,041,418; a continuation-in-part of U.S. application Ser. No. 11/311,393, filed Dec. 19, 2005, now U.S. Pat. No. 8,041,419; a continuation-in-part of U.S. application Ser. No. 11/311,456, filed Dec. 19, 2005, now U.S. Pat. No. 7,945,316, each of which claims the benefit of U.S. Provisional Application Ser. No. 60/636,929, filed Dec. 17, 2004, and all of which are incorporated herein by reference.

FIELD OF THE INVENTION

This invention relates generally to medical devices, systems and methods, and more particularly to the monitoring of cardiac signals associated with neurological events.

BACKGROUND OF THE INVENTION

Nervous system disorders affect millions of people, causing death and a degradation of life. Nervous system disorders include disorders of the central nervous system, peripheral nervous system, and mental health and psychiatric disorders. Such disorders include, for example without limitation, epilepsy, Parkinson's disease, essential tremor, dystonia, and multiple sclerosis (MS). Additionally, nervous system disorders include mental health disorders and psychiatric disorders which also affect millions of individuals and include, but are not limited to, anxiety (such as general anxiety disorder, panic disorder, phobias, post traumatic stress disorder (PTSD), and obsessive compulsive disorder (OCD)), mood disorders (such as major depression, bipolar depression, and dysthymic disorder), sleep disorders (narcolepsy), eating disorders such as obesity, and anorexia. As an example, epilepsy is the most prevalent serious neurological disease across all ages. Epilepsy is a group of neurological conditions in which a person has or is predisposed to recurrent seizures. A seizure is a clinical manifestation resulting from excessive, hypersynchronous, abnormal electrical or neuronal activity in the brain. A neurological event is an activity that is indicative of a nervous system disorder. A seizure is a type of a neurological event. This electrical excitability of the brain may be likened to an intermittent electrical overload that manifests with sudden, recurrent, and transient changes of mental function, sensations, perceptions, or involuntary body movement. Because the seizures are unpredictable, epilepsy affects a person's employability, psychosocial life, and ability to operate vehicles or power equipment. It is a disorder that occurs in all age groups, socioeconomic classes, cultures, and countries.

There are various approaches to treating nervous system disorders. Treatment therapies can include any number of possible modalities alone or in combination including, for example, electrical stimulation, magnetic stimulation, drug infusion, or brain temperature control. Each of these treatment modalities may use open loop treatment where neither the timing of the therapy nor treatment parameters are automatically set or revised based on information coming from a

sensed signal. Each of these treatment modalities may also be operated using closed-loop feedback control. Such closed-loop feedback control techniques may receive from a monitoring element a brain signal (such as EEG, ECoG, intracranial pressure, change in quantity of neurotransmitters) that carries information about a symptom or a condition of a nervous system disorder and is obtained from the head or brain of the patient.

For example, U.S. Pat. No. 5,995,868 discloses a system for the prediction, rapid detection, warning, prevention, or control of changes in activity states in the brain of a patient. Use of such a closed-loop feedback system for treatment of a nervous system disorder may provide significant advantages in that treatment can be delivered before the onset of the symptoms of the nervous system disorder.

While much work has been done in the area of detecting nervous system disorders by processing EEG signals, less has been done in the area of the brain-heart relationship as it pertains to these disorders. The relationship between the heart and the brain is complex and not fully understood. While some references discuss monitoring cardiac and brain activity, the question of what the device or system should do once it receives those signals has not been fully explored.

Sudden unexpected death in epilepsy, or SUDEP, is just one example of a nervous system disorder that involves a relationship between the brain and the heart. SUDEP, is defined as sudden, unexpected, often unwitnessed, non-traumatic and non-drowning death in patients for which no cause has been found except for the individual having a history of seizures. Depending on the cohort studied, SUDEP is responsible for 2% to 18% of all deaths in patients with epilepsy, and the incidence may be up to 40 times higher in young adults with epilepsy than among persons without seizures. Although the pathophysiological mechanisms leading to death are not fully understood, experimental, autopsy and clinical evidence implicate seizure related heart and pulmonary dysfunction or indicators. Pulmonary events may include obstructive sleep apnea (OSA), central apnea, and neurogenic pulmonary edema. Cardiac events may include cardiac arrhythmic abnormalities including sinus arrhythmia, sinus pause, premature atrial contraction (PAC), premature ventricular contraction (PVC), irregular rhythm (wandering pacemaker, multifocal atrial tachycardia, atrial fibrillation), asystole or paroxysmal tachycardia. Cardiac events may also include conduction abnormalities including AV-block (AVB) and bundle branch block (BBB) and repolarization abnormalities including T-wave inversion and ST-elevation or depression. Lastly, hypertension, hypotension and vaso-vagal syncope (VVS) are common in epilepsy patients.

Epileptic seizures are associated with autonomic neuronal dysfunction that results in a broad array of abnormalities of cardiac and pulmonary function. Different pathophysiological events may contribute to SUDEP in different patients, and the mechanism is probably multifactorial. Without intervention, respiratory events, including airway obstruction, central apnea and neurogenic pulmonary edema are probably terminal events. In addition, cardiac arrhythmia and anomalies, during the ictal and interictal periods, leading to arrest and acute cardiac failure also plays an important role in potentially terminal events. For example, the paper "Electrocardiographic Changes at Seizure Onset", Leutmezer, et al, *Epilepsia* 44(3): 348-354, 2003 describes cardiovascular anomalies, such as heart rate variability (HRV), tachycardia and bradycardia, that may precede, occur simultaneous or lag behind EEG seizure onset. "Cardiac Asystole in Epilepsy: Clinical and Neurophysiologic Features", Rocamora, et al, *Epilepsia* 44(2): 179-185, 2003 reports that cardiac asystole is "pro-

voked" by the seizure. "Electrocardiograph QT Lengthening Associated with Epileptiform EEG Discharges—a Role in Sudden Unexplained Death in Epilepsy", Tavernor, et al, Seizure 5(1): 79-83, March 1996 reports QT lengthening during seizures in SUDEP patients versus control. "Effects of Seizures on Autonomic and Cardiovascular Function", Devinsky Epilepsy Currents 4(2): 43-46, March/April 2004 describes ST segment depression and T-wave inversion, AVB, VPC and BBB during or immediately after a seizure. "Sudden Unexplained Death in Children with Epilepsy", Donner, et al, Neurology 57: 430-434, 2001 reports that bradycardia is frequently preceded by hypoventilation or apnea suggesting that heart rate changes during seizures may be a result of cardio-respiratory reflexes. Lastly, "EEG and ECG in Sudden Unexplained Death in Epilepsy", Nei, et al, Epilepsia 45(4) 338-345, 2004 reports on sinus tachycardia during or after seizures.

With the above broad and, often conflicting, array of neuro-cardiopulmonary physiological anomalies, manifestations and indicators, a device, or array of devices, is desired to allow for better diagnosis, monitoring and/or treatment of nervous system disorders including monitoring of both cardiac and brain signals.

SUMMARY OF THE INVENTION

In an embodiment of the invention, a medical device system and method are provided for monitoring cardiac signals in a patient with nervous system disorders. Embodiments of the invention include obtaining brain and cardiac signals, identifying brain events in the brain signal, identifying portions of the cardiac signal that do not correspond to brain event time periods, and calculating a measure of heart-rate variability (HRV) based on the portions of the cardiac signal that do not correspond with brain event time periods. Some embodiments further comprise modifying a therapy or an output of a medical device system based upon the calculated HRV.

BRIEF DESCRIPTION OF THE DRAWINGS

Core Monitor

FIG. 1 is a simplified schematic view of a thoracic cavity leadless medical device implanted in a patient that monitors cardiac and respiratory parameters relating to a nervous system disorder.

FIG. 2 is a simplified schematic view of an alternative embodiment cardiac leadless medical device implanted in a patient that monitors cardiac and respiratory parameters relating to nervous system disorder.

FIG. 3 is a simplified schematic view of an alternative embodiment sensor stub medical device implanted in a patient that monitors cardiac and respiratory parameters relating to nervous system disorder.

FIG. 4 is a simplified schematic view of an alternative embodiment external patch medical device used by a patient that monitors cardiac and respiratory parameters relating to nervous system disorder.

Full Monitor

FIG. 5 is a simplified schematic view of an alternative embodiment thoracic leadless and cranial leadless medical device implanted in a patient that monitors cardiac, respiratory and brain parameters relating to nervous system disorder.

FIG. 6 is a simplified schematic view of an alternative embodiment cardiac and cranial leadless medical device implanted in a patient that monitors cardiac, respiratory and brain parameters relating to nervous system disorder.

FIG. 7 is a simplified schematic view of an alternative embodiment sensor stub and cranial leadless medical device implanted in a patient that monitors cardiac, respiratory and brain parameters relating to nervous system disorder.

FIG. 8 is a simplified schematic view of an alternative embodiment external patch and cranial leadless medical device implanted in a patient that monitors cardiac, respiratory and brain parameters relating to nervous system disorder.

FIG. 9 is a simplified schematic view of an alternative embodiment integrated brain lead medical device implanted in a patient that monitors cardiac, respiratory and brain parameters relating to nervous system disorder.

FIG. 10 is a simplified schematic view of an alternative embodiment cranial implant medical device implanted in a patient that monitors cardiac and brain parameters relating to nervous system disorder.

Monitor+Treatment (Brain)

FIG. 11 is a simplified schematic view of an alternative embodiment thoracic leadless and cranial leadless medical device implanted in a patient that monitors cardiac, respiratory and brain parameters relating to nervous system disorders and provides brain treatment.

FIG. 12A is a simplified schematic view of an alternative embodiment cardiac and cranial leadless medical device implanted in a patient that monitors cardiac, respiratory and brain parameters relating to nervous system disorders and provides brain treatment.

FIG. 12B is a simplified schematic view of an alternative embodiment cardiac and cranial leadless medical device implanted in a patient that monitors cardiac, respiratory and brain parameters relating to nervous system disorders and provides brain treatment.

FIG. 13 is a simplified schematic view of an alternative embodiment sensor stub and cranial leadless medical device implanted in a patient that monitors cardiac, respiratory and brain parameters relating to nervous system disorders and provides brain treatment.

FIG. 14 is a simplified schematic view of an alternative embodiment external patch and cranial leadless medical device implanted in a patient that monitors cardiac, respiratory and brain parameters relating to nervous system disorders and provides brain treatment.

FIG. 15 is a simplified schematic view of an alternative embodiment integrated brain lead medical device implanted in a patient that monitors cardiac, respiratory and brain parameters relating to nervous system disorders and provides brain treatment.

FIG. 20 is a simplified schematic view of an alternative embodiment thoracic leadless device to cranial implant via wireless connect medical device implanted in a patient that monitors cardiac, respiratory and brain parameters relating to nervous system disorders and provides brain treatment.

FIG. 21 is a simplified schematic view of an alternative embodiment external patch to cranial implant via wireless connect medical device implanted in a patient that monitors cardiac, respiratory and brain parameters relating to nervous system disorders and provides brain treatment.

Monitor+Treatment (Brain+Respiration)

FIG. 16A is a simplified schematic view of an alternative embodiment cardiac, brain and phrenic nerve leadless medical device implanted in a patient that monitors cardiac, respiratory and brain parameters relating to nervous system disorders and provides brain and respiration treatment.

FIG. 16B is a simplified schematic view of an alternative embodiment cardiac, brain and phrenic nerve leadless medical device implanted in a patient that monitors cardiac, respira-

tory and brain parameters relating to nervous system disorders and provides brain and respiration treatment.

FIG. 17 is a simplified schematic view of an alternative embodiment sensor stub, brain and phrenic nerve lead medical device implanted in a patient that monitors cardiac, respiratory and brain parameters relating to nervous system disorders and provides brain and respiration treatment.

FIG. 18 is a simplified schematic view of an alternative embodiment integrated brain and phrenic nerve lead medical device implanted in a patient that monitors cardiac, respiratory and brain parameters relating to nervous system disorders and provides brain and respiration treatment.

FIG. 19 is a simplified schematic view of an alternative embodiment brain and integrated respiration lead medical device implanted in a patient that monitors cardiac, respiratory and brain parameters relating to nervous system disorders and provides brain and respiration treatment.

Monitor+Treatment (Brain+Cardiac)

FIG. 24A is a simplified schematic view of an alternative embodiment cardiac and brain lead medical device implanted in a patient that monitors cardiac, respiratory and brain parameters relating to nervous system disorders and provides brain and cardiac treatment.

FIG. 24B is a simplified schematic view of an alternative embodiment cardiac and brain lead medical device implanted in a patient that monitors cardiac, respiratory and brain parameters relating to nervous system disorders and provides brain and cardiac treatment.

FIG. 22 is a simplified schematic view of an alternative embodiment cranial implant to defibrillator vest via wireless connect medical device used by a patient that monitors cardiac, respiratory and brain parameters relating to nervous system disorders and provides brain and cardiac treatment.

FIG. 23 is a simplified schematic view of an alternative embodiment cranial implant to leadless defibrillator (lifeboat) via wireless connect medical device used by a patient that monitors cardiac, respiratory and brain parameters relating to nervous system disorders and provides brain and cardiac treatment.

Monitor+Treatment (Brain+Respiration+Cardiac)

FIG. 25A is a simplified schematic view of an alternative embodiment cardiac, cranial and phrenic nerve lead medical device implanted in a patient that monitors cardiac, respiratory and brain parameters relating to nervous system disorders and provides brain and respiration and cardiac treatment.

FIG. 25B is a simplified schematic view of an alternative embodiment cardiac, cranial and phrenic nerve lead medical device implanted in a patient that monitors cardiac, respiratory and brain parameters relating to nervous system disorders and provides brain and respiration and cardiac treatment.

Detailed Design

FIG. 26 is a simplified block diagram of a core monitor as shown in FIG. 1 above.

FIG. 27 is a graphical representation of the signals sensed by core monitor as shown in FIG. 1 above.

FIG. 28 is a simplified block diagram of a core monitor as shown in FIG. 2 above.

FIG. 29 is a simplified block diagram of a core monitor as shown in FIG. 3 above.

FIG. 30 is a simplified block diagram of a core monitor as shown in FIG. 4 above.

FIG. 31 is a flow diagram showing operation of a core monitor as shown in FIG. 1-4 above.

FIG. 32 is a simplified block diagram of a full monitor as shown in FIG. 5 above.

FIG. 33 is a simplified block diagram of a full monitor as shown in FIG. 6 above.

FIG. 34 is a simplified block diagram of a full monitor as shown in FIGS. 7 and 9 above.

FIG. 35 is a simplified block diagram of a full monitor as shown in FIG. 8 above.

FIG. 36 is a simplified block diagram of a full monitor as shown in FIG. 10 above.

FIG. 37 is a flow diagram showing operation of a full monitor as shown in FIG. 5-10 above.

FIG. 38 is a diagram of exemplary physiologic data from a patient with a full monitor as shown in relation to FIG. 5-10 above.

FIG. 39 shows a process for identifying ECG and respiratory abnormalities recorded during detected seizures in a full monitor as shown in relation to FIG. 5-10 above.

FIG. 40A shows a process for enabling the cardiac or respiratory detectors for neurological event detection in a full monitor as shown in relation to FIG. 5-10 above and detection/treatment as described in FIG. 41-51 below.

FIG. 40B shows a process for enabling the ECG or respiratory detectors for seizure detection in a full monitor as shown in relation to FIG. 5-10 above and detection/treatment as described in FIG. 41-51 below.

FIG. 41 is a simplified block diagram of a full monitor with brain stimulation therapy as shown in FIG. 11 above.

FIG. 42 is a simplified block diagram of a full monitor with brain stimulation therapy as shown in FIG. 12A above.

FIG. 43 is a simplified block diagram of a full monitor with brain stimulation therapy as shown in FIG. 12B above.

FIG. 44 is a simplified block diagram of a full monitor with brain stimulation therapy as shown in FIGS. 13 and 15 above.

FIG. 45 is a simplified block diagram of a full monitor with brain stimulation therapy as shown in FIG. 14 above.

FIG. 46 is a simplified block diagram of a full monitor with brain stimulation therapy as shown in FIG. 20 above.

FIG. 47 is a simplified block diagram of a full monitor with brain stimulation therapy as shown in FIG. 21 above.

FIG. 48 is a simplified block diagram of a full monitor with brain and respiration stimulation therapy as shown in FIG. 16A above.

FIG. 49 is a simplified block diagram of a full monitor with brain and respiration stimulation therapy as shown in FIG. 16B above.

FIG. 50 is a simplified block diagram of a full monitor with brain and respiration stimulation therapy as shown in FIGS. 17, 18 and 19 above.

FIG. 51 is a simplified block diagram of a full monitor with brain and cardiac stimulation therapy as shown in FIG. 24A above.

FIG. 52 is a simplified block diagram of a full monitor with brain and cardiac stimulation therapy as shown in FIG. 24B above.

FIG. 53 is a simplified block diagram of a full monitor with brain and cardiac stimulation therapy as shown in FIGS. 22 and 23 above.

FIG. 54 is a simplified block diagram of a full monitor with brain, respiration and cardiac stimulation therapy as shown in FIG. 25A above.

FIG. 55 is a simplified block diagram of a full monitor with brain, respiration and cardiac stimulation therapy as shown in FIG. 25B above.

FIG. 56 is a flow diagram showing operation of a full monitor with therapy (including brain, respiration or cardiac stimulation therapy) as shown in FIG. 11-25 above.

FIG. 57A is a flow diagram showing a process for enabling cardiac/respiratory detectors for neurological event detection and treatment including termination rules.

FIG. 57B is a flow diagram showing a process for enabling ECG/respiratory detectors for seizure detection and treatment including termination rules.

FIG. 58 is a schematic diagram of a system utilizing any of the above-described embodiments and allowing remote monitoring and diagnostic evaluation of at risk patients.

FIG. 59 is a schematic diagram of an alternative system utilizing any of the above-described embodiments and allowing remote monitoring and diagnostic evaluation of at risk patients.

FIG. 60 is a flowchart illustrating one embodiment method of identifying a portion of a cardiac signal based on a reference point in a brain signal.

FIG. 61 is a flowchart illustrating a more detailed embodiment method of identifying a portion of a cardiac signal based on starting and ending points of a neurological event in a brain signal.

FIG. 62 is a chart of EEG and ECG signals showing exemplary relationships between the two signals.

FIG. 63 is another chart of EEG and ECG signals showing exemplary relationships between the two signals.

FIG. 64 is a table describing criteria for a matching test in accordance with an embodiment of the invention.

FIG. 65 illustrates a montage of EEG and ECG signals, and detected neurological and cardiac events from a patient, for applying a matching test in accordance with an embodiment of the invention.

FIG. 66 is a flow chart describing a process for determining whether to activate cardiac event detection as a trigger for delivering therapy for treating a neurological event.

DETAILED DESCRIPTION OF THE INVENTION

The term “brain monitoring element” used herein means any device, component or sensor that receives a physiologic signal from the brain or head of a patient and outputs a brain signal that is based upon the sensed physiologic signal. Some examples of a brain monitoring element include leads, electrodes, chemical sensors, biological sensors, pressure sensors, and temperature sensors. A monitoring element does not have to be located in the brain to be a brain monitoring element. The term brain monitoring element is not the same as the term “monitor” also used herein, although a brain monitoring element could be a part of a monitor.

The term “cardiac monitoring element” used herein means any device, component or sensor that receives or infers a physiological signal from the heart of a patient and outputs a cardiac signal that is based upon sensed physiologic signal. Some examples of cardiac monitoring elements include leads, electrodes, chemical sensors, biological sensor, pressure sensors and temperature sensors. A monitoring element does not have to be located in the heart or adjacent to the heart to be a cardiac monitoring element. For example, a sensor or electrode adapted for sensing a cardiac signal and placed on the housing of an implantable device is a cardiac monitoring element. Furthermore, a cardiac monitoring element could be an externally placed sensor such as a holter monitoring system. The term “cardiac monitoring element” is not the same as the term “monitor” also used herein although a cardiac monitoring element could be a part of a monitor.

The term “respiratory monitoring element” used herein means any device, component or sensor that receives a physiologic signal indicative of activity or conditions in the lungs of a patient and outputs a respiration signal that is based upon

the sensed physiologic signal. Some examples of respiration monitoring elements are provided below. A monitoring element does not have to be located in the lungs or adjacent to the lungs to be a respiratory monitoring element. The term “respiratory monitoring element” is not the same as the term “monitor” also used herein although a respiratory monitoring element could be a part of a monitor.

It is noted that many embodiments of the invention may reside on any hardware embodiment currently understood or conceived in the future. Many example hardware embodiments are provided in this specification. These examples are not meant to be limiting of the invention.

Core Monitor

Cardiopulmonary monitoring in the Core Monitor device (as described below in more detail in conjunction with FIGS. 1-4 and 26-30) monitors cardiac (e.g., ECG, blood pressure) or respiration signals continuously and records these signals in a loop recorder either automatically or manually when the patient indicates they have had a neurological event such as a seizure. Real-time analysis of the ECG signal evaluates rate disturbances (e.g., bradycardia; tachycardia; asystole) as well as any indications of cardiac ischemia (e.g., ST segment changes; T wave inversion, etc.). Real-time analysis of the respiration signal evaluates respiration disturbances (e.g., respiration rate, minute ventilation, apnea, prolonged pauses).

Abnormalities detected during real-time analysis will lead to an immediate patient alert. This alert can be audible (beeps, buzzers, tones, spoken voice, etc.), light, tactile, or other means.

Automatic loop recording may save the data for a programmable period of time. For example, the device may be programmed to save a period of time before a cardiac detection (e.g., 30 seconds of ECG raw or processed data before detection) and a second period of time after the detection (e.g., 3 minutes of ECG raw or processed data after detection).

The medical device system may also include a manual activation mode in which the patient provides an indication (e.g., push a button on a holter, patient programmer or other external patient activator device) when a neurological event is occurring or has just occurred. In manual activation mode, to allow for the fact that the patient may not mark the neurological event until the neurological event has ended, the ECG loop recording may begin a longer time period before the event is marked. For example, the medical device system may save ECG data beginning 15 minutes before the patient mark. This time period may be programmable. Post-processing of this saved signal will analyze the data to evaluate heart rate changes during the neurological event, heart rate variability and changes in ECG waveforms. Manual patient indication of a neurological event will be done through the patient external activator device 22. The patient (or caregiver) will push a button on the external device, while communicating with the implanted device. This will provide a marker and will initiate a loop recording. In addition, prolonged ECG loop recordings are possible (e.g., in the case of SUDEP, recording all data during sleep since the incidence of SUDEP is highest in patients during sleep).

Post-processing of the signal can occur in the implanted device, the patient's external device or in the clinician external device. Intermittently (e.g., every morning, once/week, following a neurological event), the patient may download data from the implantable device to the patient external device. This data will then be analyzed by the external device (or sent through a network to the physician) to assess any ECG or respiratory abnormalities. If an abnormality is detected, the device will notify the patient/caregiver. At that

time, the patient/caregiver or device can inform the healthcare provider of the alert to allow a full assessment of the abnormality. The clinician external device is also capable of obtaining the data from the implanted device and conducting an analysis of the stored signals. If a potentially life-threatening abnormality is detected, the appropriate medical treatment can be prescribed (e.g., cardiac abnormality: a pacemaker, an implantable defibrillator, or a heart resynchronization device may be indicated or respiration abnormality: CPAP, patient positioning, or stimulation of respiration may be indicated).

FIG. 1 is a simplified schematic view of one embodiment of a core Monitor **100** implanted in a patient **10**. Monitor **100** continuously senses and monitors the cardiac and respiration function of patient **10** via one or more monitoring elements **14** (e.g., cardiac electrodes) to allow detection of neurological events, the recording of data and signals pre and post event. Stored diagnostic data is uplinked and evaluated by the patient's physician utilizing programmer **12** via a 2-way telemetry link **32**. An external patient activator **22** may optionally allow the patient **10**, or other care provider (not shown), to manually activate the recording of diagnostic data.

Monitor **100**, as stated above, typically includes one or more monitoring elements **14** such as several subcutaneous spiral electrodes that are embedded individually into three or four recessed casings placed in a compliant surround that is attached to the perimeter of implanted monitor **100** as substantially described in U.S. Pat. No. 6,512,940 "Subcutaneous Spiral Electrode for Sensing Electrical Signals of the Heart" to Brabec, et al and U.S. Pat. No. 6,522,915 "Surround Shroud Connector and Electrode Housings for a Subcutaneous Electrode Array and Leadless ECGs" to Ceballos, et al. These electrodes are electrically connected to the circuitry of the implanted Monitor **100** to allow the detection of cardiac depolarization waveforms (as substantially described in U.S. Pat. No. 6,505,067 "System and Method for Deriving a Virtual ECG or EGM Signal" to Lee, et al.) that may be further processed to detect cardiac electrical characteristics (e.g., heart rate, heart rate variability, arrhythmias, cardiac arrest, sinus arrest and sinus tachycardia). Further processing of the cardiac signal amplitudes may be used to detect respiration characteristics (e.g., respiration rate, minute ventilation, and apnea).

To aid in the implantation of Monitor **100** in a proper position and orientation, an implant aid may be used to allow the implanting physician to determine the proper location/orientation as substantially described in U.S. Pat. No. 6,496,715 "System and Method for Noninvasive Determination of Optimal Orientation of an Implantable Sensing Device" to Lee, et al.

FIG. 2 is a simplified schematic view of a second embodiment core Monitor **120** implanted in a patient **10**. Monitor **120** continuously senses and monitors cardiac and respiration function of patient **10** via cardiac lead(s) **16** to allow detection of neurological events and the recording of data and signals pre and post event. Stored diagnostic data is uplinked and evaluated by the patient's physician utilizing programmer **12** via a 2-way telemetry link **32**. An external patient activator **22** may optionally allow the patient **10**, or other care provider (not shown), to manually activate the recording of diagnostic data. Monitor **120** senses both cardiac signals and respiration parameters via standard cardiac leads implanted in the heart. Monitor **120** measures intra-cardiac impedance, varying both with the intrathoracic pressure fluctuations during respiration and with cardiac contraction is representative of the pulmonary activity and of the cardiac activity as substantially described in U.S. Pat. No. 5,003,976 "Cardiac and Pulmonary Physiological Analysis via Intracardiac Measurements with a

Single Sensor" to Alt. Cardiac leads **16** may consist of any typical lead configuration as is known in the art, such as, without limitation, right ventricular (RV) pacing or defibrillation leads, right atrial (RA) pacing or defibrillation leads, single pass RA/RV pacing or defibrillation leads, coronary sinus (CS) pacing or defibrillation leads, left ventricular pacing or defibrillation leads, pacing or defibrillation epicardial leads, subcutaneous defibrillation leads, unipolar or bipolar lead configurations, or any combinations of the above lead systems.

FIG. 3 is a simplified schematic view of a third embodiment core Monitor **140** implanted in a patient **10**. Monitor **140** continuously senses and monitors cardiac and respiration function of patient **10** via an electrode (not shown) located distally on sensor stub **20** which is inserted subcutaneously in the thoracic area of the patient to allow detection of neurological events and the recording of data and signals pre and post event. Stored diagnostic data is uplinked and evaluated by the patient's physician utilizing programmer **12** via a 2-way telemetry link **32**. An external patient activator **22** may optionally allow the patient **10**, or other care provider (not shown), to manually activate the recording of diagnostic data. Monitor **140** senses cardiac signals between an electrode on the distal end of the sensor stub and the monitor case as described in conjunction with the embodiment shown in FIG. 5 in U.S. Pat. No. 5,987,352 "Minimally Invasive Implantable Device for Monitoring Physiologic Events" to Klein, et al. Monitor **140** also senses respiration parameters such as respiration rate, minute ventilation and apnea via measuring and analyzing the impedance variations measured from the implanted monitor **140** case to the electrode (not shown) located distally on sensor stub lead **20** as substantially described in U.S. Pat. No. 4,567,892 "Implantable Cardiac Pacemaker" and U.S. Pat. No. 4,596,251 "Minute Ventilation Dependent Rate Responsive Pacer" both to Plicchi, et al.

FIG. 4 is a simplified schematic view of a fourth embodiment core Monitor **160** attached to a patient **10**. External patch Monitor **160** continuously senses and monitors cardiac and respiration function of patient **10** to allow detection of neurological events and the recording of data and signals pre and post event. Stored diagnostic data is uplinked and evaluated by the patient's physician utilizing programmer **12** via a 2-way telemetry link **32**. An external patient activator **22** may optionally allow the patient **10**, or other care provider (not shown), to manually activate the recording of diagnostic data. Also optionally, a button **38** on the external patch monitor **160** may be activated by the patient **10** to manually activate diagnostic data recording.

External patch Monitor **160** consists of a resilient substrate affixed to the patient's skin with the use of an adhesive which provides support for an amplifier, memory, microprocessor, receiver, transmitter and other electronic components as substantially described in U.S. Pat. No. 6,200,265 "Peripheral Memory Patch and Access Method for Use With an Implantable Medical Device" to Walsh, et al. The substrate flexes in a complimentary manner in response to a patient's body movements providing patient comfort and wearability. The low profile external patch Monitor **160** is preferably similar in size and shape to a standard bandage, and may be attached to the patient's skin in an inconspicuous location. Uplinking of stored physiologic telemetry data from the internal memory of external patch Monitor **160** may be employed to transfer information between the monitor and programmer **12**.

Full Monitor

The term "full monitor" is used to describe a monitor that is capable of monitoring the brain (such as by monitoring a brain signal such as an electroencephalogram (EEG)) and

additionally the heart or pulmonary system or both. This will allow the full monitor to collect neurological signals and at least one of the cardiovascular and respiratory signals in close proximity to neurological events detected (such as seizures) as well as notifying the patient/caregiver of a prolonged neurological event (such as status epilepticus). Cardiovascular and respiratory monitoring may occur around a neurological event (in the case of a seizure this is called peri-ictal). In distinction from the core monitor, in which patients/caregivers must notify the device that a neurological event has occurred, the full monitor device will detect the neurological event (based on the brain signal) and will automatically analyze the peri-ictal signals and initiate the loop recording. Monitoring of more than one physiologic signal allows for greater understanding of the total physiologic condition of the patient. For example, prolonged or generalized seizures put patients at higher risk for SUDEP, the EEG monitoring may be programmed to provide alerts when a neurological event has exceeded a pre-determined duration or severity.

FIG. 5 is a simplified schematic view of a full Monitor **200** implanted in a patient **10**. Monitor **200** continuously senses and monitors cardiac, brain and respiration function of patient **10** via one or more brain monitoring elements **18** and one or more cardiac monitoring elements **14** or one or more respiratory monitoring elements **15**. Brain monitoring elements **18** may be for example, one or more brain leads with one or more electrodes. Such a brain lead may be any lead capable of sensing brain activity such as EEG. For example, brain monitoring element **18** may be a deep brain lead, a cortical lead or an electrode placed on the head externally. Cardiac monitoring elements **14** may be cardiac leads or other types of sensors or electrodes capable of picking up cardiac signals. These monitoring elements allow detection of a neurological event and the recording of data and signals pre and post event. Stored diagnostic data is uplinked and evaluated by the patient's physician utilizing programmer **12** via a 2-way telemetry link **32**. An external patient activator **22** may optionally allow the patient **10**, or other care provider (not shown), to manually activate the recording of diagnostic data. An implant aid may be used with Monitor **200** to ensure a proper position and orientation during implant as described above in connection with the system of FIG. 1.

FIG. 6 is a simplified schematic view of a second embodiment of a full Monitor **220** implanted in a patient **10**. Monitor **220** continuously senses and monitors cardiac, brain and respiration function of patient **10** via cardiac lead(s) **16** and a brain lead **18** to allow detection of a neurological event and the recording of data and signals pre and post event. Stored diagnostic data is uplinked and evaluated by the patient's physician utilizing programmer **12** via a 2-way telemetry link **32**. An external patient activator **22** may optionally allow the patient **10**, or other care provider (not shown), to manually activate the recording of diagnostic data.

FIG. 7 is a simplified schematic view of a third embodiment of a full Monitor **240** implanted in a patient **10**. Monitor **240** continuously senses and monitors cardiac, brain and respiration function of patient **10** via sensor stub **20** and brain lead **18** to allow detection of a neurological event and the recording of data and signals pre and post event. Stored diagnostic data is uplinked and evaluated by the patient's physician utilizing programmer **12** via a 2-way telemetry link **32**. An external patient activator **22** may optionally allow the patient **10**, or other care provider (not shown), to manually activate the recording of diagnostic data.

FIG. 8 is a simplified schematic view of a fourth embodiment of a full Monitor **260** implanted in a patient **10**. Monitor **260** in combination with external patch **160** continuously

senses and monitors cardiac, brain and respiration function of patient **10** to allow detection of a neurological event and the recording of data and signals pre and post event. A 2-way wireless telemetry communication link **30** connects the Monitor unit **260** and external patch **160**. The wireless communication link **30** may consist of an RF link (such as described in U.S. Pat. No. 5,683,432 "Adaptive Performance-Optimizing Communication System for Communicating with an Implantable Medical Device" to Goedeke, et al), an electromagnetic/ionic transmission (such as described in U.S. Pat. No. 4,987,897 "Body Bus Medical Device Communication System" to Funke) or acoustic transmission (such as described in U.S. Pat. No. 5,113,859 "Acoustic Body Bus Medical Device Communication System" to Funke). Stored diagnostic data is uplinked and evaluated by the patient's physician utilizing programmer **12** via a 2-way telemetry link **32**. An external patient activator **22** may optionally allow the patient **10**, or other care provider (not shown), to manually activate the recording of diagnostic data. Also optionally, a button **38** on the external patch monitor **160** may be activated by the patient **10** to manually activate diagnostic data recording.

An alternative embodiment of the system of FIG. 8 consists of software "patches" or programs downloaded from a wearable patch **38** into an implanted neurostimulator, drug pump or monitor to allow research evaluation of new therapies, detection algorithms, clinical research and data gathering and the use of the patient as their own "control" by randomly downloading or enabling a new detection algorithm or therapy and gathering the resultant clinical data (as substantially described in U.S. Pat. No. 6,200,265 "Peripheral Memory Patch and Access Method for Use with an Implantable Medical Device" to Walsh, et al). The clinical and diagnostic data may be uploaded into the memory of the patch for later retrieval and review by the patient's physician or device clinical manager. This embodiment also allows the upgrading of the existing implant base with temporary new or additional therapeutic and diagnostic features.

FIG. 9 is a simplified schematic view of a fifth embodiment of a full Monitor **280** implanted in a patient **10**. Monitor **280** continuously senses and monitors cardiac, brain and respiration function of patient **10** via brain lead **18** with integrated electrode **24** to allow detection of a neurological event and the recording of data and signals pre and post event. Stored diagnostic data is uplinked and evaluated by the patient's physician utilizing programmer **12** via a 2-way telemetry link **32**. An external patient activator **22** may optionally allow the patient **10**, or other care provider (not shown), to manually activate the recording of diagnostic data. Integrated electrode **24** senses ECG signals as described above in the referenced Klein '352 patent and respiration signals as described above in the referenced Plicchi '892 and '251 patents.

FIG. 10 is a simplified schematic view of a sixth embodiment of a full Monitor **26** implanted cranially in a patient **10**. Monitor **26** continuously senses and monitors cardiac, brain and respiration function of patient **10** to allow detection of a neurological event and the recording of data and signals pre and post event. Stored diagnostic data is uplinked and evaluated by the patient's physician utilizing programmer **12** via a 2-way telemetry link **32**. An external patient activator **22** may optionally allow the patient **10**, or other care provider (not shown), to manually activate the recording of diagnostic data.

Monitor **26** may be constructed as substantially described in US Publication No. 20040176817 "Modular implantable medical device" to Wahlstrand et al. or U.S. Pat. No. 5,782,891 "Implantable Ceramic Enclosure for Pacing, Neurological and Other Medical Applications in the Human Body" to

Hassler, et al. or U.S. Pat. No. 6,427,086 "Means and Method for the Intracranial Placement of a Neurostimulator" to Fischell et al. EEG sensing is accomplished by the use of integrated electrodes in the housing of monitor **26** or, alternatively, by cranially implanted leads.

ECG sensing in the cranium may be accomplished by leadless ECG sensing as described in the above Brabec '940, Ceballos '915 and Lee '067 referenced patents. Alternatively, ECG rate and asystole may be inferred (along with a blood pressure signal) from a capacitive dynamic pressure signal (ie, dP/dt) as substantially described in U.S. Pat. No. 4,485,813 "Implantable Dynamic Pressure Transducer System" to Anderson, et al. ECG rate and asystole may be inferred by monitoring an acoustic signal (i.e., sound) as substantially described in U.S. Pat. No. 5,554,177 "Method and Apparatus to Optimize Pacing Based on Intensity of Acoustic Signal" to Kieval, et al. The sensed acoustic signal is low pass filtered to limit ECG signals to 0.5-3 Hz while filtering out speech, swallowing and chewing sounds. ECG rate and asystole may be inferred (along with a blood saturation measurement) by monitoring a reflectance oximetry signal (i.e., O.sub.2sat) as substantially described in U.S. Pat. No. 4,903,701 "Oxygen Sensing Pacemaker" to Moore, et al. ECG rate and asystole may be inferred by monitoring a blood temperature signal (i.e., dT/dt) as substantially described in U.S. Pat. No. 5,336,244 "Temperature Sensor Based Capture Detection for a Pacer" to Weijand. ECG rate and asystole may be inferred (along with an arterial flow measurement) by monitoring a blood flow signal (from an adjacent vein via impedance plethysmography, piezoelectric sensor or Doppler ultrasound) as substantially described in U.S. Pat. No. 5,409,009 "Methods for Measurement of Arterial Blood Flow" to Olson. ECG rate and asystole may be inferred (along with a blood pressure measurement) by monitoring a blood pressure signal utilizing a strain gauge substantially described in U.S. Pat. No. 5,168,759 "Strain Gauge for Medical Applications" to Bowman. ECG rate and asystole may be inferred by monitoring a blood parameter sensor (such as oxygen, pulse or flow) located on a V-shaped lead as substantially described in U.S. Pat. No. 5,354,318 "Method and Apparatus for Monitoring Brain Hemodynamics" to Taepke.

Monitor **26** may warn or alert the patient **10** via an annunciator such as buzzes, tones, beeps or spoken voice (as substantially described in U.S. Pat. No. 6,067,473 "Implantable Medical Device Using Audible Sound Communication to Provide Warnings" to Greeninger, et al.) via a piezo-electric transducer incorporated in the housing of monitor **26** and transmitting sound to the patient's **10** inner ear.

Monitor+Treatment (Brain)

FIG. **11** is a simplified schematic view of a full Monitor/Brain Therapy unit **300** implanted in a patient **10**. Monitor/Brain Therapy unit **300** continuously senses and monitors cardiac, brain and respiration function of patient **10** via monitoring elements **14** and **18**. Such monitoring elements may be subcutaneous electrodes and a brain lead to allow detection of a neurological event, the recording of data and signals pre and post event, and the delivery of therapy via brain lead. Stored diagnostic data is uplinked and evaluated by the patient's physician utilizing programmer **12** via a 2-way telemetry link **32**. An external patient activator **22** may optionally allow the patient **10**, or other care provider (not shown), to manually activate the recording of diagnostic data and delivery of therapy. An implant aid may be used with Monitor/Brain Therapy device **300** to assist with positioning and orientation during implant as described above in connection with the system of FIG. **1**.

FIG. **12A** is a simplified schematic view of a second embodiment of a full Monitor/Brain Therapy unit **320** implanted in a patient **10**. Monitor/Brain Therapy unit **320** continuously senses and monitors cardiac, brain and respiration function of patient **10** via cardiac lead(s) **16** and a brain lead **18** to allow detection of a neurological event, the recording of data and signals pre and post event, and the delivery of therapy via brain lead **18**. Stored diagnostic data is uplinked and evaluated by the patient's physician utilizing programmer **12** via a 2-way telemetry link **32**. An external patient activator **22** may optionally allow the patient **10**, or other care provider (not shown), to manually activate the recording of diagnostic data and delivery of therapy.

FIG. **12B** is a simplified schematic view of a third embodiment of a full Monitor/Brain Therapy system consisting of a thoracically implanted Monitor unit **321** in combination with a cranially implanted brain Monitor/Therapy unit **26**. Monitor unit **321** continuously senses and monitors the cardiac and respiration function of patient **10** via cardiac lead(s) **16** to allow detection of a neurological event, the recording of data and signals pre and post event, and the delivery of therapy via Monitor/Therapy unit **26**. A 2-way wireless telemetry communication link **30** connects the Monitor/Therapy unit **26** and cardiac/respiration monitor **321**. The wireless communication link **30** may consist of an RF link (such as described in U.S. Pat. No. 5,683,432 "Adaptive Performance-Optimizing Communication System for Communicating with an Implantable Medical Device" to Goedeke, et al), an electromagnetic/ionic transmission (such as described in U.S. Pat. No. 4,987,897 "Body Bus Medical Device Communication System" to Funke) or acoustic transmission (such as described in U.S. Pat. No. 5,113,859 "Acoustic Body Bus Medical Device Communication System" to Funke). Monitor **26** may be constructed as substantially described in US Publication No. 20040176817 "Modular implantable medical device" to Wahlstrand et al. or U.S. Pat. No. 5,782,891 "Implantable Ceramic Enclosure for Pacing, Neurological and Other Medical Applications in the Human Body" to Hassler, et al or U.S. Pat. No. 6,427,086 "Means and Method for the Intracranial Placement of a Neurostimulator" to Fischell, et al. EEG sensing and brain stimulation is accomplished by the use of integrated electrodes in the housing of Monitor/Therapy unit **26** or, alternatively, by cranially implanted leads (not shown in FIG. **12B**). Stored diagnostic data is uplinked and evaluated by the patient's physician utilizing programmer **12** via a 2-way telemetry link **32**. An external patient activator **22** may optionally allow the patient **10**, or other care provider (not shown), to manually activate the recording of diagnostic data and delivery of therapy.

FIG. **13** is a simplified schematic view of a fourth embodiment of a full Monitor/Brain Therapy unit **340** implanted in a patient **10**. Monitor/Brain Therapy unit **340** continuously senses and monitors cardiac, brain and respiration function of patient **10** via sensor stub **20** and a brain lead **18** to allow detection of a neurological event such as a neurological event, the recording of data and signals pre and post event, and the delivery of therapy via brain lead **18**. Stored diagnostic data is uplinked and evaluated by the patient's physician utilizing programmer **12** via a 2-way telemetry link **32**. An external patient activator **22** may optionally allow the patient **10**, or other care provider (not shown), to manually activate the recording of diagnostic data and delivery of therapy.

FIG. **14** is a simplified schematic view of a fifth embodiment of a full Monitor/Brain Therapy unit **360** implanted in a patient **10**. Monitor/Brain Therapy unit **360** in combination with external patch **160** continuously senses and monitors cardiac, brain and respiration function of patient **10** via exter-

nal patch **160** and a brain lead **18** to allow detection of neurological events, the recording of data and signals pre and post event, and the delivery of therapy via brain lead **18**. A 2-way wireless telemetry communication link **30** connects the Monitor/Brain Therapy unit **360** and external patch **160**. The wireless communication link **30** may consist of an RF link (such as described in U.S. Pat. No. 5,683,432 "Adaptive Performance-Optimizing Communication System for Communicating with an Implantable Medical Device" to Goedeke, et al), an electromagnetic/ionic transmission (such as described in U.S. Pat. No. 4,987,897 "Body Bus Medical Device Communication System" to Funke) or acoustic transmission (such as described in U.S. Pat. No. 5,113,859 "Acoustic Body Bus Medical Device Communication System" to Funke). Stored diagnostic data is uplinked and evaluated by the patient's physician utilizing programmer **12** via a 2-way telemetry link **32**. An external patient activator **22** may optionally allow the patient **10**, or other care provider (not shown), to manually activate the recording of diagnostic data and delivery of therapy. Also optionally, a button **38** on the external patch monitor **160** may be activated by the patient **10** to manually activate diagnostic data recording and therapy delivery.

FIG. **15** is a simplified schematic view of a sixth embodiment of a full Monitor/Brain Therapy unit **380** implanted in a patient **10**. Monitor/Brain Therapy unit **380** continuously senses and monitors cardiac, brain and respiration function of patient **10** via a brain lead **18** with integrated electrode **24** to allow detection of neurological events, the recording of data and signals pre and post event, and the delivery of therapy via brain lead **18**. Stored diagnostic data is uplinked and evaluated by the patient's physician utilizing programmer **12** via a 2-way telemetry link **32**. An external patient activator **22** may optionally allow the patient **10**, or other care provider (not shown), to manually activate the recording of diagnostic data and delivery of therapy. Integrated electrode **24** senses ECG signals as described above in the referenced Klein '352 patent and respiration signals as described above in the referenced Plicchi '892 and '251 patents.

FIG. **20** is a simplified schematic view of a seventh embodiment of a full Monitor/Brain Therapy unit **26** implanted cranially in a patient **10**. Monitor/Brain Therapy unit **26** in combination with leadless Monitor **400** continuously senses and monitors cardiac, brain and respiration function of patient **10** to allow detection of neurological events, the recording of data and signals pre and post event, and the delivery of therapy via brain lead **18**. Stored diagnostic data is uplinked and evaluated by the patient's physician utilizing programmer **12** via a 2-way telemetry link **32**. An external patient activator **22** may optionally allow the patient **10**, or other care provider (not shown), to manually activate the recording of diagnostic data and delivery of therapy. A 2-way wireless telemetry communication link **30** connects the Monitor/Therapy unit **26** and leadless Monitor **400**. The wireless communication link **30** may consist of an RF link (such as described in U.S. Pat. No. 5,683,432 "Adaptive Performance-Optimizing Communication System for Communicating with an Implantable Medical Device" to Goedeke, et al), an electromagnetic/ionic transmission (such as described in U.S. Pat. No. 4,987,897 "Body Bus Medical Device Communication System" to Funke) or acoustic transmission (such as described in U.S. Pat. No. 5,113,859 "Acoustic Body Bus Medical Device Communication System" to Funke). An implant aid may be used with Monitor device **400** to ensure a proper position and orientation during implant as described above in connection with the system of FIG. **1**. Monitor **26** may be constructed as substantially described in US Publication No. 20040176817 "Modular implantable medical

device" to Wahlstrand et al. or U.S. Pat. No. 5,782,891 "Implantable Ceramic Enclosure for Pacing, Neurological and Other Medical Applications in the Human Body" to Hasler, et al or U.S. Pat. No. 6,427,086 "Means and Method for the Intracranial Placement of a Neurostimulator" to Fischell. et al. EEG sensing is accomplished by the use of integrated electrodes in the housing of monitor **26** or, alternatively, by cranially implanted leads.

Monitor **26** may warn/alert the patient **10** via an annunciator such as, but not limited to, buzzes, tones, beeps or spoken voice (as substantially described in U.S. Pat. No. 6,067,473 "Implantable Medical Device Using Audible Sound Communication to Provide Warnings" to Greeninger, et al.) via a piezo-electric transducer incorporated in the housing of monitor **26** and transmitting sound to the patient's **10** inner ear.

FIG. **21** is a simplified schematic view of an eighth embodiment of a full Monitor/Brain Therapy unit **420** implanted cranially in a patient **10**. Monitor/Brain Therapy unit **400** in combination with external patch core monitor **160** continuously senses and monitors cardiac, brain and respiration function of patient **10** to allow detection of neurological events, the recording of data and signals pre and post event, and the delivery of therapy via brain lead **18**. Stored diagnostic data is uplinked and evaluated by the patient's physician utilizing programmer **12** via a 2-way telemetry link **32**. An external patient activator **22** may optionally allow the patient **10**, or other care provider (not shown), to manually activate the recording of diagnostic data and delivery of therapy. A 2-way wireless telemetry communication link **30** connects the Monitor/Therapy unit **26** and leadless Monitor **400**. The wireless communication link **30** may consist of an RF link (such as described in U.S. Pat. No. 5,683,432 "Adaptive Performance-Optimizing Communication System for Communicating with an Implantable Medical Device" to Goedeke, et al), an electromagnetic/ionic transmission (such as described in U.S. Pat. No. 4,987,897 "Body Bus Medical Device Communication System" to Funke) or acoustic transmission (such as described in U.S. Pat. No. 5,113,859 "Acoustic Body Bus Medical Device Communication System" to Funke). Monitor **26** may be constructed as substantially described in US Publication No. 20040176817 "Modular implantable medical device" to Wahlstrand et al. or U.S. Pat. No. 5,782,891 "Implantable Ceramic Enclosure for Pacing, Neurological and Other Medical Applications in the Human Body" to Hasler, et al or U.S. Pat. No. 6,427,086 "Means and Method for the Intracranial Placement of a Neurostimulator" to Fischell. et al. EEG sensing is accomplished by the use of integrated electrodes in the housing of monitor **26** or, alternatively, by cranially implanted leads.

Monitor **26** may warn/alert the patient **10** via an annunciator such as, but not limited to, buzzes, tones, beeps or spoken voice (as substantially described in U.S. Pat. No. 6,067,473 "Implantable Medical Device Using Audible Sound Communication to Provide Warnings" to Greeninger, et al.) via a piezo-electric transducer incorporated in the housing of monitor **26** and transmitting sound to the patient's **10** inner ear.

Monitor+Treatment (Brain+Respiration)

FIG. **16A** is a simplified schematic view of a full Monitor/Brain and Respiration Therapy unit **440** implanted in a patient **10**. Monitor/Brain and Respiration Therapy unit **440** continuously senses and monitors cardiac, brain and respiration function of patient **10** via cardiac lead(s) **16** and a brain lead **18** to allow detection of neurological events, the recording of data and signals pre and post event, and the delivery of therapy via brain lead **18** and phrenic nerve lead **28**. Stored diagnostic

data is uplinked and evaluated by the patient's physician utilizing programmer 12 via a 2-way telemetry link 32. An external patient activator 22 may optionally allow the patient 10, or other care provider (not shown), to manually activate the recording of diagnostic data and delivery of therapy. Optionally, lead 28 may connect to the diaphragm to provide direct diaphragmatic stimulation.

FIG. 16B is a simplified schematic view of a second embodiment of a full Monitor/Brain and Respiration Therapy system consisting of a thoracically implanted Monitor/Respiration Therapy unit 441 in combination with a cranially implanted brain Monitor/Therapy unit 26. Monitor unit 441 continuously senses and monitors the cardiac and respiration function of patient 10 via cardiac lead(s) 16 to allow detection of neurological events, the recording of data and signals pre and post event, the delivery of respiration therapy via phrenic nerve lead 28 and the delivery of brain stimulation via Monitor/Therapy unit 26. A 2-way wireless telemetry communication link 30 connects the Monitor/Therapy unit 26 and cardiac/respiration monitor and respiration therapy unit 441. The wireless communication link 30 may consist of an RF link (such as described in U.S. Pat. No. 5,683,432 "Adaptive Performance-Optimizing Communication System for Communicating with an Implantable Medical Device" to Goedeke, et al), an electromagnetic/ionic transmission (such as described in U.S. Pat. No. 4,987,897 "Body Bus Medical Device Communication System" to Funke) or acoustic transmission (such as described in U.S. Pat. No. 5,113,859 "Acoustic Body Bus Medical Device Communication System" to Funke). Monitor 26 may be constructed as substantially described in US Publication No. 20040176817 "Modular implantable medical device" to Wahlstrand et al. or U.S. Pat. No. 5,782,891 "Implantable Ceramic Enclosure for Pacing, Neurological and Other Medical Applications in the Human Body" to Hassler, et al or U.S. Pat. No. 6,427,086 "Means and Method for the Intracranial Placement of a Neurostimulator" to Fischell, et al. EEG sensing and brain stimulation is accomplished by the use of integrated electrodes in the housing of monitor 26 or, alternatively, by cranially implanted leads (not shown in FIG. 16B). Stored diagnostic data is uplinked and evaluated by the patient's physician utilizing programmer 12 via a 2-way telemetry link 32. An external patient activator 22 may optionally allow the patient 10, or other care provider (not shown), to manually activate the recording of diagnostic data and delivery of therapy. Optionally, lead 28 may connect to the diaphragm to provide direct diaphragmatic stimulation.

FIG. 17 is a simplified schematic view of a third embodiment of a full Monitor/Brain and Respiration Therapy unit 460 implanted in a patient 10. Monitor/Brain and Respiration Therapy unit 460 continuously senses and monitors cardiac, brain and respiration function of patient 10 via sensor stub 20 and a brain lead 18 to allow detection of neurological events, the recording of data and signals pre and post event, and the delivery of therapy via brain lead 18 and phrenic nerve lead 28. Stored diagnostic data is uplinked and evaluated by the patient's physician utilizing programmer 12 via a 2-way telemetry link 32. An external patient activator 22 may optionally allow the patient 10, or other care provider (not shown), to manually activate the recording of diagnostic data and delivery of therapy. Optionally, lead 28 may connect to the diaphragm to provide direct diaphragmatic stimulation.

FIG. 18 is a simplified schematic view of a fourth embodiment of a full Monitor/Brain and Respiration Therapy unit 480 implanted in a patient 10. Monitor/Brain and Respiration Therapy unit 480 continuously senses and monitors cardiac, brain and respiration function of patient 10 via a brain lead 18

with integrated electrode 24 to allow detection of neurological events, the recording of data and signals pre and post event, and the delivery of therapy via brain lead 18 and phrenic nerve lead 28. Stored diagnostic data is uplinked and evaluated by the patient's physician utilizing programmer 12 via a 2 way telemetry link 32. An external patient activator 22 may optionally allow the patient 10, or other care provider (not shown), to manually activate the recording of diagnostic data and delivery of therapy. Optionally, lead 28 may connect to the diaphragm to provide direct diaphragmatic stimulation. Integrated electrode 24 senses ECG signals as described above in the referenced Klein '352 patent and respiration signals as described above in the referenced Plicchi '892 and '251 patents.

FIG. 19 is a simplified schematic view of a fifth embodiment of a full Monitor/Brain and Respiration Therapy unit 500 implanted in a patient 10. Monitor/Brain and Respiration Therapy unit 500 continuously senses and monitors cardiac, brain and respiration function of patient 10 via brain lead 18 and respiration lead 28 with integrated electrode 24 to allow detection of neurological events, the recording of data and signals pre and post event, and the delivery of therapy via brain lead 18 and phrenic nerve lead 28. Stored diagnostic data is uplinked and evaluated by the patient's physician utilizing programmer 12 via a 2-way telemetry link 32. An external patient activator 22 may optionally allow the patient 10, or other care provider (not shown), to manually activate the recording of diagnostic data and delivery of therapy. Optionally, lead 28 may connect to the diaphragm to provide direct diaphragmatic stimulation. Integrated electrode 24 senses ECG signals as described above in the referenced Klein '352 patent and respiration signals as described above in the referenced Plicchi '892 and '251 patents.

Monitor+Treatment (Brain+Cardiac)

FIG. 24A is a simplified schematic view of a full Monitor/Brain and Cardiac Therapy unit 520 implanted in a patient 10. Monitor/Brain and Cardiac Therapy unit 520 continuously senses and monitors cardiac, brain and respiration function of patient 10 via cardiac lead(s) 16 and a brain lead 18 to allow detection of neurological events, the recording of data and signals pre and post event, and the delivery of therapy via brain lead 18 and cardiac lead(s) 16. Stored diagnostic data is uplinked and evaluated by the patient's physician utilizing programmer 12 via a 2-way telemetry link 32. An external patient activator 22 may optionally allow the patient 10, or other care provider (not shown), to manually activate the recording of diagnostic data and delivery of therapy.

FIG. 24B is a simplified schematic view of a second embodiment of a full Monitor/Brain and Cardiac Therapy system consisting of a thoracically implanted Monitor/Therapy unit 521 implanted in patient 10 in combination with a cranially implanted brain Monitor/Therapy unit 26. Monitor/Therapy unit 521 continuously senses and monitors the cardiac and respiration function of patient 10 via cardiac lead(s) 16 to allow detection of neurological events, the recording of data and signals pre and post event, the delivery of cardiac therapy via Monitor/Therapy unit 521 and the delivery of therapy via Monitor/Therapy unit 26. A 2-way wireless telemetry communication link 30 connects the Monitor/Therapy unit 26 and cardiac/respiration Monitor/Therapy unit 521. The wireless communication link 30 may consist of an RF link (such as described in U.S. Pat. No. 5,683,432 "Adaptive Performance-Optimizing Communication System for Communicating with an Implantable Medical Device" to Goedeke, et al), an electromagnetic/ionic transmission (such as described in U.S. Pat. No. 4,987,897 "Body Bus Medical Device Communication System" to Funke) or

acoustic transmission (such as described in U.S. Pat. No. 5,113,859 "Acoustic Body Bus Medical Device Communication System" to Funke). Monitor **26** may be constructed as substantially described in US Publication No. 20040176817 "Modular implantable medical device" to Wahlstrand et al. or U.S. Pat. No. 5,782,891 "Implantable Ceramic Enclosure for Pacing, Neurological and Other Medical Applications in the Human Body" to Hassler, et al or U.S. Pat. No. 6,427,086 "Means and Method for the Intracranial Placement of a Neurostimulator" to Fischell, et al. EEG sensing and brain stimulation is accomplished by the use of integrated electrodes in the housing of monitor **26** or, alternatively, by cranially implanted leads (not shown in FIG. 24B). Stored diagnostic data is uplinked and evaluated by the patient's physician utilizing programmer **12** via a 2-way telemetry link **32**. An external patient activator **22** may optionally allow the patient **10**, or other care provider (not shown), to manually activate the recording of diagnostic data and delivery of therapy.

FIG. 22 is a simplified schematic view of a third embodiment of a full Monitor/Brain and Cardiac Therapy unit **540** implanted cranially in a patient **10**. Monitor/Brain and Cardiac Therapy unit **540** in combination with external patient worn vest **34** continuously senses and monitors cardiac, brain and respiration function of patient **10** to allow detection of neurological events, the recording of data and signals pre and post event, and the delivery of therapy via brain lead **18** and vest **34**. Stored diagnostic data is uplinked and evaluated by the patient's physician utilizing programmer **12** via a 2-way telemetry link **32**. An external patient activator **22** may optionally allow the patient **10**, or other care provider (not shown), to manually activate the recording of diagnostic data and delivery of therapy. A 2-way wireless telemetry communication link **30** connects the monitor/therapy unit **540** and patient worn vest **34**. The wireless communication link **30** may consist of an RF link (such as described in U.S. Pat. No. 5,683,432 "Adaptive Performance-Optimizing Communication System for Communicating with an Implantable Medical Device" to Goedeke, et al), an electromagnetic/ionic transmission (such as described in U.S. Pat. No. 4,987,897 "Body Bus Medical Device Communication System" to Funke) or acoustic transmission (such as described in U.S. Pat. No. 5,113,859 "Acoustic Body Bus Medical Device Communication System" to Funke).

Monitor/Therapy unit **540** may be constructed as substantially described in US Publication No. 20040176817 "Modular implantable medical device" to Wahlstrand et al. or U.S. Pat. No. 5,782,891 "Implantable Ceramic Enclosure for Pacing, Neurological and Other Medical Applications in the Human Body" to Hassler, et al or U.S. Pat. No. 6,427,086 "Means and Method for the Intracranial Placement of a Neurostimulator" to Fischell, et al. EEG sensing is accomplished by the use of integrated electrodes in the housing of Monitor/Therapy unit **540** or, alternatively, by cranially implanted leads.

Monitor/Therapy unit **540** may warn/alert the patient **10** via an annunciator such as, but not limited to, buzzes, tones, beeps or spoken voice (as substantially described in U.S. Pat. No. 6,067,473 "Implantable Medical Device Using Audible Sound Communication to Provide Warnings" to Greeninger, et al.) via a piezo-electric transducer incorporated in the housing of monitor **26** and transmitting sound to the patient's **10** inner ear.

FIG. 23 is a simplified schematic view of a fourth embodiment of a full Monitor/Brain and Cardiac Therapy unit **560** implanted cranially in a patient **10**. Monitor/Brain and Cardiac Therapy unit **560** in combination with leadless defibrillator **36** continuously senses and monitors cardiac, brain and

respiration function of patient **10** to allow detection of neurological events, the recording of data and signals pre and post event, and the delivery of therapy via brain lead **18** and defibrillator **36**. Stored diagnostic data is uplinked and evaluated by the patient's physician utilizing programmer **12** via a 2-way telemetry link **32**. An external patient activator **22** may optionally allow the patient **10**, or other care provider (not shown), to manually activate the recording of diagnostic data and delivery of therapy. A 2-way wireless telemetry communication link **30** connects the monitor/therapy unit **560** and leadless defibrillator **36**. The wireless communication link **30** may consist of an RF link (such as described in U.S. Pat. No. 5,683,432 "Adaptive Performance-Optimizing Communication System for Communicating with an Implantable Medical Device" to Goedeke, et al), an electromagnetic/ionic transmission (such as described in U.S. Pat. No. 4,987,897 "Body Bus Medical Device Communication System" to Funke) or acoustic transmission (such as described in U.S. Pat. No. 5,113,859 "Acoustic Body Bus Medical Device Communication System" to Funke).

Monitor/Therapy unit **560** may be constructed as substantially described in US Publication No. 20040176817 "Modular implantable medical device" to Wahlstrand et al. or U.S. Pat. No. 5,782,891 "Implantable Ceramic Enclosure for Pacing, Neurological and Other Medical Applications in the Human Body" to Hassler, et al or U.S. Pat. No. 6,427,086 "Means and Method for the Intracranial Placement of a Neurostimulator" to Fischell, et al. EEG sensing is accomplished by the use of integrated electrodes in the housing of Monitor/Therapy unit **560** or, alternatively, by cranially implanted leads.

Monitor/Therapy unit **560** may warn/alert the patient **10** via an annunciator such as, but not limited to, buzzes, tones, beeps or spoken voice (as substantially described in U.S. Pat. No. 6,067,473 "Implantable Medical Device Using Audible Sound Communication to Provide Warnings" to Greeninger, et al.) via a piezo-electric transducer incorporated in the housing of Monitor/Therapy unit **560** and transmitting sound to the patient's **10** inner ear.

Monitor+Treatment (Brain+Respiration+Cardiac)

FIG. 25A is a simplified schematic view of a full Monitor/Brain, Respiration and Cardiac Therapy unit **580** implanted in a patient **10**. Monitor/Brain, Respiration and Cardiac Therapy unit **580** continuously senses and monitors cardiac, brain and respiration function of patient **10** via cardiac lead(s) **16** and a brain lead **18** to allow detection of neurological events, the recording of data and signals pre and post event, and the delivery of therapy via brain lead **18**, cardiac lead(s) **16** and phrenic nerve lead **28**. Stored diagnostic data is uplinked and evaluated by the patient's physician utilizing programmer **12** via a 2-way telemetry link **32**. An external patient activator **22** may optionally allow the patient **10**, or other care provider (not shown), to manually activate the recording of diagnostic data and delivery of therapy. Optionally, lead **28** may connect to the diaphragm to provide direct diaphragmatic stimulation.

FIG. 25B is a simplified schematic view of a second embodiment of a full Monitor/Brain, Respiration and Cardiac Therapy system consisting of a thoracically implanted Monitor/Respiration Therapy unit **581** in combination with a cranially implanted brain Monitor/Therapy unit **26**. Monitor/Therapy unit **581** continuously senses and monitors the cardiac and respiration function of patient **10** via cardiac lead(s) **16** to allow detection of neurological events, the recording of data and signals pre and post event, the delivery of respiration therapy via phrenic nerve lead **28** and the delivery of brain stimulation via Monitor/Therapy unit **26**. A 2-way wireless telemetry communication link **30** connects

the Monitor/Therapy unit **26** and cardiac/respiration monitor/therapy unit **581**. The wireless communication link **30** may consist of an RF link (such as described in U.S. Pat. No. 5,683,432 "Adaptive Performance-Optimizing Communication System for Communicating with an Implantable Medical Device" to Goedeke, et al), an electromagnetic/ionic transmission (such as described in U.S. Pat. No. 4,987,897 "Body Bus Medical Device Communication System" to Funke) or acoustic transmission (such as described in U.S. Pat. No. 5,113,859 "Acoustic Body Bus Medical Device Communication System" to Funke). Monitor **26** may be constructed as substantially described in US Publication No. 20040176817 "Modular implantable medical device" to Wahlstrand et al. or U.S. Pat. No. 5,782,891 "Implantable Ceramic Enclosure for Pacing, Neurological and Other Medical Applications in the Human Body" to Hassler, et al or U.S. Pat. No. 6,427,086 "Means and Method for the Intracranial Placement of a Neurostimulator" to Fischell, et al. EEG sensing and brain stimulation is accomplished by the use of integrated electrodes in the housing of monitor **26** or, alternatively, by cranially implanted leads (not shown in FIG. **25B**). Stored diagnostic data is uplinked and evaluated by the patient's physician utilizing programmer **12** via a 2-way telemetry link **32**. An external patient activator **22** may optionally allow the patient **10**, or other care provider (not shown), to manually activate the recording of diagnostic data and delivery of therapy. Optionally, lead **28** may connect to the diaphragm to provide direct diaphragmatic stimulation.

Core Monitor Design

Turning now to FIG. **26**, there is shown a block diagram of the electronic circuitry that makes up core Monitor **100** (FIG. **1**) in accordance with one embodiment of the invention. As can be seen from FIG. **26**, Monitor **100** comprises a primary control circuit **720**. Much of the circuitry associated with primary control circuit **720** is of conventional design, in accordance, for example, with what is disclosed in U.S. Pat. No. 5,052,388 to Sivula et al, entitled "Method and Apparatus for Implementing Activity Sensing in a Pulse Generator." To the extent that certain components of Monitor **100** are purely conventional in their design and operation, such components will not be described herein in detail, as it is believed that design and implementation of such components would be a matter of routine to those of ordinary skill in the art. For example, primary control circuit **720** in FIG. **26** includes sense amplifier circuitry **724**, a crystal clock **728**, a random-access memory and read-only memory (RAM/ROM) unit **730**, a central processing unit (CPU) **732**, a MV Processor circuit **738** and a telemetry circuit **734**, all of which are well-known in the art.

Monitor **100** preferably includes internal telemetry circuit **734** so that it is capable of being programmed by means of external programmer/control unit **12** via a 2-way telemetry link **32** (shown in FIG. **1**). Programmers and telemetry systems suitable for use in the practice of the present invention have been well known for many years. Known programmers typically communicate with an implanted device via a bi-directional radio-frequency telemetry link, so that the programmer can transmit control commands and operational parameter values to be received by the implanted device, and so that the implanted device can communicate diagnostic and operational data to the programmer. Programmers believed to be suitable for the purposes of practicing the present invention include the Models 9790 and CareLink® programmers, commercially available from Medtronic, Inc., Minneapolis, Minn. Various telemetry systems for providing the necessary communications channels between an external programming unit and an implanted device have been developed and are

well known in the art. Telemetry systems believed to be suitable for the purposes of practicing the present invention are disclosed, for example, in the following U.S. Pat. No. 5,127,404 to Wyborny et al. entitled "Telemetry Format for Implanted Medical Device"; U.S. Pat. No. 4,374,382 to Markowitz entitled "Marker Channel Telemetry System for a Medical Device"; and U.S. Pat. No. 4,556,063 to Thompson et al. entitled "Telemetry System for a Medical Device".

Typically, telemetry systems such as those described in the above referenced patents are employed in conjunction with an external programming/processing unit. Most commonly, telemetry systems for implantable medical devices employ a radio-frequency (RF) transmitter and receiver in the device, and a corresponding RF transmitter and receiver in the external programming unit. Within the implantable device, the transmitter and receiver utilize a wire coil as an antenna for receiving downlink telemetry signals and for radiating RF signals for uplink telemetry. The system is modeled as an air-core coupled transformer. An example of such a telemetry system is shown in the above-referenced Thompson et al. '063 patent.

In order to communicate digital data using RF telemetry, a digital encoding scheme such as is described in the above-reference Wyborny et al. '404 patent can be used. In particular, for downlink telemetry a pulse interval modulation scheme may be employed, wherein the external programmer transmits a series of short RF "bursts" or pulses in which the interval between successive pulses (e.g., the interval from the trailing edge of one pulse to the trailing edge of the next) is modulated according to the data to be transmitted. For example, a shorter interval may encode a digital "0" bit while a longer interval encodes a digital "1" bit.

For uplink telemetry, a pulse position modulation scheme may be employed to encode uplink telemetry data. For pulse position modulation, a plurality of time slots are defined in a data frame, and the presence or absence of pulses transmitted during each time slot encodes the data. For example, a sixteen-position data frame may be defined, wherein a pulse in one of the time slots represents a unique four-bit portion of data.

As depicted in FIG. **26**, programming units such as the above-referenced Medtronic Models 9790 and CareLink® programmers typically interface with the implanted device through the use of a programming head or programming paddle, a handheld unit adapted to be placed on the patient's body over the implant site of the patient's implanted device. A magnet in the programming head effects reed switch closure in the implanted device to initiate a telemetry session. Thereafter, uplink and downlink communication takes place between the implanted device's transmitter and receiver and a receiver and transmitter disposed within the programming head.

As previously noted, primary control circuit **720** includes central processing unit **732** which may be an off-the-shelf programmable microprocessor or microcontroller, but in the presently preferred embodiment of the invention is a custom integrated circuit. Although specific connections between CPU **732** and other components of primary control circuit **720** are not shown in FIG. **26**, it will be apparent to those of ordinary skill in the art that CPU **732** functions to control the timed operation of sense amplifier circuit **724** under control of programming stored in RAM/ROM unit **730**. It is believed that those of ordinary skill in the art will be familiar with such an operative arrangement.

With continued reference to FIG. **26**, crystal oscillator circuit **728**, in the presently preferred embodiment a 32,768-

Hz crystal controlled oscillator, provides main timing clock signals to primary control circuit 720.

It is to be understood that the various components of monitor 100 depicted in FIG. 26 are powered by means of a battery (not shown), which is contained within the hermetic enclosure of monitor 100, in accordance with common practice in the art. For the sake of clarity in the figures, the battery and the connections between it and the other components of monitor 100 are not shown.

With continued reference to FIG. 26, sense amplifier 724 is coupled to monitoring elements 14 such as subcutaneous electrodes. Cardiac intrinsic signals are sensed by sense amplifier 724 as substantially described in U.S. Pat. No. 6,505,067 "System and Method for Deriving a Virtual ECG or EGM Signal" to Lee, et al. Further processing by CPU 732 allows the detection of cardiac electrical characteristics/anomalies (e.g., heart rate, heart rate variability, arrhythmias, cardiac arrest, sinus arrest and sinus tachycardia) that would be a matter of routine to those of ordinary skill in the art.

Further processing of the cardiac signal amplitudes may be used to detect respiration characteristics/anomalies (e.g., respiration rate, tidal volume, minute ventilation, and apnea) in MV Processor 738. FIG. 27 shows the intracardiac signals 770 presented to sense amplifier 724 from monitoring elements 14. Note the amplitude variation of cardiac signals caused by the change in thoracic cavity pressure due to respiration (ie, inspiration and expiration). By low pass filtering the cardiac signals 770, a signal representing minute ventilation may be obtained as depicted in waveform 772 (FIG. 27). This respiration signal may further be examined to detect respiration rate and reduced or absence of inspiration and expiration (central apnea) by CPU 732 and software resident in RAM/ROM 730.

Upon detection of either a cardiac or respiration anomaly, CPU 732, under control of computer executable instruction in firmware resident in RAM/ROM 730, will initiate recording of the appropriate diagnostic information into RAM of RAM/ROM 730, initiate a warning or alert to the patient, patient caregiver, or remote monitoring location. See flow diagram and description as described below in association with FIG. 31.

Turning now to FIG. 28, there is shown a block diagram of the electronic circuitry that makes up core Monitor 120 (FIG. 2) in accordance with another disclosed embodiment of the invention. As can be seen from FIG. 28, Monitor 120 comprises a primary control circuit 720 and a minute ventilation circuit 722. Much of the circuitry associated with primary control circuit 720 is of conventional design, in accordance, for example, with what is disclosed in U.S. Pat. No. 5,052,388 to Sivula et al, entitled "Method and Apparatus for Implementing Activity Sensing in a Pulse Generator." To the extent that certain components of Monitor 120 are purely conventional in their design and operation, such components will not be described herein in detail, as it is believed that design and implementation of such components would be a matter of routine to those of ordinary skill in the art. For example, primary control circuit 720 in FIG. 28 includes sense amplifier circuitry 724, a crystal clock 728, a random-access memory and read-only memory (RAM/ROM) unit 730, a central processing unit (CPU) 732, and a telemetry circuit 734, all of which are well-known in the art.

Monitor 120 preferably includes internal telemetry circuit 734 so that it is capable of being programmed by means of external programmer/control unit 12 via a 2-way telemetry link 32 (shown in FIG. 2). Programmers and telemetry systems suitable for use in the practice of the present invention have been well known for many years. Known programmers

typically communicate with an implanted device via a bi-directional radio-frequency telemetry link, so that the programmer can transmit control commands and operational parameter values to be received by the implanted device, and so that the implanted device can communicate diagnostic and operational data to the programmer. Programmers believed to be suitable for the purposes of practicing the present invention include the Models 9790 and CareLink® programmers, commercially available from Medtronic, Inc., Minneapolis, Minn. Various telemetry systems for providing the necessary communications channels between an external programming unit and an implanted device have been developed and are well known in the art. Telemetry systems believed to be suitable for the purposes of practicing the present invention are disclosed, for example, in the following U.S. patents: U.S. Pat. No. 5,127,404 to Wyborny et al. entitled "Telemetry Format for Implanted Medical Device"; U.S. Pat. No. 4,374,382 to Markowitz entitled "Marker Channel Telemetry System for a Medical Device"; and U.S. Pat. No. 4,556,063 to Thompson et al. entitled "Telemetry System for a Medical Device".

Typically, telemetry systems such as those described in the above referenced patents are employed in conjunction with an external programming/processing unit. Most commonly, telemetry systems for implantable medical devices employ a radio-frequency (RF) transmitter and receiver in the device, and a corresponding RF transmitter and receiver in the external programming unit. Within the implantable device, the transmitter and receiver utilize a wire coil as an antenna for receiving downlink telemetry signals and for radiating RF signals for uplink telemetry. The system is modeled as an air-core coupled transformer. An example of such a telemetry system is shown in the above-referenced Thompson et al. '063 patent.

In order to communicate digital data using RF telemetry, a digital encoding scheme such as is described in the above-reference Wyborny et al. '404 patent can be used. In particular, for downlink telemetry a pulse interval modulation scheme may be employed, wherein the external programmer transmits a series of short RF "bursts" or pulses in which the interval between successive pulses (e.g., the interval from the trailing edge of one pulse to the trailing edge of the next) is modulated according to the data to be transmitted. For example, a shorter interval may encode a digital "0" bit while a longer interval encodes a digital "1" bit.

For uplink telemetry, a pulse position modulation scheme may be employed to encode uplink telemetry data. For pulse position modulation, a plurality of time slots are defined in a data frame, and the presence or absence of pulses transmitted during each time slot encodes the data. For example, a sixteen-position data frame may be defined, wherein a pulse in one of the time slots represents a unique four-bit portion of data.

As depicted in FIG. 28, programming units such as the above-referenced Medtronic Models 9790 and CareLink® programmers typically interface with the implanted device through the use of a programming head or programming paddle, a handheld unit adapted to be placed on the patient's body over the implant site of the patient's implanted device. A magnet in the programming head effects reed switch closure in the implanted device to initiate a telemetry session. Thereafter, uplink and downlink communication takes place between the implanted device's transmitter and receiver and a receiver and transmitter disposed within the programming head.

With continued reference to FIG. 28, Monitor 120 is coupled to leads 16 which, when implanted, extend trans-

venously between the implant site of Monitor **120** and the patient's heart (not shown). For the sake of clarity, the connections between leads **16** and the various components of Monitor **120** are not shown in FIG. **28**, although it will be clear to those of ordinary skill in the art that, for example, leads **16** will necessarily be coupled, either directly or indirectly, to sense amplifier circuitry **724** in accordance with common practice, such that cardiac electrical signals may be conveyed to sensing circuitry **724**, via leads **16**. Cardiac leads **16** may consist of any typical lead configuration as is known in the art, such as, without limitation, right ventricular (RV) pacing or defibrillation leads, right atrial (RA) pacing or defibrillation leads, single pass RA/RV pacing or defibrillation leads, coronary sinus (CS) pacing or defibrillation leads, left ventricular pacing or defibrillation leads, pacing or defibrillation epicardial leads, subcutaneous defibrillation leads, unipolar or bipolar lead configurations, or any combinations of the above lead systems.

Sensed cardiac events are evaluated by CPU **732** and software stored in RAM/ROM unit **730**. Cardiac anomalies detected include heart rate variability, QT variability, QT.sub.C, sinus arrest, syncope, ST segment elevation and various arrhythmias such as sinus, atrial and ventricular tachycardias.

Heart rate variability may be measured by the method and apparatus as described in U.S. Pat. No. 5,749,900 "Implantable Medical Device Responsive to Heart Rate Variability Analysis" to Schroepfel, et al and U.S. Pat. No. 6,035,233 "Implantable Medical Device Responsive to Heart Rate Variability Analysis" to Schroepfel, et al. Schroepfel '900 and '233 patents describe an implantable cardiac device that computes time intervals occurring between successive heartbeats and then derive a measurement of heart rate variability from epoch data for predetermined time periods. The Schroepfel device then compares measurement of heart rate variability with previously stored heart rate variability zones, which define normal and abnormal heart rate variability.

QT variability may be measured by the method and apparatus as described in U.S. Pat. No. 5,560,368 "Methodology for Automated QT Variability Measurement" to Berger. The Berger '368 patent utilizes a "stretchable" QT interval template started at the beginning of the QRS complex and terminating on the T-wave to determine beat-to-beat variability.

QT_C may be measured by the method and apparatus as described in U.S. Pat. No. 6,721,599 "Pacemaker with Sudden Rate Drop Detection Based on QT Variations" to de Vries. The de Vries '599 patent measures QT interval real time and compares the instantaneous value to a calculated mean via a preprogrammed threshold change value.

Syncope may be detected by the methods and apparatus as described in U.S. Pat. No. 6,721,599 "Pacemaker with Sudden Rate Drop Detection Based on QT Variations" to de Vries. The de Vries '599 patent utilizes a sudden rate change and a real time QT interval measurement compared to a QT mean to detect sudden rate drop and neurally mediated syncope.

ST segment elevation (an indicator of myocardial ischemia) may be detected by the methods and apparatus as described in U.S. Pat. No. 6,128,526 "Method for Ischemia Detection and Apparatus for Using Same" to Stadler, et al and U.S. Pat. No. 6,115,630 "Determination of Orientation of Electrocardiogram Signal in Implantable Medical devices" to Stadler, et al. The Stadler '526 and '630 patents describe a system that compares a sampled data point prior to an R-wave complex peak amplitude to multiple samples post R-wave event to detect ST segment elevation.

Arrhythmias such as sinus, atrial and ventricular tachycardias may be detected by the methods and apparatus as described in U.S. Pat. No. 5,545,186 "Prioritized Rule Based Method and Apparatus for Diagnosis and Treatment of Arrhythmias" to Olson, et al. Sinus arrest may be detected by the methods and apparatus as described above in the Olson '186 patent.

In the presently disclosed embodiment, two leads are employed—an atrial lead **16A** having atrial TIP and RING electrodes, and a ventricular lead **16V** having ventricular TIP and RING electrodes. In addition, as noted above, the conductive hermetic canister of Monitor **120** serves as an indifferent electrode.

As previously noted, primary control circuit **720** includes central processing unit **732** which may be an off-the-shelf programmable microprocessor or microcontroller, but in the presently preferred embodiment of the invention is a custom integrated circuit. Although specific connections between CPU **732** and other components of primary control circuit **720** are not shown in FIG. **28**, it will be apparent to those of ordinary skill in the art that CPU **732** functions to control the timed operation of sense amplifier circuit **724** under control of programming stored in RAM/ROM unit **730**. It is believed that those of ordinary skill in the art will be familiar with such an operative arrangement.

With continued reference to FIG. **28**, crystal oscillator circuit **728**, in the presently preferred embodiment a 32,768-Hz crystal controlled oscillator, provides main timing clock signals to primary control circuit **720** and to minute ventilation circuit **722**.

It is to be understood that the various components of Monitor **120** depicted in FIG. **28** are powered by means of a battery (not shown), which is contained within the hermetic enclosure of Monitor **120**, in accordance with common practice in the art. For the sake of clarity in the figures, the battery and the connections between it and the other components of Monitor **120** are not shown.

As shown in FIG. **28**, primary control circuit **720** is coupled to minute ventilation circuit **722** by means of multiple signal lines, designated collectively as **738** in FIG. **28**. An I/O interface **740** in primary control circuit **720** and a corresponding I/O interface **742** in minute ventilation circuit **722**, coordinate the transmission of signals between the two units via control lines **738**.

Minute ventilation circuit **722** measures changes in transthoracic impedance, which has been shown to be proportional to minute ventilation. Minute ventilation is the product of tidal volume and respiration rate, and as such is a physiologic indicator of changes in metabolic demand.

Monitor **120**, in accordance with the presently disclosed embodiment of the invention, measures transthoracic impedance using a bipolar lead **16** and a tripolar measurement system. As will be hereinafter described in greater detail, minute ventilation circuit **722** delivers 30-microSec biphasic current excitation pulses of 1-mA (peak-to-peak) between a RING electrode of bipolar lead **16** and the conductive canister of monitor **120**, functioning as an indifferent electrode CASE, at a rate of 16-Hz. The resulting voltage is then measured between a TIP electrode of lead **16** and the monitor **120** CASE electrode. Such impedance measurement may be programmed to take place in either the atrium or ventricle of the patient's heart.

The impedance signal derived by minute ventilation circuit **722** has three main components: a DC offset voltage; a cardiac component resulting from the heart's function; and a respiratory component. The frequencies of the cardiac and respiratory components are assumed to be identical to their

physiologic origin. Since the respiratory component of the impedance signal derived by minute ventilation circuit 722 is of primary interest for this aspect of the present invention, the impedance signal is subjected to filtering in minute ventilation low-pass filter (MV LPF) 750 having a passband of 0.05- to 0.8-Hz (corresponding to 3-48 breaths per minute) to remove the DC and cardiac components.

With continuing reference to FIG. 28, minute ventilation circuit 722 includes a Lead Interface circuit 744 which is essentially a multiplexer that functions to selectively couple and decouple minute ventilation circuit 722 to the VTIP, VRING, ATIP, ARING, and CASE electrodes, as will be hereinafter described in greater detail.

Coupled to lead interface circuit 744 is a minute ventilation (MV) Excitation circuit 746 which functions to deliver the biphasic constant-current pulses between various combinations of lead electrodes (VTIP, VRING, etc.) for the purpose of measuring cardiac impedance. In particular, MV Excitation circuit 746 delivers biphasic excitation pulses (at a rate of 16-Hz between the ventricular ring electrode VRING and the pacemaker canister CASE) of the type delivered in accordance with the method and apparatus described in U.S. Pat. No. 5,271,395 "Method and Apparatus for Rate Responsive Cardiac Pacing" to Wahlstrand et al.

To measure cardiac impedance, minute ventilation circuit 722 monitors the voltage differential present between pairs of electrodes as excitation pulses are being injected as described above. Again, the electrodes from which voltage differentials are monitored will vary depending upon whether atrial or ventricular measurements are being made. In one embodiment of the invention, the same electrodes (i.e., VRING and CASE for ventricular, ARING and CASE for atrial) are used for both delivery of excitation pulses and voltage differential monitoring. It is contemplated, however, that the electrode combinations for excitation and measurement may be among the programmable settings, which may be altered post-implant with the programming system.

With continued reference to FIG. 28, the 16-Hz sampled output voltages from ZMEAS PREAMP circuit 748 are presented to the minute ventilation low-pass filter circuit MV LPF 750, which has a passband of 0.05-0.8 Hz in the presently preferred embodiment of the invention. Again, it is believed that the design and implementation of MV LPF circuit 750 would be a matter of routine engineering to those of ordinary skill in the art. The output from MV LPF circuit 750 is a voltage waveform whose level at any given time is directly proportional to cardiac impedance measured between the selected electrodes. Thus, the MV LPF output signal will be referred to herein as an impedance waveform. MV Calculation 752 analyzes the impedance waveform to determine/detect respiration rate, tidal volume, minute ventilation and presence of apnea.

The circuit of FIG. 28 may additionally monitor pulmonary edema by measuring the DC impedance between the distal electrodes of cardiac leads 16 and the case of core monitor 120. Measurement technique may be as substantially described in U.S. Pat. No. 6,512,949 "Implantable Medical Device for Measuring Time Varying Physiologic Conditions Especially Edema and for Responding Thereto" by Combs, et al. Upon detection of a cardiac or respiration anomaly, CPU 732, under control of firmware resident in RAM/ROM 730, will initiate recording of the appropriate diagnostic information into RAM of RAM/ROM 730, initiate a warning or alert to the patient, patient caregiver, or remote monitoring location. See flow diagram and description as described below in association with FIG. 31.

Turning now to FIG. 29, there is shown a block diagram of the electronic circuitry that makes up core Monitor 140 with sensor stub 20 (FIG. 3) in accordance with another disclosed embodiment of the invention. As can be seen from FIG. 29, Monitor 140 comprises a primary control circuit 720 and a minute ventilation circuit 722, the function of which has been described in detail above in conjunction with the system of FIG. 28. Monitor 140 measures thoracic impedance from the case of monitor 140 to the distal end of a sensor stub lead 20 (a subcutaneously implanted sensor lead) via an impedance/voltage converter using a sampling frequency of approximately 16 Hz as substantially described in U.S. Pat. No. 4,596,251 "Minute Ventilation Dependant Rate Responsive Pacer" to Plicchi, et al. Respiration parameters are evaluated by CPU 732 and software resident in RAM/ROM 730.

Cardiac signals are sensed by sense amplifier 724 and evaluated by CPU 732 and software resident in RAM/ROM 730.

Upon detection of either/or a cardiac or respiration anomaly, CPU 732, under control of firmware resident in RAM/ROM 730, will initiate recording of the appropriate diagnostic information into RAM of RAM/ROM 730, initiate a warning or alert to the patient, patient caregiver, or remote monitoring location. See flow diagram and description as described below in association with FIG. 31.

Turning now to FIG. 30, there is shown a block diagram of the electronic circuitry that makes up external patch core Monitor 160 (FIG. 4) in accordance with another disclosed embodiment of the invention. As can be seen from FIG. 30, Monitor 160 comprises a primary control circuit 720 and a minute ventilation circuit 722, the function of which has been described in detail above in conjunction with the system of FIG. 28. Intrinsic cardiac signals are sensed by electrodes 161 affixed to the patient's skin, amplified by amplifier 724 and processed by CPU 732 and software program resident in RAM/ROM 730. Cardiac anomalies are detected such as heart rate variability, QT variability, QT.sub.C, sinus arrest, and various arrhythmias such as sinus, atrial and ventricular tachycardias. Respiration sensing is accomplished by low pass filtering the sensed and amplified intrinsic cardiac signals as shown in FIG. 27. Respiration anomalies (such as reduced or cessation of tidal volume and apnea) are evaluated and detected by CPU 732 and software resident in RAM/ROM 730.

Upon detection of either/or a cardiac or respiration anomaly, CPU 732, under control of firmware resident in RAM/ROM 730, will initiate recording of the appropriate diagnostic information into RAM of RAM/ROM 730, initiate a warning or alert to the patient, patient caregiver, or remote monitoring location. See flow diagram and description as described below in association with FIG. 31.

FIG. 31 is a flow diagram 800 showing operation of a core Monitor sensing/monitoring cardiac and respiration parameters for the detection of neurological events as shown and described in embodiments in FIG. 1-4 above. Beginning at block 802, the interval between sensed cardiac signals are measured. At block 804, a rate stability measurement is made on each cardiac interval utilizing a heart rate average from block 806. At block 808, a rate stable decision is made based upon preprogrammed parameters. If YES, the flow diagram returns to the HR Measurement block 802. If NO, the rate stability information is provided to Format Diagnostic Data block 812.

At block 816, thoracic impedance is continuously measured in a sampling operation. At block 818, a MV and respiration rate calculation is made. At block 822, a pulmonary apnea decision is made based upon preprogrammed criteria.

If NO, the flow diagram returns to MV Measurement block 816. If YES, the occurrence of apnea and MV information is provided to Format Diagnostic Data block 812. Format Diagnostic Data block 812 formats the data from the cardiac and respiration monitoring channels, adds a time stamp (ie, date and time) and provides the data to block 814 where the data is stored in RAM, SRAM or MRAM memory for later retrieval by a clinician via telemetry. Optionally, block 812 may add examples of intrinsic ECG or respiration signals recorded during a sensed episode/seizure. Additionally, optionally, block 815 may initiate a warning or alert to the patient, patient caregiver, or remote monitoring location (as described in U.S. Pat. No. 5,752,976 "World Wide Patient Location and Data Telemetry System for Implantable Medical Devices" to Duffin, et al.

Full Monitor Design

FIG. 32 is a block diagram of the electronic circuitry that makes up full Monitor 200 (FIG. 5) in accordance with the presently disclosed alternative embodiment of the invention. As can be seen from FIG. 32, Monitor 200 includes a primary control circuit 720 that is described herein above in conjunction with FIG. 26. In addition the full monitor of FIG. 30 also includes an amplifier 725 to amplify and sense EEG signals from a cranially implanted lead 18. The CPU 732, in conjunction with a software program resident in RAM/ROM 730, evaluates the information from the sensed cardiac, respiration and EEG signals, detects the onset of cerebral, cardiac or respiratory anomalies, may perform one or more algorithms or methods as described in this specification (such as determination of concordance between EEG and cardiac or respiratory signals, comparison of heart rates associated with certain neurological event time periods, etc.), formats and stores diagnostic data for later retrieval by the patient's clinician and, optionally, may warn or alert the patient, patient caregiver or remote monitoring location. See flow diagram and description below in association with FIG. 37.

FIG. 33 is a block diagram of the electronic circuitry that makes up full Monitor 220 with brain 18 and cardiac 16 leads (FIG. 6) in accordance with the presently disclosed alternative embodiment of the invention. As can be seen from FIG. 33, Monitor 220 comprises a primary control circuit 720 and MV circuit 722 that are described herein above in conjunction with FIG. 28. In addition, the full Monitor 220 of FIG. 33 also includes an amplifier 725 to amplify and sense EEG signals from a cranially implanted lead 18. The CPU 732, in conjunction with a software program resident in RAM/ROM 730, integrates the information from the sensed cardiac, respiration and EEG signals, detects the onset of cerebral, cardiac or respiratory anomalies, formats and stores diagnostic data for later retrieval by the patient's clinician and, optionally, may warn or alert the patient, patient caregiver or remote monitoring location. See flow diagram and description as described below in association with FIG. 37.

FIG. 34 is a block diagram of the electronic circuitry that makes up full Monitor 240 with a brain lead 18 and sensor stub 20 (FIG. 7) in accordance with the presently disclosed alternative embodiment of the invention. As can be seen from FIG. 34, Monitor 240 comprises a primary control circuit 720 and MV circuit 722 that are described herein above in conjunction with FIG. 28. In addition, the full Monitor 240 of FIG. 34 also includes an amplifier 725 to amplify and sense EEG signals from a cranially implanted lead 18. The CPU 732, in conjunction with a software program resident in RAM/ROM 730, integrates the information from the sensed cardiac, respiration and EEG signals, detects the onset of cerebral, cardiac or respiratory anomalies, formats and stores diagnostic data for later retrieval by the patient's clinician

and, optionally, may warn or alert the patient, patient caregiver or remote monitoring location. See flow diagram and description as described below in association with FIG. 37.

FIG. 35 is a block diagram of the electronic circuitry that makes up external patch 160/full Monitor 260 with a brain lead 18 (FIG. 8) in accordance with the presently disclosed alternative embodiment of the invention. As can be seen from FIG. 35, Monitor 260 comprises a primary control circuit 720 and external patch comprises a cardiac/MV (minute ventilation) circuit 160, the functions of which have been described in detail above in conjunction with the system of FIG. 28. Intrinsic cardiac signals are sensed by electrodes affixed to the patient's skin, amplified by amplifier 724, sent to primary control circuit 720 and processed by CPU 732 and software program resident in RAM/ROM 730. Cardiac anomalies are detected such as heart rate variability, QT variability, QT.sub.C, sinus arrest, and various arrhythmias such as sinus, atrial and ventricular tachycardias. Respiration sensing is accomplished by low pass filtering the sensed and amplified intrinsic cardiac signals as shown in FIG. 27 or, alternatively, by using the MV/Z measurement circuitry of external patch 160 as described above in connection with FIG. 28. Respiration anomalies (such as reduced or cessation of tidal volume and apnea) are evaluated and detected by CPU 732 and software resident in RAM/ROM 730.

The CPU 732, in conjunction with a software program resident in RAM/ROM 730, integrates the information from the sensed cardiac, respiration and EEG signals, detects the onset of cerebral, cardiac or respiratory anomalies, formats and stores diagnostic data for later retrieval by the patient's clinician and, optionally, may warn or alert the patient, patient caregiver or remote monitoring location. See flow diagram and description as described below in association with FIG. 37.

The circuitry and function of the device 240 shown in FIG. 34 and described herein above may also be used for the full Monitor 280 with integrated electrode 24 brain lead 18 (FIG. 9). As described above in association with core Monitor 240, thoracic impedance via impedance/voltage converter as measured from the case of monitor 240 to the sensor stub 20 using a sampling frequency of approximately 16 Hz as substantially described in U.S. Pat. No. 4,596,251 "Minute Ventilation Dependant Rate Responsive Pacer" to Plicchi, et al. The Monitor 280 of this alternative embodiment utilizes the same circuitry of Monitor 240 but connected to the integrated electrode 24 on brain lead 18 instead of the sensor stub of Monitor 240.

Upon detection of either/or a cardiac or respiration anomaly, CPU 732, under control of firmware resident in RAM/ROM 730, will initiate recording of the appropriate diagnostic information into RAM of RAM/ROM 730, initiate a warning or alert to the patient, patient caregiver, or remote monitoring location. See flow diagram and description as described below in association with FIG. 37.

FIG. 36 is a block diagram of the electronic circuitry that makes up full Monitor 26 (FIG. 10) in accordance with the presently disclosed alternative embodiment of the invention. As can be seen from FIG. 32, Monitor 26 comprises a primary control circuit 720 whose function is described herein above in conjunction with FIG. 26. In addition the full Monitor 26 of FIG. 32 also includes an EEG amplifier 725 to amplify and sense EEG signals from a cranially implanted lead 18 or, alternatively, device mounted electrodes. Additionally, Sensor Interface 727 powers up, amplifies and senses the cardiac and respiratory signals from anyone or more of the following cranially implanted sensors. ECG sensing in the cranium may be accomplished by leadless ECG sensing as described in the

above Brabec '940, Ceballos '915 and Lee '067 referenced patents. Alternatively, cardiac rate and asystole may be inferred from a dP/dt signal described above in the Anderson '813 patent; an acoustic signal described above in the Kieval '177 patent; an O.sub.2sat signal described above in Moore '701 patent; a dT/dt signal described above in the Weijand '244 patent; a flow signal described above in the Olson '009; a strain gauge signal described above in the Bowman '759 patent; and a blood parameter sensor (such as oxygen, pulse or flow) located on a V-shaped lead described in the Taepke '318 patent.

The CPU 732, in conjunction with a software program resident in RAM/ROM 730, integrates the information from the sensed cardiac, respiration and EEG signals, detects the onset of cerebral, cardiac or respiratory anomalies, formats and stores diagnostic data for later retrieval by the patient's clinician and, optionally, may warn or alert the patient, patient caregiver or remote monitoring location. See flow diagram and description as described below in association with FIG. 37.

FIG. 37 is a flow diagram 840 showing operation of a full monitor sensing and monitoring cardiac, respiration and electroencephalogram parameters for the detection of neurological events as shown and described in embodiments in FIG. 5-10 above. Beginning at block 802, the interval between sensed cardiac signals are measured. At block 804, a rate stability measurement is made on each cardiac interval utilizing a heart rate average from block 806. At block 808, a rate stable decision is made based upon preprogrammed parameters. If YES, the flow diagram returns to the HR Measurement block 802. If NO, the rate stability information is provided to Format Diagnostic Data block 812.

At block 816, thoracic impedance is continuously measured in a sampling operation. At block 818, a MV and respiration rate calculation is made. At block 822, a pulmonary apnea decision is made based upon preprogrammed criteria. If NO, the flow diagram returns to MV Measurement block 816. If YES, the occurrence of apnea and MV information is provided to Format Diagnostic Data block 812.

At block 824, the electroencephalogram is sensed and measured. An EEG seizure determination is performed at block 826 as described in US published application 2004/0138536 "Clustering of Recorded Patient Neurological Activity to Determine Length of a Neurological Event" to Frei, et al incorporated herein by reference. At block 828, a seizure cluster episode is determined. If NO, the flow diagram returns to EEG Measurement block 824. If YES, the occurrence of a seizure cluster is provided to Format Diagnostic Data block 812. Format Diagnostic Data block 812 formats the data from the cardiac, respiration and EEG monitoring channels, adds a time stamp (ie, date and time) and provides the data to block 814 where the data is stored in RAM memory for later retrieval by a clinician via telemetry. Optionally, block 812 may add examples of intrinsic ECG, respiration or EEG signals recorded during a sensed episode/seizure. Additionally, optionally, block 815 may initiate a warning or alert to the patient, patient caregiver, or remote monitoring location (as described in U.S. Pat. No. 5,752,976 "World Wide Patient Location and Data Telemetry System for Implantable Medical Devices" to Duffin, et al.

FIG. 38 is a diagram 850 of exemplary physiologic data from a patient 10 with a full monitor as described herein above showing an EEG signal 852 and an ECG signal 854. A first epileptic seizure is shown at 856 (pre-ictal segment 851, ictal segment 853 and post-ictal segment 855) and detected at 864 and a second seizure is shown at 858 (pre-ictal segment 857, ictal segment 859 and post-ictal segment 861) and

detected at 866 by the full monitor. The ECG signal 854 shows a first arrhythmic episode at 860 and detected at 868 and a second arrhythmic episode at 862 and detected at 870 by the full monitor. Note that the first epileptic seizure 864 and arrhythmic episode 868 are co-incident and "matched". Note that in the diagram 850 arrhythmic episode 870 and seizure episode 866 are not co-incident and are "unmatched".

Segmenting a Cardiac Signal According to Brain Detection Results.

One embodiment of the inventive system provides an automated method of processing cardiac and/or respiratory signals in a full monitoring device (brain-heart, brain-respiratory or brain, heart and respiratory) for a nervous system disorder, to screen for cardiac abnormalities/heart rate changes and respiratory abnormalities during or within a specified time period of a neurological event. This embodiment medical device system and method may report a patient's heart or pulmonary condition for each neurological event detected in the brain signal.

In the case of epilepsy for example, changes in cardiac rate, presence of ECG abnormalities, and respiratory conditions (i.e., pulmonary edema) have been associated with seizures. Such changes in autonomic functioning have been postulated as important factors in epilepsy patients at risk of sudden death (SUDEP). The capability to monitor cardiac or respiratory function during seizures is important, as it allows for identification of co-existing autonomic conditions that may underlie SUDEP.

To determine changes in cardiovascular function that may arise from seizures, a method called ictal-ECG segmentation has been developed for use in a medical device system. Upon detection of a brain event, as defined by a seizure-detection algorithm operating on EEG/ECOG signals, a corresponding portion of data in the ECG signal is identified. The identified portion of data may be further segmented into pre-ictal, ictal and post-ictal portions. For each portion, heart rate metrics (mean, median, min, max, and standard deviation) may be calculated and ECG abnormalities (bradycardia, tachycardia, asystole, ST segment depression, QTc prolongation, etc.) may be identified. Measures of change between indices are then calculated by comparing the metrics.

Desirable features of such a seizure-heart rate monitoring system includes the ability to monitor the following: (1) HR levels (R-R intervals) associated with the time-course of the seizure, including pre-ictal, ictal, and post-ictal periods; (2) HR changes associated with the onset and termination of the seizure; (3) time taken for heart rate to return to pre-ictal levels (within specified range) following seizure termination; and (4) presence of ECG abnormalities associated with the seizure and timing of occurrence (before, during, or after ictal period).

Such a system provides useful clinical information, in the form of an ECG seizure profile, for use in diagnosing and treating co-morbid cardiac conditions. For example, a physician would be able to determine the number and percentage of detected seizures for which there was an associated serious cardiac condition (e.g., tachycardia, asystolic pause, etc.), and be provided a detailed listing/summary of heart rate indices. Subsequent assessments could then determine whether the detected events necessitate cardiac treatment.

A seizure-heart rate monitoring system that employs ictal ECG segmentation may also be used to help determine whether cardiac function is affected by the patient's seizure type. In some patients, large changes in heart rate or specific types of arrhythmias may be triggered with certain seizure types and/or their location of onset. Assessments for trend over time may be made by comparing ECG seizure metrics

between detected neurological events. For example, by plotting and comparing % change in heart rate metrics over time.

In one embodiment, the medical device system includes a brain monitoring element, a cardiac monitoring element and one or more processors in communication with the brain monitoring element and the cardiac monitoring element and configured to perform a variety of operations. The various processing steps discussed may be performed within any hardware embodiment envisioned including but not limited to the various hardware embodiments presented throughout this application. For example, all of the processing steps may be performed within one or more implantable devices. Alternatively, some processing steps may be performed within one or more implantable devices and other processing steps performed by an external component of the system such as a programmer or computer that receives the appropriate information from the implanted device(s) by telemetry.

The one or more processors perform a number of operations. In one embodiment shown in FIG. 60, the one or more processors receive a brain signal at block 1102. The brain signal comes from the brain monitoring element. For example, the brain signal could be the output of an electrode that senses an EEG signal from the brain. The one or more processors determine at least one reference point for a brain event time period at block 1104. A brain event time period is the time period over which a neurological event is detected in the brain signal. In the epilepsy example, the brain event is a seizure and the brain event time period is the period of time identified by the detection or prediction algorithm as the seizure event. An appropriate algorithm determines the reference point of the neurological event based on the analysis of the brain signal. It is noted that some neurological events may have a more abrupt onset and offset while other neurological events may have a more gradual onset and offset. A reference point for a brain event time period may be any point in time that has some relationship to a detected event in the brain signal. For example, the reference point may be the starting point or ending point of a seizure according to a seizure detection algorithm evaluating the brain signal. Alternatively, the reference point could be the midpoint of a neurological event. Alternatively, the reference point could be a maximum point in the brain event (e.g., highest reading of whatever quantitative measure being used to evaluate the brain signal). Alternatively the reference point could be some point in time before seizure onset that is identified by the detection or prediction algorithm and that has some relationship to the brain event. The one or more processors receive a cardiac signal from the cardiac monitoring element at block 1106. The one or more processors then identify a first portion of the cardiac signal based on the at least one reference point at block 1108. Identifying a portion of a cardiac signal involves determining a beginning and an end of the portion. Some examples of a portion of the cardiac signal include pre-event portion, event portion and post-event portion. A pre-event portion is some portion that occurs before the starting point of a brain event time period. An event portion is a portion that occurs during a brain event time period. A post-event portion is a portion that occurs after the ending point of a brain event time period. In the example of epilepsy, the pre-event, event and post-event portions are referred to as the pre-ictal, ictal and post-ictal portions respectively.

The flowchart at FIG. 61 illustrates an alternative embodiment of the operations performed by the one or more processors. At block 1202, the one or more processors receive a brain signal. An algorithm is performed by the one or more processors to determine at least one reference point (e.g., the starting point, the ending point or both) of the brain event time

period at block 1204. Note that in the case of determining more than one reference point, the second reference point may be determined based on the first reference point. For example, if an algorithm detects the starting point of a neurological event, the algorithm may make an assumption that the ending point is a period of time after the starting point. Alternatively, both reference points may be determined by evaluation of the brain signal using a detection algorithm or other algorithm. The one or more processors receive a cardiac signal at block 1206. The one or more processors next identify two or more portions of the cardiac signal based on the starting and ending points of the brain event time period at block 1208. For example, one or more processors may identify a pre-event portion, event portion and post-event portion of the cardiac signal. Specifically in the case of epilepsy, the portions identified may be the pre-ictal, ictal and post-ictal portions of the cardiac signal. The identification of portions of the cardiac signal based on starting and ending points of the brain event time period may be by a simple relationship between the starting and ending points and the portions or it may be complex. Some examples of ways to identify portions of the cardiac signal are provided. In one embodiment illustrated in FIG. 62, identification of a pre-ictal portion of the cardiac signal involves identifying the portion of the cardiac signal between a programmable first period of time before the starting point to the starting point. The post-ictal portion of the cardiac signal may be identified as the portion of the cardiac signal between the ending point of the brain event time period and a third period of time after the ending point. Another exemplary embodiment method of identifying portions of a cardiac signal is illustrated in FIG. 63. Here, the pre-ictal portion is identified as the portion between a first period of time before the starting point to a second period of time before the starting point. Furthermore, the post-ictal portion is identified as the portion between a fourth period of time after the ending point to a third period of time after the ending point. In one embodiment, the time periods may be programmable. In another embodiment, they may be fixed.

The process may start with analysis of the brain signal. The terms "starting point" and "ending point" include points in time determined by an algorithm that may not necessarily correlate with a sharp or distinct change in the brain signal. For example a slight increase in features indicative of major depressive disorder may be sufficient for the algorithm to make the determination of a starting point even though a distinct or abrupt change in the brain signal is not observed. In the case of epilepsy a seizure detection algorithm may be used some of which have been cited elsewhere in this application. In the case of psychiatric disorders such as depression, a psychiatric monitoring algorithm may be used. For example, EEG asymmetry across different hemispheres of the brain may be evaluated to detect a depression event. One exemplary algorithm that may be used for depression is described in U.S. Published Patent Application 2005/0216071. The methods described in U.S. Pat. No. 6,622,036 may also be used.

Once one or more portions of the cardiac signal are identified, they may be stored in memory at block 1210. The phrase "stored in memory" means keeping the information so that it can be analyzed. For example, the phrase "stored in memory" includes retaining (rather than discarding) information in a circular buffer such as in a loop recording scheme. In one embodiment monitoring device for epilepsy, brain signals are monitored/processed with a seizure detection algorithm; the cardiac and respiratory signals are passively recorded during the brain signal processing. When a seizure has been detected in the brain signal data stream, a recording containing a montage of brain, cardiac and respiratory signals

is created. The signals in the recording are then processed to evaluate the patient's heart and pulmonary condition.

At block 1212, the one or more processors may determine metrics of one or more of the pre-event, event and post-event portions of the cardiac signal. In one embodiment, the metrics may relate to heart rate. Some of the heart rate metrics that may be determined include the following that may be taken over the entire portion of the cardiac signal or over a subset of the portion: mean heart rate, median heart rate, maximum heart rate, minimum heart rate and standard deviation of the heart rate.

Once metrics are determined they may be compared at block 1214. Comparison of metrics means any comparison between two metrics. For example, percentage change from one metric to a second metric may be computed. In one embodiment, the pre-event metric may be compared to the post-event metric. In one embodiment the post-event portion may be divided into sub-portions, metrics computed for the sub-portions, and the sub-portion metrics compared to the pre-event metric. This may be done to determine how long it takes the patient's heart rate to return to normal after a brain event such as a seizure. In another embodiment, the pre-event metric may be compared to the event metric. In yet another embodiment, the event metric may be compared to the post-event metric.

In one embodiment, it may be desirable to have a processor in the implantable medical device portion of the system identify the portions of the cardiac signal (e.g., pre-ictal, ictal, post-ictal) and to store them, and to have a second processor in a programmer or other external device receive the portions of cardiac signal via telemetry and determine metrics and compare metrics. In yet another embodiment, the implanted processor may determine the metrics associated with the portions and send only the metrics to the external device via telemetry. The external device may then evaluate or compare the metrics. In yet another embodiment, the brain and cardiac signals may be telemetered to the external device and post-processed by the external device to identify the portions, determine the metrics and compare the metrics.

FIG. 39 shows one embodiment process 750 for identifying ECG and respiratory abnormalities recorded during detected seizures. At block 751, the full monitor monitors EEG and ECG or respiratory signals. At block 752, the monitor detects seizures in EEG signals. At block 753, seizure detection triggers recording and retention of EEG, ECG and respiratory signals. After uplinking to a programmer, the ECG/respiratory signals are post-processed. At this point one or more processors may identify an event portion, pre-event portion and post-event portion of the cardiac signal based on the starting point and the ending point of the brain event time period. The event portion of the cardiac signal may correspond in time exactly to the brain event time period such as an ictal period, or it may be different but computed based on the starting and ending points of the brain event time period. The pre-event portion of the cardiac signal may be everything before the event time period or it may be a period beginning a programmable period of time before the event time period to the beginning of the event time period. Likewise, the post-event time period may be everything after an event time period or it may be a period beginning at the end of the event time period and extending to a programmable period of time after the end of the event time period. For the seizure example, at block 755, ECG and respiratory signals are segmented into (a) pre-ictal, (b) ictal, and (c) post-ictal periods based upon the determined starting and ending points of the neurological event in the brain signal. The ictal periods are automatically derived from a seizure-detection algorithm operating on the

EEG signals. For example, the beginning of the ictal period may be time-marked to detection cluster onset; the end of the ictal period by detection cluster offset (as described in published US Application No. 2004/0138536 "Clustering of Recorded Patient Neurological Activity to Determine Length of a Neurological Event" to Frei, et al incorporated herein by reference in its entirety). The durations of the pre-ictal and post-ictal periods are programmable. It may be desirable to program the pre-ictal period for purposes of a cardiac baseline or respiratory baseline as ending some period of time before or after the true ictal period as determined by the EEG detector. In this way a better baseline may be obtained that is not distorted by changes in cardiac or respiratory activity near in time to the neurological event.

At block 756, the loop-recorded data is screened for abnormalities. After the ECG and respiratory signals are segmented, the different intervals of ECG and respiratory data are separately processed to determine metrics associated with those signals. The term metric is used interchangeably herein with the term indices. These metrics may assist in detecting events or determining features or other activity reflected in those signals. Exemplary cardiac metrics that may be computed include indices of heart rate (HR) (i.e., mean, median, max, std. dev., etc.) or indications of abnormal heart activity such as an arrhythmia which are displayed in the physician programmer for each detected event. Exemplary respiratory metrics that may be computed include minute ventilation, respiration rate, apnea, or edema, which are displayed in the physician programmer for each detected event. Metrics from different segmented intervals or time periods of the cardiac or respiratory signal may be compared to one another. For example, to monitor changes in cardiovascular and pulmonary function that may arise from or cause seizures, percentage of change between indices/metrics may be calculated. For example, to indicate magnitude of change in heart rate from a baseline to seizure state, the percentage of change between the pre-ictal (baseline) and ictal (seizure) periods is computed/displayed.

$$\% \text{ Chg. Detect Onset} = (\text{Ictal HR indices} - \text{Base HR indices}) / \text{Base HR indices}$$

Comparison between the post-ictal and baseline periods is also performed to evaluate if and when a return to baseline is achieved.

$$\% \text{ Chg. Detect End} = (\text{Post-Ictal HR indices} - \text{Base HR indices}) / \text{Base HR indices}$$

During processing, the time at which the post-ictal heart rate returns to baseline, relative to the end of the ictal period, is identified. The physician may choose to increase the duration of the post-ictal period if, during detected seizures, the patient's HR indices do not consistently return to baseline levels.

At block 757, detection times for arrhythmic and respiratory anomalies are determined. The ECG and respiratory signals are further processed, via an arrhythmia/abnormality detection algorithm, to identify ECG and respiratory abnormalities (bradycardia, tachycardia, asystole, ST segment depression, QTc prolongation, apnea, edema, etc.). Such events may occur in different periods of data, and cross ictal boundaries (e.g., a tachy event may begin prior to seizure onset, and continue well after seizure termination, resulting in a detection that includes all intervals of data). Thus, during screening the entire ECG and respiration signals in the loop recording data is processed in a single step, without segmentation. The start and end times for each identified arrhythmia/abnormality in the loop recording data is stored and later retrieved for analysis.

The physician may further run a matching test (EEG detections versus ECG or respiratory detections) at block 758. The matching test is run to compare the EEG detections and ECG/respiratory detections in the loop recording data. The matching test reports whether each ECG/respiratory abnormality is coincident with (i.e., matched), or is temporally separated from, the detected seizure (i.e., unmatched). In the case of a match, the time difference between EEG detection onset and ECG/respiratory detection onset is computed.

At block 759, the matching test results are evaluated to determine if the seizure is associated with an arrhythmia or respiratory anomaly. At block 760, additional seizures are determined. If NO, block 761 reports results of ECG/respiratory screening procedures for each seizure. At block 760, if the result is YES the flow diagram returns to block 752.

ECG/respiratory post-processing may occur in the implantable device, after the loop recorded data has been stored to memory. Alternatively, the post-processing may occur on loop-recorded data transmitted to an external wearable device or physician programmer or other computer.

In another embodiment of cardiac signal segmentation it may be desirable to record the amount of time it takes a metric of the cardiac signal to return to some baseline metric after a change in the brain signal has been discovered. For example, the system may determine a first metric such as heart rate associated with a pre-event portion of the cardiac signal. The first metric is the baseline. The system then determines a second metric for the post-event portion and determines whether it meets predetermined criteria about its relationship to the first metric. The predetermined criteria may be any way of determining or estimating whether the second metric (e.g., heart rate after the seizure) has reached or is close enough to the first metric (e.g., the heart rate before the seizure). For example, the predetermined criteria may simply be to determine whether the second metric equals the first metric. Another example of predetermined criteria may be a determination of whether the second metric is within a specified range of the first metric. In another exemplary embodiment, the predetermined criteria may evaluate whether successive metrics cross from being greater than the first metric to less than the first metric or vice versa. Once the value of the first metric is crossed the predetermined criteria are met. If the predetermined criteria are met, a second metric time is recorded or otherwise transmitted. The second metric time means some time value related to the amount of time from the at least one reference point to the occurrence of the second portion. For example, in one embodiment, the second metric time is the amount of time from the ending point of the seizure to the point in time when the heart rate has returned to its pre-ictal level. In this way the clinician may learn for each event the amount of time it took a particular metric of the patient's cardiac signal to return to baseline. In one embodiment the second portion may be a short or very short period of time such as, for example, 10 seconds, 5 seconds, 2 seconds, 1 second, or less than 1 second, or even on a sample by sample basis (e.g., determine a new metric each time there is a heart beat). By using a short second portion, successive portions may be evaluated until the metric associated with the portions meets the predetermined criteria.

Heart Rate Variability (HRV)

Nervous system disorders are often associated with comorbid life-threatening conditions, which in some cases may have a cardiac cause. For example, a subset of epilepsy patients may be at risk for SUDEP (sudden unexplained death in epilepsy patients). Epilepsy patients who have compromised autonomic cardiovascular control, for example, may be at increased risk of sudden cardiac death.

With some neurological disorders, brain state changes may occur and may be associated with changes in cardiac function. For example, patients with epilepsy often experience tachycardia or bradycardia episodes (e.g., fast or slow heart rhythm episodes, respectively) during their seizures. Likewise, psychiatric patients often experience heart rate fluctuations caused by anxiety (e.g., during panic attacks) or depression. In such cases, measures of heart rate variability may be affected by the frequency and/or severity of the patient's neurological condition, and thus, monitoring heart rate variability may provide information useful in the treatment in such patients.

Patients with certain psychiatric illnesses, such as major depressive disorder (MDD), are also at higher risk for developing cardiac problems. A strong link between depression and cardiac death has been established. Some have postulated cardiac vagal control (CVC) is impaired in patients with depression. Others have shown major depression is associated with reduced baroreflex sensitivity (BRS), a predisposing factor for sudden cardiac death. Anxiety, which is central to OCD, has also been shown to be related with a reduction in baroreflex receptor activity. Thus, evidence suggests autonomic function is altered in depression patients, with decreased vagal activity and/or increased sympathetic arousal as possible explanations for the observed cardiac problems.

It has been suggested that compromised autonomic cardiovascular control may be identified by a change in the patient's heart rate variability (HRV). For example, a decrease in a patient's baseline HRV over a period of time may be an indication that the patient is at an increased risk of SUDEP. Also, during neurological events, for example, an HRV value calculated during the event that changes from a baseline HRV value by more than a specified amount or percentage may be indicative of a condition related to SUDEP that may warrant further attention and/or therapy. Thus, various embodiments of the invention include systems and methods for monitoring HRV in epilepsy patients, and for using the HRV information as the basis for making therapy-related decisions.

In certain embodiments of the invention, an adjusted baseline measure (e.g., a daily measure) of HRV is determined in which heart rate information (e.g., R-R intervals and information derived therefrom) obtained during neurological events (e.g., seizure detections or seizure detection clusters) is excluded from the calculation of the baseline measure of HRV. In other words, the baseline HRV is "adjusted" so that it excludes heart rate information corresponding in time to neurological events. An "unadjusted" measure of HRV may also be determined for a patient incorporating heart rate information from both the Event and Inter-event portions of the cardiac signal; the adjusted and unadjusted measures of HRV may be compared to each other and some action taken in response thereto according to certain embodiments of the invention. Thus, a baseline measure of HRV according to certain embodiments of the invention would be determined based on cardiac signal information corresponding in time to one or more inter-event portions of the cardiac signal (e.g., portions of the cardiac signal that do not correspond in time with detected neurological events). Such a baseline measure of HRV may also be referred to as an "Inter-event HRV."

As used herein, a portion of a cardiac signal may be said to "correspond in time" to a portion of a brain signal (such as a brain event time period, for example) when it occurs generally during the same period of time. In certain cases, two signal portions are said to "correspond in time" with each other when they have coincident (or nearly coincident) starting and ending times, but there are situations where a looser concept of "corresponding in time" may also be useful (for

example, to encompass a cardiac signal portion that is somewhat wider or narrower than the brain signal portion to which it corresponds, or to also cover various timing delays between two corresponding signals).

The adjusted baseline measure of HRV may be calculated periodically (e.g., hourly, daily, weekly, monthly, etc.), and may be plotted and/or tracked to identify a trend over time. In some embodiments, an Inter-event HRV may be calculated as a periodic value representative of variability of the R-R intervals in the inter-event portions of the cardiac signal over a defined period, such as a one-day period, for example. A series of daily values may be recorded to identify a trend in the Inter-event HRV according to some embodiments. In certain embodiments, a threshold criterion may be established, and some action may be taken (e.g., a warning indicated and/or a treatment provided) if the Inter-event HRV drops below the threshold, or if the HRV trend shows a decrease by a certain amount or percentage within a specified period of time, for example. In some embodiments, it may also be desirable to provide an indication of an improving condition, for example, an increase in the Inter-event HRV.

SUDEP may occur most often during sleep, thus there is a need to study HRV during sleep periods. In certain embodiments of the invention, the baseline measure of HRV may be determined separately for different parts of a patient's circadian cycle. For example, the adjusted baseline measure of HRV could be broken out into separate measures of HRV, such as a night-time baseline HRV (e.g., using only cardiac signal information acquired during periods of known or expected sleep), or a day-time baseline HRV, and each of these could be calculated based on varying periods of time (e.g., hourly, daily, weekly, monthly, etc.). Sleep periods may be identified by predetermined night-time periods (e.g., known time periods) or can have programmable start and end times. Alternately, a sleep sensor may be employed that determines when a patient has actually fallen asleep based on factors such as body position, respiration rate, etc. In one embodiment, for example, both a day-time and a night-time adjusted baseline HRV are calculated and recorded for each 24-hour period; a full 24-hour HRV may also be calculated in conjunction with these measures that does not account for sleeping versus awake periods. In certain embodiments, baseline HRV calculations may be "adjusted" to account for periods of therapy delivery. For example, the adjusted baseline HRV in such an embodiment may exclude cardiac signal information obtained during periods when therapy is being delivered to the patient. In such embodiments, therapy delivery could include electrical stimulation therapy (e.g., to the brain and/or heart of the patient), and drug therapy, and could include other types of therapy as well.

In some embodiments of the invention, a measure of HRV may be separately and/or additionally calculated for periods of time during neurological events (e.g., during brain event time periods, such as seizure detections or seizure detection clusters). In some embodiments, an "Event HRV" value may be calculated for portions of the cardiac signal corresponding in time to each detected neurological event (or each brain event time period, for example), or may alternately be aggregated into a representative event HRV based on a number of neurological events. In certain embodiments, an event HRV may alternately be called an "Ictal HRV," where the neurological events are epileptic seizures, for example. In certain particular embodiments, an Event HRV value calculated based on cardiac signal information corresponding in time to a brain event time period may be compared to an Inter-event HRV value, and an action may be taken or an output modified based upon the result of the comparison (e.g., a warning

indicated and/or a treatment provided). For example, if the Event HRV determined during a neurological event is different from the Inter-event HRV by more than a specified amount or percentage, a warning may be indicated (e.g., an audible alarm), a therapy may be delivered to the patient (e.g., electrical stimulation therapy to the heart or the brain or both), or a detection or therapy parameter may be adjusted (e.g., a cardiac defibrillation programmable setting may be temporarily modified/adjusted to have a lower rate threshold, or an increased therapy output).

In certain embodiments, segmentation of a cardiac signal (e.g., an ECG signal) may be performed based on the timing of a detected neurological event (e.g., a seizure detected by analysis of an EEG signal by a seizure detection algorithm, for example), and comparisons can be made between the HRV values calculated for each of the pre-event, event, and post-event periods identified by such segmentation. For example, the pre-event HRV could be the adjusted baseline HRV (or Inter-event HRV) according to certain embodiments, or it could be an HRV value calculated for a specified period of time prior to a particular neurological event in other embodiments, or it could be an HRV value based upon a period of time between neurological events in still other embodiments. An Inter-event "interval" may also be defined to further assess the comparison between the Event HRV and the Inter-event HRV. For example, if the Inter-event HRV is based on cardiac signal information obtained during a relatively brief period of time (e.g., a relatively brief Inter-event interval between two neurological events that occur a short time apart), a weighting measure may be assigned to the comparison between the Event HRV and the Inter-event HRV in which the shorter the Inter-event interval, the less meaningful the comparison, and hence, the less "weight" given to the comparison for diagnostic purposes, for example. The weighting measure may be an actual numerical scaling factor that effectively discounts the value of comparisons between Event and Inter-event HRVs when the Inter-event interval is very short, for example. In some embodiments, a warning and/or a treatment may be provided to the patient if, for example, a change in HRV occurs from the pre-event to the event periods that meets threshold criteria (e.g., a change in HRV of more than a certain amount or percentage). Note that in such embodiments, the threshold criteria for a change in HRV could be either an increase or a decrease in HRV when going from the pre-event to the event portion of the cardiac signal.

As noted above, segmentation of a cardiac signal (such as an ECG signal) may include determining one or more reference points in a brain event time period and using the one or more reference points to segment the cardiac signal. As described above, this may be done using a time-based reference, such as a beginning of a brain event time period, or an end of a brain event time period, or some intermediate point therebetween. Alternately, the reference point within a brain event time period could be defined based upon analysis of the brain signal during the brain event time period, rather than based upon a time-based reference (e.g., the start, end, mid-point, etc., of the brain event time period). For example, the reference point within a brain event time period could be defined as the point in time during the brain event time period in which the brain signal has its maximum brain signal amplitude, or maximum brain signal frequency, or the maximum brain signal power level, or the point in time marking a certain percentage (e.g., 50% or X %) of the signal energy within the brain event time period.

In further embodiments of the invention, a patient-triggered HRV comparison may be performed in which the

patient could indicate the timing (e.g., the occurrence or presence) of symptoms (e.g., by using button presses to indicate start and stop times associated with certain symptoms) to indicate which periods to exclude from the baseline HRV calculations. This might be done, for example, in lieu of using a neurological event detection algorithm, or it may be done in conjunction with such a detection algorithm, according to various embodiments of the invention. Thus, a comparison of the patient-triggered HRV to the baseline HRV may be performed, for example, and a warning and/or a treatment may be provided to the patient if, for example, a change in HRV meets certain defined threshold criteria.

Treatment therapies for epilepsy, psychiatric illness, and other nervous system disorders can include any number of possible modalities alone or in combination including, for example, electrical stimulation, magnetic stimulation, drug infusion, and/or brain temperature control. Each of these treatment modalities can be operated using an open loop scheme, where therapy is continuously or intermittently delivered based on preprogrammed schedule. Alternatively, a closed-loop scheme may be used, in which the therapy is delivered to the patient based on information coming from a sensed signal.

For implantable devices that perform EEG sensing, it is desirable to have the reference electrode contained within the body. If the signals are to be used for seizure detection, it is desirable that the reference electrode be remote from the seizure focus. The active electrodes are positioned either in direct or indirect contact with brain structures affecting a neurological condition for which sensing is being performed. For example, to treat epilepsy the active electrodes may be implanted in brain tissue at or near the seizure focus where they can sense EEG signals, detect a seizure event, and provide stimulation therapy. Conversely, the active electrodes may be positioned in an anatomical target distant from the seizure focus, but which is connected to the seizure focus by way of neuronal pathway projections. Activating pathway projections with electrical stimulation from a distant site (i.e., thalamus) may influence seizure activity at the focus (i.e., hippocampus/amygdala). Similarly, to treat a psychiatric illness such as major depressive disorder or OCD, the active electrodes may be implanted directly in brain tissue involved in mood regulation for depression or OCD, such as the internal capsule or subgenual cingulate cortex (Area 25). Alternatively, the active electrodes may be positioned at distant sites within the limbic-cortical circuit, which have connections to these mood regulating regions of the brain. With either approach, it is desirable to have a single electrode positioned away from the active electrodes, which can function as a reference for EEG sensing and/or function as an indifferent electrode for monopolar stimulation.

A medical device system according to various embodiments of the invention may include a brain monitoring element for sensing activity of a brain of a patient and outputting a brain signal, a cardiac monitoring element for sensing activity of a heart of the patient and outputting a cardiac signal, and one or more processors adapted to communicate with the brain monitoring element and the cardiac monitoring element and configured to perform a number of processing steps. The various processing steps discussed herein may be performed within any hardware embodiment envisioned including but not limited to the various hardware embodiments presented throughout this application. For example, all of the processing steps may be performed within one or more implantable devices. Alternatively, some processing steps may be performed within one or more implantable devices and other processing steps performed by an external component of the

system such as a programmer or computer that receives the appropriate information from the implanted device(s) by telemetry.

A medical device system according to certain embodiments of the invention includes one or more processors adapted to communicate with the brain monitoring element and the cardiac monitoring element. The one or more processors are configured to receive the brain signal from the brain monitoring element, and identify brain events that may occur in the brain signal, each of the identified brain events having a start time and an end time defining a brain event time period for each brain event. The one or more processors are configured to receive the cardiac signal from the cardiac monitoring element and store cardiac signal information in one or more data buffers. The one or more processors identifies one or more Inter-event portions of the cardiac signal, each Inter-event portion corresponding in time to a period between brain event time periods (or before a first brain event time period, for example), and then calculates an Inter-event heart-rate variability (HRV) based on the cardiac signal information stored for the one or more Inter-event portions of the cardiac signal. The medical device system may then modify an output of the medical device system based upon the Inter-event HRV. The modified output may include an information signal or a warning signal (e.g., an audible signal that may be heard by the patient, or a warning that is reported to a physician during a system programming session), or a changed therapy output, or a modified programmable detection setting, as but a few possible examples.

A medical device system according to certain embodiments of the invention may be adapted to enable and/or deliver various types of therapy based on the Inter-event HRV, or based on the comparison between an Event HRV and an Inter-event HRV. For example, therapy may be delivered to treat a neurological condition associated with the brain event, and may include electrical stimulation therapy to the brain and/or drug therapy. Since patients at risk of SUDEP are also considered to be at increased risk of sudden cardiac death, a medical device system according to embodiments of the invention may also include various forms of cardiac therapy. For example, cardiac therapy may be delivered in an attempt to prevent and/or terminate certain types of cardiac episodes (e.g., arrhythmias). In some embodiments, cardiac therapy may include cardiac pacing therapy, which can encompass overdrive pacing and anti-tachycardia pacing schemes, for example, and may also include cardiac defibrillation therapy, such as defibrillation and/or cardioversion shocks of varying energies designed to terminate certain cardiac arrhythmias. Cardiac therapy may be used to address ventricular and/or atrial arrhythmias according to various embodiments of the invention.

A number of heart rate variability (HRV) measures may be calculated by analyzing the beat-to-beat R-R interval time series. HRV measures fall into two broad categories: (1) frequency or spectral domain HRV measures and (2) time domain HRV measures. The following discussion describes several examples of calculating time domain HRV measures, although frequency domain measures could also be used according to various embodiments of the invention.

One time domain measure of HRV is the standard deviation of the normal R-R intervals in a 24 period, hereinafter the SDNN. The SDNN reflects the overall heart rate variability in all frequency bands (ULF+VLF+LF+HF+[>HF]) frequency bands).

Another time domain measure of HRV is the SDNN Index, which is the mean value over 24 hours of the standard deviation of R-R intervals per 5 minute non-overlapping time

period. The SDNN Index reflects the HRV for cycles shorter than about 5 minutes (VLF+LF+HF+[>HF]) frequency bands).

Another time domain measure of HRV is the standard deviation over 24 hours of the mean R-R interval per 5 minute non-overlapping time period, hereinafter the SDANN. The SDANN reflects the HRV in the ULF frequency band.

Yet another time domain measure of HRV is the percent of R-R intervals over 24 hours whose consecutive difference exceeds 50 msec, hereinafter the PNN50. The PNN50 reflects high frequency variations in HRV.

Other time domain measures of HRV could be implemented in a medical device system according to embodiments of the invention, for example, to reduce the computational complexity of determining HRV. For example, rather than calculate a standard deviation, other measures of the difference between R-R intervals in a given time window may be determined using techniques known in the art.

Heart Rate Block Counter—Indication of Measurement Quality

In some embodiments of the invention, it is desirable to account for situations in which a number of brain events occurs in a relatively short period of time. In such situations, the periods of time between closely spaced events may be so short that comparisons between pre-event and event heart rate measures (such as average heart rate, or heart rate variability, for example) may not be as valuable or meaningful for diagnostic purposes (since the closely spaced brain events may be part of a single neurological event, for example). In such situations, an embodiment of the invention accounts for relatively brief pre-event periods by providing an indication of the quality of the measurement. In some embodiments, a medical device system counts the number of data buffers acquired since the last event (or ictal period in the case of epileptic seizures), and provides an indication of whether the pre-event period contains enough data to enable a meaningful or valuable comparison of pre-event to event heart rate comparison measures. For example, if the measurement quality indicator (e.g., the number of data buffers since the last event) is too low, indicating a very short pre-event interval (e.g., a very short pre-ictal period), any subsequent measure that compares pre-event and event data (such as comparisons of HR Average or HRV between pre-event and event periods) are discounted to reflect that the pre-event period was probably not a true pre-event period, but rather just a continuation of the preceding event period.

In some embodiments of the invention, a medical device system comprises a brain monitoring element for sensing activity of a brain of a patient and for outputting a brain signal, and a cardiac monitoring element for sensing activity of a heart of the patient and outputting a cardiac signal. A cardiac monitoring element, for example, may comprise an implantable cardiac sensing and/or pacing lead, as is well known in the art of cardiac pacing. Alternately, the cardiac monitoring element may comprise a leadless ECG electrode substantially as described herein. A medical device system in accordance with embodiments of the invention further comprises one or more processors adapted to communicate with the brain monitoring element and the cardiac monitoring element. The processor(s) are configured to receive the brain signal from the brain monitoring element and identify one or more brain events in the brain signal. Each of the identified brain events has a start time and an end time which defines a brain event time period for each brain event. The processor(s) are configured to determine a reference point for a particular ("current") brain event time period by evaluation of the brain signal; the "current" brain event time period is determined to follow a

"preceding" brain event time period by an inter-event interval. The processor(s) also receive the cardiac signal from the cardiac monitoring element and store cardiac signal information in one or more data buffers. Next, the processor(s) are configured to identify a first portion and a second portion of the cardiac signal based on the at least one reference point of the current brain event time period, calculate a first cardiac metric from the first portion of the cardiac signal and a second cardiac metric from the second portion of the cardiac signal, and compare the first cardiac metric to the second cardiac metric. The processor(s) may be further adapted to assign a weighting measure to the comparison of the first and second cardiac metrics based upon the size of the inter-event interval (e.g., how long the time interval is), and may then modify an output of the medical device system based on the weighting measure and on the comparison of the first cardiac metric to the second cardiac metric.

For convenience, we refer to the analysis and comparison of particular brain event time periods by designating "current" and "preceding" brain event time periods. For example, a given brain event time period being analyzed is considered the "current" brain event time period, and the last brain event time period to occur prior to the "current" brain event time period is considered the "preceding" brain event time period. This naming convention is, of course, understood to be flexible in that, for example, a given brain event time period will typically serve as a "current" brain event time period when analyzed in conjunction with a particular "preceding" brain event time period, but will subsequently become the "preceding" brain event time period for analysis in conjunction with the next brain event time period that occurs after the given brain event time period.

In certain embodiments of the invention, the weighting measure assigned to the comparison of the first and second cardiac metrics may be zero if the Inter-event interval (e.g., the amount of time elapsed between events, as determined by the count of data buffers) is less than some predetermined amount. In certain embodiments, the weighting measure may be 1 (e.g., given full weight) if the Inter-event interval is greater than some predetermined amount. In some embodiments, the weighting measure may be a fraction between zero and one if the Inter-event interval is between two predetermined amounts; the weighting measure may vary as a function of the length of the Inter-event interval.

Determination of Improvements in Neurological Event Detection Using Cardiac or Respiratory Input

Another embodiment of the invention is a medical device system and method for determining whether cardiac or respiratory signals may be used to improve neurological event detection. This medical device system includes a brain monitoring element (e.g., lead 18, external electrode), a cardiac monitoring element (e.g., lead 16, sensor stub 20, sensor 14, integrated electrode 24, external electrode, etc.) or respiratory monitoring element (e.g., lead 16, sensor stub 20, sensor 14, integrated electrode 24, external electrode, etc.) and a processor (e.g., CPU 732 or any other processor or combination of processors implanted or external). This determination of whether cardiac or respiratory signals may be used to improve neurological event detection may be very beneficial to understanding a patient's condition and that in turn is helpful to determining appropriate treatment or prevention options. The medical device system may include the ability to determine relationships between brain and heart only, brain and respiratory only, or both. Once these relationships are better understood, they may be utilized to make decisions about enabling the use of cardiac signals or cardiac detections or respiratory signals or respiratory detections in the monitoring or treat-

ment of the neurological disorder. Note that this medical device system and method may be performed by many different types of hardware embodiments including the example hardware embodiments provided in this specification as well as in an external computer or programmer. The executable instructions executed by a processor may be stored in any computer readable medium such as, for example only, RAM 730.

The determination of improvements in neurological event detection using cardiac or respiratory input includes determination of concordance between brain and cardiac signals or between brain and respiratory signals, determination of detection latency, and the false positive rate in the cardiac or respiratory signal relative to a neurological event detected in the brain signal.

An example of the usefulness of this determination is provided here. If it is determined that a patient with epilepsy has improvement in neurological event detection based on a cardiac signal it may be desirable to enable the use of a cardiac activity detection algorithm to trigger application of therapy to the brain. Another example of the benefit of concordance information is that a high concordance between brain and heart (including perhaps concordance with a particular type of cardiac event) for an individual with epilepsy, may mean that the patient is more susceptible to SUDEP. Perhaps steps can be taken such as use or implantation of a heart assist device such as a pacemaker or defibrillator for this patient to reduce the likelihood of death. There are of course many other examples of situations that may be discovered by operation of this concordance system and method that result in better health care.

The medical device system with concordance capability may include a brain monitoring element 18 (e.g., EEG lead with one or more electrodes) for sensing activity of the brain and outputting a brain signal, and a cardiac or respiratory monitoring element 14 (e.g., electrodes or other sensors) or both, for sensing a cardiac or respiratory activity and outputting a cardiac or respiratory signal, and a processor. The processor is configured to receive the brain signal and one or more of the cardiac and respiratory signals and to compare the brain signal and one of the cardiac or respiratory signals to each other.

Comparison of the brain and cardiac signals to each other may take many different forms. In one embodiment, the processor is configured to obtain information identifying one or more neurological events in the brain signal, and to also obtain information identifying one or more cardiac events in the cardiac signal. "Obtain" means 1) automatically generating the information by executing an algorithm that evaluates the signal, or 2) receiving the information from a user such as a physician reviewing the brain and cardiac signals (this second aspect of obtain is hereinafter referred to as "manual identification of events"). The algorithm or physician may create or generate various features of the neurological event such as a determination of when the event begins and ends and hence a duration of the event. For example automatic generation of the information may be performed by a seizure detection algorithm such as described in US published application 2004/0138536 "Clustering of Recorded Patient Neurological Activity to Determine Length of a Neurological Event" to Frei, et al. Likewise in the case of a cardiac signal, any algorithm that evaluates a cardiac signal and outputs information about cardiac activity or abnormalities would be an automatic generation of the information. Some examples are presented above in the discussion of the core monitor. An example of a manual identification of an event includes a physician indicating to a physician programmer the temporal

location of a neurological event and also indicating the temporal location of cardiac or respiratory events. This temporal location of an event may include marking of the beginning and end of the event.

In the case of manual identification of an event, the medical device system may include a user interface (for example, on a programmer or computer), for display of the brain, cardiac and respiration signals. The user, such as a physician, may mark events on the programmer. For example, the physician could mark the location by clicking a cursor over the location on the monitor. In another example, the physician could mark a location with a stylus on a touch sensitive screen. The physician markings may include marks that indicate the beginning and the end of an event.

In a more specific embodiment, the comparison of the brain signal to the cardiac or respiration signal includes for each neurological event, determining whether the neurological event is within a specified time period of one of the one or more cardiac or respiratory events, and for each of the one or more cardiac or respiratory events determining whether the cardiac or respiratory event is within a specified time period of one of the one or more neurological events. Two events are "within a specified time period" of each other if the two events are overlapping in time or the amount of time between two reference points of the two events is less than a time period that is previously determined and set in the device or that has been programmed or may be programmed into the device. Reference points of an event are some measure or indication of the temporal position of the event. For example, the two reference points may be the end of the first of the events to end and the beginning of the other event. Other reference points may be used such as, but not limited to, the midpoints of each of the events. An example of a specified time period that could be programmed into the device is 10 seconds. So in this example, the neurological event and the cardiac event would be within the specified time period of each other if a chosen reference point for the cardiac event (e.g., end of the cardiac event) was within 10 seconds of a chosen reference point (e.g., beginning of the neurological event) for the neurological event.

The comparison of brain signal to cardiac signal may include the following: determining the number of neurological events that are matched with a cardiac event (i.e., within a specified time period of a cardiac event); determining the number of neurological events that are matched with a cardiac event (i.e., not within the specified time period of a cardiac event); and determining the number of cardiac events that are not within the specified time period of a neurological event (the false positive rate in the ECG signal). The same steps may be applied in the case of comparison of a brain signal to a respiratory signal.

Furthermore for matched events (events that are within the specified time period of each other), the processor may determine the temporal relationship of the neurological event and the matched cardiac event or between the neurological event and the matched respiratory event. Because matched events may overlap or they may not overlap, the temporal relationship may be defined or described in many different ways. One embodiment of determining the temporal relationship is determining the temporal order (which event is first to occur) of the matched events. In order to determine the temporal order between two events, a reference point must be determined. As mentioned earlier the reference point may be the end, start or midpoint of an event, or the reference point may be computed in some other way. In general a reference point indicates some temporal information about the event. The reference points may then be compared to determine which

occurred first. The event associated with the first to occur reference point is then the first to occur event.

In another embodiment of comparing the brain signal to a cardiac or respiratory signal, the processor is configured to compute a rate of concordance between the neurological events and the cardiac or respiratory events. In this embodiment, the processor is configured to categorize the neurological event as cardiac matched when there is a cardiac event within a specified time period of the neurological event. The processor computes the rate of concordance between the neurological events and the cardiac events based on the number of cardiac matched events and the number of neurological events. For example, the processor may compute the rate of concordance by calculating the number of cardiac matched events divided by the number of neurological events. The more matches the greater the concordance.

In another embodiment the processor is further configured to perform the following: dividing the neurological event into at least two segments (portions); and assigning the cardiac event to one or more of the segments according to when the cardiac event occurred relative to the segments. For example, if the neurological event is a seizure, then there may be three segments: a pre-ictal segment, an ictal segment, and a post ictal segment. Various methods may be used to assign a cardiac event to one of these segments. For example, an algorithm executed by the processor (e.g., any of the processors of the many hardware embodiments in this application such as CPU 732, or a processor in a programmer or other computer external to the body) may determine when the cardiac event started relative to the three segments and assign the cardiac event to the segment in which it started. Of course other methods, more complex or simple may be used to make this assignment.

The ECG algorithm may be automatically enabled/disabled for use in monitoring or treatment (as described herein below) if concordance, detection latency and false positive rates meet selected and programmable criteria, indicating an improvement in neurological event detection performance. Alternatively, the patient's clinician may choose to review matching results and manually enable/disable the ECG detector based on information provided. For example, detection of a cardiac event may result in turning a neurostimulator or drug delivery device on to prevent the onset of a seizure. Alternatively, detection of a cardiac event may result in modification of therapy parameters. In another alternative, the ECG detector may be enabled for purposes of recording ECG, EEG or some other data.

In the embodiment that includes therapeutic output, the medical device system further includes a neurological therapy delivery module configured to provide a therapeutic output to treat a neurological disorder when the cardiac event detection algorithm detects a cardiac event. A neurological therapy delivery module may be any module capable of delivering a therapy to the patient to treat a neurological disorder. For example, but not limited to, a neurological therapy delivery module may be an electrical stimulator (e.g., stimulator 729), drug delivery device, therapeutic patch, brain cooling module.

Depending on the individual patient, and depending on the particular neurological disorder of concern, there may be different levels of concordance between different types of cardiac events and the neurological events. Therefore, in another embodiment, the processor is further configured to obtain information categorizing each cardiac event as one or more of two or more types of cardiac events. Types of cardiac events are known by different signals or aspects of signals coming from the heart. Examples of different types of cardiac

events include: tachyarrhythmia, ST segment elevation, bradycardia, asystole. In this embodiment, the processor may then determine concordance between each type of cardiac event or subset of cardiac events and neurological events. One embodiment of such determination is a processor configured to categorize each neurological event as first type cardiac matched when there is a first type cardiac event within a specified time period of the neurological event. The processor further categorizes the neurological event as second type cardiac matched when there is a second type cardiac event within a specified time period of the neurological event. The processor further computes a first rate of concordance between the neurological events and the first type cardiac events based on the number of first type cardiac matched events and the number of neurological events. The processor also computes a second rate of concordance between the neurological events and the second type cardiac events based on the number of second type cardiac matched events and the number of neurological events. This computation of rate of concordance may be performed as many times as there are types of cardiac events. The categorization of events as well as the various computed rates of concordance may be stored in memory.

In the embodiment allowing for computation of specific type of cardiac event rates of concordance, the medical device system may further include the capability to enable the use of detection of a particular type of cardiac event to affect the provision of therapy to the patient for the neurological disorder. For example, if it is determined that a high rate of concordance exists between tachyarrhythmia and seizure, the enablement of cardiac detection for affecting seizure therapy may be limited to the detection of tachyarrhythmia. In this case the seizure therapy will not be affected by other types of cardiac events.

It is noted that the medical device system may be external to the patient's body, implanted or some combination. The processor itself may be either external or implanted. For example, the processor may be in a handheld unit such as a programmer, or the processor could be in a general purpose computer.

The various processor operations described above may be embodied in executable instructions and stored in a computer readable medium. The processor then operates to perform the various steps via execution of these instructions. At one level, the executable instructions cause the processor to receive a brain signal from a brain monitoring element, receive a cardiac signal from a hear monitoring element, and compare the brain signal to the cardiac signal.

As described above, in a full monitor device for epilepsy, EEG, respiratory and cardiac (ECG) physiologic signals are simultaneously monitored and processed by different algorithms. A seizure-detection algorithm detects seizure activity in the EEG signals. A second algorithm detects heart-rate changes, ECG abnormalities, or unique waveform patterns in the ECG signals, which may or may not be coincident with seizures. Additionally, a third algorithm detects minute ventilation, respiration rate and apnea, which also may or may not be coincident with seizures.

By default, the EEG is considered a 'primary signal'—detections from this signal are used to represent seizure. The ECG and respiratory signals are 'secondary signals'—it is not initially known whether events detected in these two signals are useful for seizure detection. In a treatment setting, the patient's clinician considers the stored signals and data to determine if processing the ECG and respiratory signals provides added benefit in improving detection performance.

To make this determination, the patient is monitored until a sufficient number of detections in one or both of the data streams are observed (number of required events is programmable). Events detected in the EEG data stream may be classified by the user, via the programmer interface, to indicate whether they are clinical seizures (TP-C), sub-clinical seizures (TP-N), or false positive detections (FP). Likewise, events detected in the ECG and respiratory signals may be classified to indicate type of abnormality detected.

The concordance between the EEG seizure detections and ECG and respiratory signals is then evaluated. This is accomplished in one of two ways:

The relation between the EEG and ECG detections is initially unknown. Determination of the relationship between EEG and ECG may be performed with post processing or in real time.

In the post processing embodiment, automated matching tests are performed to identify the temporal relationship of detections in the different data streams. The matching tests identify the number of EEG detections that are within a specified time period with ECG or respiratory abnormalities (EEG-ECG Match or EEG-Respiratory Match, see **864** and **868** FIG. **38**), and those that are not (EEG detect-ECG Normal or EEG detect-Respiratory Normal). For matched detections, the time difference between EEG detection onset and ECG or respiratory detection onset is computed (detection latency). The number of detected events in the ECG or respiratory signals, independent of EEG triggered events, are also computed (ECG Un-matched or Respiratory Un-Matched, see **870** FIG. **38**).

With the real time implementation, the device controls a flag set by the seizure-detection algorithm operating on EEG signals. The flag is a real-time indicator of the subject's seizure state (1=in EEG detection state; 0=out of EEG detection state). In real-time, the device monitors the co-occurrence of the EEG and ECG/respiratory detection states.

The following conditions are assessed:

Brain-Cardiac Match—The EEG event (e.g., seizure) is classified as matched with ECG event if the ECG detection state occurs during an EEG detection state or within a specified time period of an EEG detection state.

Brain-Respiratory Match—The EEG event (e.g., seizure) is classified as matched with respiratory event if the respiratory detection state occurs during an EEG detection state or within a specified time period of an EEG detection state.

Brain Detect-Cardiac Normal—The EEG event (e.g., seizure) is classified as matched with normal ECG if no ECG detection state occurs during an EEG detection state or within a specified time period of an EEG detection state.

Brain Detect-Respiratory Normal—The EEG event (e.g., seizure) is classified as matched with normal respiration if no respiratory detection state occurs during an EEG detection state or within a specified time period of the EEG detection state.

Cardiac Un-Matched—An ECG event is classified as unmatched to EEG event (e.g., seizure) if no EEG detection state occurs during the ECG detection state or within a specified time period of an ECG detection state.

Respiratory Un-Matched—A respiratory event is classified as unmatched to EEG event (e.g., seizure) if no EEG detection state occurs during the respiratory detection state or within a specified time period of the respiratory detection state.

After EEG-ECG or EEG-respiratory matching has been performed, the physician programmer indicates whether the following conditions are true: (1) a high rate of concordance between detections in the EEG and ECG data streams (or between the EEG and respiratory data streams); (2) earlier

detection in the ECG signal (or respiratory signal) relative to neurological event onset as indicated in the EEG signal; and (3) a low rate of FP's in the ECG signal (or in the respiratory signal). If these conditions are all true, this may indicate that the ECG signal (or respiratory signal) provides value in neurological event detection (e.g., seizure detection).

Using this information, the physician may choose to activate the ECG algorithm or activate the respiration algorithm—that is, enable it as a primary signal for use in neurological event detection. Determination of whether to “add in” the ECG or respiratory signals (activate it in combination with the EEG signal) for seizure monitoring or treatment is based on satisfying one or more of the above stated conditions. This process can be automated by defining programmable threshold values for each of the stated conditions.

Note that ECG detection and respiratory detection may both be enabled or activated for neurological event detection if they both meet the conditions above.

The physician may decide not to enable the ECG/respiratory algorithms if the matching tests show no additional improvements in detection performance using the ECG or respiratory signals, or if specificity in the ECG/respiratory signals is low. In such cases, the physician may enable a mode of passive ECG recording, with the intended use of documenting cardiovascular changes during ictal periods in the EEG.

FIG. **40A** shows a process **971** for determining whether to enable the cardiac or respiratory detection algorithms for neurological event detection. At block **974** the medical device system monitors a brain signal and, cardiac or respiratory signals. At block **975** detections in any of the 3 signals (brain, cardiac, respiratory) triggers loop recording. Determination of the bounds of the neurological, cardiac and respiratory events may be performed in various ways. In one embodiment this determination of the bounds of events may be performed by a physician. In another embodiment, such determination of the bounds of the events may be performed by detection algorithms executed by a processor. Block **991** represents this choice between physician marked events and algorithm marked events. In the physician marking embodiment, the loop recording stored data must be uplinked to an external device such as a programmer or other computer. Upon uplinking the loop recording stored data, the physician may score the onset, offset or other reference points in the brain signal at block **976**. The physician may also classify the events as related or not to the particular neurological event being targeted. A matching test (brain detections versus cardiac or respiratory detections) is executed at block **977**. The brain inputs to the matching test may be either physician markings (e.g., onset, offset of neurological event) or the automated scores from the neurological event detection algorithm. The matching test results from block **977** result in a summary of comparisons made between the brain and cardiac detections (or between the brain and respiratory detections). At block **978** the matching test results are evaluated. The evaluation at block **978** includes blocks **979**, **980** and **981** (i.e., blocks **979**, **980** and **981** are components of block **978**). At block **979** concordance between brain and cardiac/respiratory detections is determined. At block **980** a cardiac or respiratory false positive rate (relative to the neurological signal) is evaluated using the cardiac unmatched events or the respiratory unmatched events in the cardiac or respiratory signals. At block **981** cardiac/respiratory latency is evaluated for the matched detections. At block **982**, neurological event detection improvement using cardiac or respiration signals is considered based upon the above determinations. If use of cardiac signals or respiratory signals does not improve

neurological event detection ("NO" condition), then the physician or other user may maintain or disable the cardiac event detection algorithm monitoring at block 983. If at block 982 the result is YES, the cardiac or respiratory signal is activated for neurological event monitoring or treatment.

Process 871 in FIG. 40B is one specific embodiment of process 971 in FIG. 40A. Process 871 is a process for determining whether to enable the ECG or respiratory detection algorithms for seizure detection. At block 874 the full monitor monitors EEG and ECG or respiratory signals. At block 875 10 detections in any of the 3 signals (EEG, ECG or respiratory) triggers loop recording. Determination of the bounds of the seizure, ECG and respiratory events may be performed in various ways. In one embodiment this determination of the bounds of a seizure may be performed by a physician. In another embodiment, such determination of the bounds of the events may be performed by detection algorithms executed by a processor. Block 891 represents this choice between physician marked events and algorithm marked events. In the physician marking embodiment, the loop recording stored data must be uplinked to an external device such as a programmer or other computer. Upon uplinking the loop recording stored data, the physician may score the onset, offset or other reference points in the EEG signal at block 876. The physician may also classify the events as seizure related or not. A matching test (EEG detections versus ECG or respiratory detections) is executed at block 877. The EEG inputs to the matching test may be either physician scores (e.g., onset, offset of seizure) or the automated scores from the neurological event detection algorithm. The matching test results from block 877 result in a summary of comparisons made between the EEG and ECG detections (or between the EEG and respiratory detections). At block 878 the matching test results are evaluated. The evaluation at block 878 includes blocks 879, 880 and 881 (i.e., blocks 879, 880 and 881 are components of block 878. At block 879 concordance between EEG and ECG/respiratory detections is determined. At block 880 an ECG false positive rate (relative to the neurological signal) is evaluated using the unmatched events in the ECG or respiratory signals. At block 881 ECG/respiratory latency is evaluated for the matched detections. At block 882, seizure detection improvement using ECG or respiration signals is considered based upon the above determinations. If use of ECG signals or respiratory signals does not improve seizure detection ("NO" condition), then the physician or other user may maintain or disable the ECG algorithm monitoring at block 883. The monitor begins monitoring or treatment at block 885. If at block 882 the result is YES, the ECG or respiratory signal is activated for seizure monitoring.

EEG-ECG/Respiration Event Detection Signal Matching

A matching test in accordance with embodiments of the invention compares the relative timing of events detected from different physiological signals obtained from a patient. The methods described may be implemented in either a physician programmer or in a monitoring device, and may be used, for example, to determine the suitability of enabling one type of event detection signal to facilitate detection of another type of event. For example, based on the results of the matching test, it may be determined that the detection of certain cardiac events (and/or respiratory events) may be useful in detecting, confirming, and/or predicting neurological events. In the discussion that follows, the examples and drawings make comparisons between cardiac and neurological event detection signals, for example, to determine whether a cardiac event detection signal may be enabled to facilitate detection of neurological events. Other similar types of comparisons may also be made (e.g., to determine whether a

respiratory event detection signal may facilitate detection of cardiac events, or whether a neurological event detection signal may facilitate detection of respiratory events, etc.).

An event detection signal may be a signal that indicates the timing of certain events, such as the start and end times of a neurological event, for example. As used in the examples that follow, a neurological event detection signal may be a signal that indicates the start times and end times of neurological events, and a cardiac event detection signal may be a signal that indicates the beginning times and termination times of cardiac events. An event detection signal may be the output of a detection algorithm that operates, for example, on EEG/ECOG signals (e.g., in the case of neurological signals), on ECG signals (e.g., in the case of cardiac signals), and/or on signals related to breathing (e.g., in the case of respiratory signals). A cardiac event detection signal may, for example, indicate the occurrence of any of a number of different types of cardiac abnormalities, including heart rate changes, signal morphology changes, etc. It may be determined from the matching test that only a certain type (or only a few types) of cardiac event (e.g., the occurrence of PVCs, or a sudden increase in heart rate) may be useful to improve or augment neurological event detection (and in some cases, to predict neurological events), but that other types of cardiac events do not have a similar relationship. Thus, a cardiac event detection signal can be a signal that includes multiple types of cardiac events, or it may be particularized to a specific type of cardiac event.

FIG. 65 shows a montage of signals from a patient, including an EEG signal, an ECG signal, a neurological event detection signal, and a cardiac event detection signal. As shown in FIG. 65, the neurological event detection signal shows a seizure event occurring (Seizure #1), corresponding to a portion of the EEG signal enclosed by a rectangular box. Similarly, the cardiac event detection signal shows a detected cardiac event corresponding to a portion of the ECG signal enclosed by a rectangular box. In the particular example illustrated, the cardiac events being detected are of a particular type, namely, increases in heart rate, as shown by the faster ECG signal patterns enclosed by the rectangular boxes in FIG. 65. FIG. 65 also shows the occurrence of a detected cardiac event which is not matched with a neurological event (labeled "false positive" in FIG. 65). Similarly, FIG. 65 provides an example of a detected neurological event which is not matched with a cardiac event (labeled "false negative" in FIG. 65).

A matching test may analyze the timing relationships between detected neurological events and detected cardiac events, and categorize each event (or each matched pair of events) according to a series of defined rules. Exemplary matching test criteria and outcomes are presented in the table provided in FIG. 64. In its most simple form, events are classified as "matched events" when a detected neurological event is temporally related to one of the detected cardiac events. That is, a matched event may be determined to occur when the elapsed time between a reference point of a detected neurological event and a reference point of a detected cardiac event is less than some predetermined amount. The reference point for a given type of event can be defined in any number of ways. For example, the beginning time of a cardiac event and the start time of a neurological event may form the respective reference points for determining an elapsed time, or the elapsed time may be measured between the end time of a neurological event and the midpoint of a cardiac event (e.g., the midpoint may be half-way between the beginning and termination times of a cardiac event). Based on the choice of reference points selected, the elapsed time may then be mea-

sured and compared to a predetermined value to determine whether the events are matched.

Events that are un-matched may be further categorized, for example, un-matched cardiac events (e.g., cardiac events that are not temporally related to a neurological event) may be categorized as “false positives.” Similarly, un-matched neurological events may be categorized as “false negatives.” The choice of these terms may be somewhat arbitrary, and/or may be based on the assumption (in this example) that the neurological event detection signal would normally be the initial or primary way of identifying neurological events, and that a second signal, such as a cardiac event detection signal, would be considered a secondary signal being evaluated for potential use in detecting (or assisting in detecting) neurological events. Thus, a false negative in this context describes a situation where a neurological event, as indicated by the neurological event detection signal, is not temporally related to a cardiac event, as indicated by the cardiac event detection signal.

Events that are matched may be further categorized to provide additional information. For example, a matched event may comprise a detected cardiac event and a detected neurological event that are overlapping in time. An overlapping event may be defined to occur when, for example, the cardiac event has a beginning time that occurs before an end time of the matched neurological event, and the cardiac event has a termination time that occurs after a start time of the matched neurological event. Matched events that are non-overlapping would be events that do not meet the above criteria (e.g., some period of time elapses between the end of the first event and the beginning of the second event).

Overlapping and non-overlapping events may be further categorized according to the table of FIG. 64. A code representing the particular matching category or scenario may also be stored to facilitate further analysis. For example, in the case of a matched, overlapping event, the event may be further categorized into one of five possible matching scenarios, labeled with codes TP1 through TP5 in FIG. 64. In the case of a matched, non-overlapping event, the event may be further categorized into one of four possible matching scenarios, labeled with codes TP6 through TP9 in FIG. 64.

For overlapping events, the matching scenarios may be defined as follows:

TP1: Cardiac detections may be classified as “Equal-Equal” (e.g., the beginning time and termination time of the cardiac event are roughly equal to the start time and end time of the neurological event) if: (i) the cardiac event has a beginning time that roughly equals a start time of the matched neurological event, and (ii) the cardiac event has a termination time that roughly equals an end time of the matched neurological event. The timing of two events may be considered to be “roughly equal” if they occur within a small time window (e.g., less than about one second) of each other, according to some embodiments of the invention.

TP2: Cardiac detections may be classified as “Out-In” (e.g., the beginning time of the cardiac event occurs before the neurological event begins, and the termination time of the cardiac event occurs during the neurological event) if: (i) the cardiac event has a beginning time that occurs before a start time of the matched neurological event, and (ii) the cardiac event has a termination time that occurs after the start time of the matched neurological event, and (iii) the cardiac event termination time occurs before an end time of the matched neurological event.

TP3: Cardiac detections may be classified as “Out-Out” (e.g., the beginning time of the cardiac event occurs before the neurological event, and the termination time of the cardiac

event occurs after the neurological event) if: (i) the cardiac event has a beginning time that occurs before a start time of the matched neurological event, and (ii) the cardiac event has a termination time that occurs after an end time of the matched neurological event.

TP4: Cardiac detections may be classified as “In-Out” if: (i) the cardiac event has a beginning time that occurs after a start time of the matched neurological event, and (ii) the cardiac event beginning time occurs before an end time of the matched neurological event, and (iii) the cardiac event has a termination time that occurs after the end time of the matched neurological event.

TP5: Cardiac detections may be classified as “In-In” if: (i) the cardiac event has a beginning time that occurs after a start time of the matched neurological event, and (ii) the cardiac event beginning time occurs before an end time of the matched neurological event, and (iii) the cardiac event has a termination time that occurs after the start time of the matched neurological event, and (iv) the cardiac event termination time occurs before the end time of the matched neurological event.

For non-overlapping events, the matching scenarios may be defined as follows:

TP6: Cardiac detections may be classified as “Out-Equal” if: (i) the cardiac event has a beginning time that occurs before a start time of the matched neurological event, and (ii) the cardiac event has a termination time that is equal to the start time of the matched neurological event.

TP7: Cardiac detections may be classified as “Equal-Out” if: (i) the cardiac event has a beginning time that is equal to an end time of the matched neurological event, and (ii) the cardiac event has a termination time that occurs after the end time of the matched neurological event.

TP8: Cardiac detections may be classified as “Out-Out After Detect” if the cardiac event has a beginning time that occurs within a predetermined window of time after an end time of the matched neurological event. The predetermined window of time may be a programmable setting, and may include values of time such as 2 seconds, for example, for considering a cardiac event to be matched with a neurological event. Such an event classification could be useful, for example, in situations where it may be desirable to have confirmation of a neurological event. This event classification may also be useful in conjunction with other event classifications, for example, in determining a rate of concordance between detected cardiac events and detected neurological events, since the inclusion of cardiac events that are “Out-Out After Detect” will tend to increase the rate of concordance. Thus, varying the predetermined window for TP8 events could have an impact on computed rates of concordance.

TP9: Cardiac detections may be classified as “Out-Out Before Detect” if the cardiac event has a termination time that occurs within a predetermined window of time before a start time of the matched neurological event. The predetermined window of time may be a programmable setting, and may include values of time such as 1 minute, for example, for considering a cardiac event to be matched with a neurological event. Such matched events may be further identified as “precursors,” since they may provide the ability to identify (e.g., predict) a neurological event before it actually occurs. Some embodiments of the invention may additionally provide the ability to use precursors to trigger therapy prophylactically, which can potentially prevent a subsequent neurological event (such as a seizure) from occurring, or lessen the severity of any subsequent neurological event that does occur.

Thus, in a device for monitoring neurological events, EEG and ECG signals are obtained and processed by different

algorithms. For example, a neurological event detection algorithm detects events (e.g., seizure activity) in the EEG signals, while a cardiac event detection algorithm detects events in the ECG signals such as heart-rate changes, ECG abnormalities, and/or unique waveform patterns, which may or may not be coincident with neurological events.

By convention, the EEG signal may be considered a 'primary signal'—event detections from this signal may be used to represent "actual" or "true" neurological events, since they will form a standard to which other event detection signals will be compared. In the various scenarios illustrated in FIG. 64, the neurological event detection signal is graphically shown as the upper signal in each of the examples shown in the left-hand column, while the cardiac event detection signal is graphically shown as the lower signal in each of the examples. The neurological event detection signal is typically the output of a detection algorithm (e.g., a seizure detection algorithm) that is based on an EEG input signal, and is basically an "ON-OFF" type signal that indicates the start times ($START_N$ in FIG. 64) and end times (END_N) of detected neurological events (such as seizures). The ECG signal may be considered a "secondary signal"—it is not initially known whether events detected from the ECG signal may be useful to facilitate neurological event detection. One goal of certain embodiments of the invention is to determine if processing the ECG signal provides added benefit in improving neurological event detection performance.

In some embodiments, the patient may be monitored until a sufficient number of detections in one or both of the data streams are observed (the number of required events may be programmable). In some embodiments, neurological events detected in the EEG data stream may be further classified by the user, via a programmer interface, to indicate whether they are clinical seizures (TP-C), sub-clinical seizures (TP-N), or false positive detections (FP), for example. Likewise, cardiac events detected in the ECG signal may be further classified to indicate the type of cardiac abnormality. The further classification of detected neurological and cardiac events may, in some cases, provide additional information helpful in determining whether (and how) a cardiac event detection signal may improve neurological event detection. For example, removing false positives from the neurological event detection signal might improve the quality of the information obtained from comparing a cardiac event detection signal to the neurological event detection signal. Similarly, comparing certain types of detected cardiac events (e.g., a defined subset of the detected cardiac events) to the detected neurological events might provide an indication of which types of cardiac events facilitate neurological event detection (and which do not).

In some embodiments, a number of comparisons may be made (e.g., a number of concordance calculations may be performed) between event detection signals simply by restricting one or both signals to certain event types (e.g., calculating concordance between TP-C neurological events and atrial fibrillation cardiac events).

The concordance between the neurological and cardiac event detection signals may be evaluated in a number of ways. The concordance may be defined as the number of matched events divided by the number of neurological events detected over a given period of time. The concordance may also be defined as the number of matched events divided by the total number of detected events (both cardiac and neurological events). Other ways of defining the concordance calculation may produce useful information, and such variants may be deemed to fall within the scope of the invention as claimed.

Other ways of defining concordance may be similarly established, for example, by using information obtained from the matching test. For example, rather than counting the number of matched events uniformly, a weighting factor could be applied to each matched event according to the category assigned from the matching test. A weighting factor of 1.0 might be applied for TP1 (Equal-Equal) matched events, for example. A weighting factor less than 1.0 (e.g., 0.5) may be applied for matched events in which the cardiac event lags behind the neurological event somewhat (e.g., TP4, TP7, and TP8), for example. A weighting factor greater than 1.0 (e.g., 2.0) may be applied for matched events in which the cardiac event precedes the neurological event somewhat (e.g., TP2, TP3, TP6, and TP9), for example. The weighting factors themselves could be programmable parameters, for example, and could be modified by a physician/operator for the particular needs of an individual patient. Thus, a concordance value calculated using weighting factors as described above could produce a result that accounts for the timing of the cardiac events relative to the matched neurological events.

In some embodiments, the matching test may be performed in a "post-processing" mode, typically by an external programmer system and/or computer. For example, neurological and cardiac event detection signals may be stored in an implantable device, and may be subsequently retrieved for analysis and post-processing by a programmer via a telemetry link, as is known in the art. The programmer and/or other computing equipment may include software instructions that can perform the matching test on the retrieved event detection signals, and may also have the ability to compute a rate of concordance, for example, according to certain embodiments of the invention.

In some embodiments, "real-time" performance of the matching test may be performed, for example, by an implantable medical device. A device according to certain embodiments of the invention may obtain a predefined minimum number of detected events (e.g., 10 detected neurological events) before performing the matching test on stored cardiac and neurological events. In some embodiments, the results of the matching test (including measured rates of concordance, false positive rates, etc.) may be stored in memory in the device and may be retrieved by a programming system for subsequent analysis. In some embodiments, the device may determine that, based upon the matching test results, the cardiac signal (and the associated cardiac event detection signal) should be enabled for detecting neurological events. In an embodiment of the invention, the device may be further adapted to deliver therapy to treat a neurological event in response to a detected cardiac event based upon the results of the matching test.

Certain embodiments of the invention may include an implantable device adapted to deliver therapy for treating cardiac events (e.g., pacing pulses to treat a bradycardia episode, or defibrillation shocks to treat ventricular fibrillation). In such an embodiment, it may be desirable to employ different cardiac event detection parameters and/or cardiac therapy parameters based upon real-time matching test results. For example, a detected high heart rate cardiac event that is not matched with a neurological event may warrant a certain type of cardiac therapy (e.g., anti-tachycardia pacing to treat ventricular tachycardia), whereas a comparable detected high heart rate that is matched with a neurological event may warrant either (i) a different type or level of cardiac therapy, or (ii) a different threshold for triggering cardiac therapy, or (iii) both. Examples of cardiac therapy outputs that can be varied include pacing rate, amplitude, and pulse width, and energy levels of defibrillation shocks. Examples of thresholds for

cardiac detection parameters that can be varied include heart rate, change in heart rate, and number of PVCs.

After the matching test has been performed, the physician (via a programmer, for example) may indicate whether the following conditions are true: (1) a high rate of concordance between detections in the EEG and ECG data streams; (2) earlier detection in the ECG signal relative to the EEG signal; and (3) a low rate of false positives and/or false negatives in the ECG signal. If true, this may indicate that the ECG provides value in neurological event detection.

Using this information, the physician may choose to activate the ECG algorithm—that is, to enable the cardiac event detection signal for use in neurological event detection. Determination of whether to “add in” the ECG signal (e.g., to activate it in combination with the EEG signal) for neurological event monitoring and/or treatment may be based on satisfying one or more of the above stated conditions. This process can be automated by defining programmable threshold values for each of the stated conditions. The process is described in FIG. 66.

Alternatively, the physician could also compare matching test results run on the EEG signals only (Test 1) vs. the combined EEG+ECG signals (Test 2). This method may, for example, require a physician to manually mark the electrographic onset (EO) and the electrographic termination (ET) (e.g., using a programmer) for all neurological events identified by the physician during the monitoring period. This would form the “primary” signal against which the Test 1 and Test 2 signals would be compared (e.g., using the matching test). Using the physician-marked neurological event detection signal as the primary signal, detections from the single (Test 1) and combined (Test 2) data streams are separately run through the matching test. The programmer may display matching test results for the two signals, providing values for concordance, sensitivity and specificity, for example, for both the single and combined algorithms, which can be compared.

The physician may decide not to enable the ECG algorithm for detecting neurological events if, for example, the matching tests show no additional improvement in neurological event detection performance using the ECG, or if the specificity using the ECG signal and detection algorithm is low. In such cases, the physician may enable a mode of passive ECG recording, substantially as described in U.S. Published Patent Application 2006/0224067 (P0021630.00), with the intended use of documenting cardiovascular changes during ictal periods in the EEG.

Monitor+Treatment (Brain)

FIG. 41 is a block diagram of the electronic circuitry that makes up full Monitor/Brain Therapy device 300 (FIG. 11) in accordance with the presently disclosed alternative embodiment of the invention. As can be seen from FIG. 41, Monitor/Brain Therapy device 300 comprises a primary control circuit 720 that is described herein above in conjunction with FIG. 26. In addition the Monitor/Brain Therapy device 300 of FIG. 41 also includes an amplifier 725 to amplify and sense EEG signals from a cranially implanted lead (one embodiment of a brain monitoring element 18) and a therapy module for providing therapy to the brain. The therapy module may be a drug delivery pump or an electrical stimulator or a brain cooling mechanism or other components depending on the treatment modality. In the embodiment of FIG. 41, the therapy module is an output stimulator 729 for stimulation of the brain. The CPU 732, in conjunction with software program in RAM/ROM 730, integrates the information from the sensed cardiac, respiration and EEG signals, detects the onset of cerebral, cardiac or respiratory anomalies, provides preprogrammed stimulation therapy to the patient's brain via a brain lead that

may be the same as monitoring element 18, formats and stores diagnostic data for later retrieval by the patient's clinician and, optionally, may warn or alert the patient, patient caregiver or remote monitoring location. See flow diagram and description as described below in association with FIG. 56.

FIG. 42 is a block diagram of the electronic circuitry that makes up full Monitor/Brain Therapy device 320 (FIG. 12A) in accordance with the presently disclosed alternative embodiment of the invention. As can be seen from FIG. 42, Monitor/Brain Therapy device 320 comprises a primary control circuit 720 and MV circuit 722 that are described herein above in conjunction with FIG. 28. In addition the Monitor/Brain Therapy device of FIG. 42 also includes an amplifier 725 to amplify and sense EEG signals from a cranially implanted monitoring element 18 and an output stimulator 729 to provide brain stimulation. The CPU 732, in conjunction with software program in RAM/ROM 730, integrates the information from the sensed cardiac, respiration and EEG signals, detects the onset of cerebral, cardiac or respiratory anomalies, provides preprogrammed stimulation therapy to the patient's brain via a lead that may be the same as brain monitoring element 18, formats and stores diagnostic data for later retrieval by the patient's clinician and, optionally, may warn or alert the patient, patient caregiver or remote monitoring location. See flow diagram and description as described below in association with FIG. 56.

FIG. 43 is a block diagram of the electronic circuitry that makes up full Monitor/Brain Therapy device 321 (FIG. 12B) in accordance with the presently disclosed alternative embodiment of the invention. As can be seen from FIG. 43, Monitor/Brain Therapy device 321 in combination with a cranially implanted Monitor/Brain Therapy unit 26 in a patient 10 includes a primary control circuit 720 and MV circuit 722 that are described herein above in conjunction with FIG. 28. A 2-way wireless telemetry communication link 30 connects the Monitor/Therapy unit 26 and Monitor/Brain Therapy unit 321 via antennas 736. The wireless communication link 30 may consist of an RF link (such as described in U.S. Pat. No. 5,683,432 “Adaptive Performance-Optimizing Communication System for Communicating with an Implantable Medical Device” to Goedeke, et al, an electromagnetic/ionic transmission (such as described in U.S. Pat. No. 4,987,897 “Body Bus Medical Device Communication System” to Funke) or acoustic transmission (such as described in U.S. Pat. No. 5,113,859 “Acoustic Body Bus Medical Device Communication System” to Funke). Monitor/Brain Therapy unit 26 contains an amplifier 725 to amplify and sense EEG signals from a cranially implanted brain monitoring element 18 such as a lead and an output stimulator 729 for stimulation of the brain. Monitor 26 may be constructed as substantially described in US Publication No. 20040176817 “Modular implantable medical device” to Wahlstrand et al. or U.S. Pat. No. 5,782,891 “Implantable Ceramic Enclosure for Pacing, Neurological and Other Medical Applications in the Human Body” to Hassler, et al or U.S. Pat. No. 6,427,086 “Means and Method for the Intracranial Placement of a Neurostimulator” to Fischell, et al. EEG sensing is accomplished by the use of integrated electrodes in the housing of monitor 26 or, alternatively, by a brain monitoring element 18 such as a cranially implanted leads.

Specifically, CPU 732, in conjunction with software program in RAM/ROM 730, integrates the information from the sensed cardiac, respiration and EEG signals, detects the onset of cerebral, cardiac or respiratory anomalies, provides preprogrammed stimulation therapy to the patient's brain via a lead or other therapy delivery device (that could be the same as brain monitoring element 18), formats and stores diagnos-

tic data for later retrieval by the patient's clinician and, optionally, may warn or alert the patient, patient caregiver or remote monitoring location. See flow diagram and description as described below in association with FIG. 56.

FIG. 44 is a block diagram of one embodiment of the electronic circuitry that makes up full Monitor/Brain Therapy device 340 with a brain monitoring element 18 (e.g., lead) and cardiac or respiratory monitoring element 14 such as sensor stub 20 (FIG. 13) in accordance with the presently disclosed alternative embodiment of the invention. As can be seen from FIG. 44, Monitor/Brain Therapy device 340 comprises a primary control circuit 720 and MV circuit 722 that were described herein above in conjunction with FIG. 28. In addition, the full Monitor/Brain Therapy device 340 of FIG. 44 also includes an amplifier 725 to amplify and sense EEG signals from a brain monitoring element 18 such as a cranially implanted lead. Additionally, the full Monitor/Brain Therapy device 340 of FIG. 44 also includes a stimulator 729 for providing stimulation to the brain through brain monitoring element 18 such as a cranially implanted lead. The CPU 732, in conjunction with a software program resident in RAM/ROM 730, integrates the information from the sensed cardiac, respiration and EEG signals, detects the onset of cerebral, cardiac or respiratory anomalies, provides preprogrammed stimulation therapy to the patient's brain via a therapeutic element such as brain monitoring element 18 which may be a lead, formats and stores diagnostic data for later retrieval by the patient's clinician and, optionally, may warn or alert the patient, patient caregiver or remote monitoring location. See flow diagram and description as described below in association with FIG. 56.

FIG. 45 is a block diagram of one embodiment of the electronic circuitry that makes up external patch 160/full Monitor/Brain Therapy device 360 with a brain monitoring element 18 that may be used for sensing and application of therapy (in the case of therapy being electrical stimulation) (FIG. 8) in accordance with the presently disclosed alternative embodiment of the invention. As can be seen from FIG. 45, Monitor/Brain Therapy device 360 comprises a primary control circuit 720 and external patch comprises a cardiac/MV (minute ventilation) circuit 160, the functions of which have been described in detail above in conjunction with the system of FIG. 28. Intrinsic cardiac signals are sensed by electrodes affixed to the patient's skin, amplified by amplifier 724, sent to primary control circuit 720 and processed by CPU 732 and software program resident in RAM/ROM 730. Cardiac anomalies are detected such as heart rate variability, QT variability, QT.sub.C, sinus arrest, and various arrhythmias such as sinus, atrial and ventricular tachycardias. Respiration sensing is accomplished by low pass filtering the sensed and amplified intrinsic cardiac signals as shown in FIG. 27 or, alternatively, by using the MV/Z measurement circuitry of external patch 160 as described above in connection with FIG. 28. Respiration anomalies (such as reduced or cessation of tidal volume and apnea) are evaluated and detected by CPU 732 and software resident in RAM/ROM 730.

The CPU 732, in conjunction with a software program resident in RAM/ROM 730, integrates the information from the sensed cardiac, respiration and EEG signals, detects the onset of cerebral, cardiac or respiratory anomalies, provides preprogrammed stimulation therapy to the patient's brain via lead 18, formats and stores diagnostic data for later retrieval by the patient's clinician and, optionally, may warn or alert the patient, patient caregiver or remote monitoring location. See flow diagram and description as described below in association with FIG. 56.

The circuitry and function of the device 340 shown in FIG. 44 and described herein above may also be used for the full Monitor/Brain Therapy device 380 with integrated electrode 24 brain lead 18 (FIG. 15). As described above in association with core Monitor 340, thoracic impedance via impedance/voltage converter as measured from the case of monitor 340 to the integrated electrode 24 using a sampling frequency of approximately 16 Hz as substantially described in U.S. Pat. No. 4,596,251 "Minute Ventilation Dependant Rate Responsive Pacer" to Plicchi, et al. The Monitor 380 of this alternative embodiment utilizes the same circuitry of Monitor 340 but connected to the integrated electrode 24 on brain lead 18 instead of the sensor stub of Monitor 340.

Upon detection of either/or a cardiac or respiration anomaly, CPU 732, under control of firmware resident in RAM/ROM 730, will initiate recording of the appropriate diagnostic information into RAM of RAM/ROM 730, provides preprogrammed stimulation therapy to the patient's brain via lead 18, formats and stores diagnostic data for later retrieval by the patient's clinician and, optionally, may warn or alert the patient, patient caregiver or remote monitoring location. See flow diagram and description as described below in association with FIG. 56.

FIG. 46 is a block diagram of the electronic circuitry that makes up full Monitor/Brain Therapy device 400 (FIG. 20) in accordance with the presently disclosed alternative embodiment of the invention. As can be seen from FIG. 46, Monitor/Brain Therapy device 400 comprises a primary control circuit 720 (sensing cardiac and respiration parameters) that is described herein above in conjunction with FIG. 26. In addition the Monitor/Brain Therapy device 400 connects via a 2-way wireless communication link 30 to a cranially implanted EEG sensor and brain stimulator 26. EEG sensor and brain stimulator 26 contains an amplifier 725 to amplify and sense EEG signals from a cranially implanted lead 18 and an output stimulator 729 for stimulation of the brain. The CPU 732, in conjunction with software program in RAM/ROM 730, integrates the information from the sensed cardiac, respiration and EEG signals, detects the onset of cerebral, cardiac or respiratory anomalies, provides preprogrammed stimulation therapy to the patient's brain via lead 18, formats and stores diagnostic data for later retrieval by the patient's clinician and, optionally, may warn or alert the patient, patient caregiver or remote monitoring location. See flow diagram and description as described below in association with FIG. 56.

FIG. 47 is a block diagram of the electronic circuitry that makes up full Monitor/Brain Therapy device 420 (FIG. 21) in accordance with the presently disclosed alternative embodiment of the invention. As can be seen from FIG. 47, Monitor/Brain Therapy device 420 comprises a primary control circuit 720 (sensing cardiac and respiration parameters) that is configured as an external patch affixed to a patient and whose function is described herein above in conjunction with FIG. 26. In addition, the Monitor/Brain Therapy device 420 comprises to a cranially implanted EEG sensor and brain stimulator 26 connected to the primary control circuit 720 via a 2-way wireless communication link 30. The wireless communication link 30 may consist of an RF link (such as described in U.S. Pat. No. 5,683,432 "Adaptive Performance-Optimizing Communication System for Communicating with an Implantable Medical Device" to Goedeke, et al.), an electromagnetic/ionic transmission (such as described in U.S. Pat. No. 4,987,897 "Body Bus Medical Device Communication System" to Funke) or acoustic transmission (such as described in U.S. Pat. No. 5,113,859 "Acoustic Body Bus Medical Device Communication System" to Funke). EEG

sensor and brain stimulator **26** contains an amplifier **725** to amplify and sense EEG signals from a cranially implanted lead **18** and an output stimulator **729** for stimulation of the brain. The CPU **732**, in conjunction with software program in RAM/ROM **730**, integrates the information from the sensed cardiac, respiration and EEG signals, detects the onset of cerebral, cardiac or respiratory anomalies, provides preprogrammed stimulation therapy to the patient's brain via lead **18**, formats and stores diagnostic data for later retrieval by the patient's clinician and, optionally, may warn or alert the patient, patient caregiver or remote monitoring location. See flow diagram and description as described below in association with FIG. **56**.

Monitor+Treatment (Brain+Respiration)

FIG. **48** is a block diagram of the electronic circuitry that makes up full Monitor/Brain and Respiration Therapy device **440** (FIG. **16A**) in accordance with the presently disclosed alternative embodiment of the invention. As can be seen from FIG. **48**, Monitor/Brain and Respiration Therapy device **440** comprises a primary control circuit **720** and MV circuit **722** whose function was described herein above in conjunction with FIG. **28**. In addition the Monitor/Brain and Respiration Therapy device of FIG. **48** also includes an amplifier **725** to amplify and sense EEG signals from a cranially implanted lead **18** and an output stimulator **729** to provide brain stimulation via cranially implanted lead **18** and phrenic nerve stimulation via respiration lead **28**. The CPU **732**, in conjunction with software program in RAM/ROM **730**, integrates the information from the sensed cardiac, respiration and EEG signals, detects the onset of cerebral, cardiac or respiratory anomalies, provides preprogrammed stimulation therapy to the patient's brain via lead **18** and stimulation of the patient's phrenic nerve via respiration lead **28**, formats and stores diagnostic data for later retrieval by the patient's clinician and, optionally, may warn or alert the patient, patient caregiver or remote monitoring location. Optionally, lead **28** may connect to the diaphragm to provide direct diaphragmatic stimulation. See flow diagram and description as described below in association with FIG. **56**.

FIG. **49** is a block diagram of the electronic circuitry that makes up full Monitor/Brain and Respiration Therapy device **441** (FIG. **16B**) in accordance with the presently disclosed alternative embodiment of the invention. As can be seen from FIG. **49**, Monitor/Brain and Respiration Therapy device **441** in combination with a cranially implanted Monitor/Brain Therapy unit **26** in a patient **10** includes a primary control circuit **720** and MV circuit **722** that are described herein above in conjunction with FIG. **28**. A 2-way wireless telemetry communication link **30** connects the Monitor/Therapy unit **26** and Monitor/Brain and Respiration Therapy unit **441** via antennas **736**. The wireless communication link **30** may consist of an RF link (such as described in U.S. Pat. No. 5,683,432 "Adaptive Performance-Optimizing Communication System for Communicating with an Implantable Medical Device" to Goedeke, et al), an electromagnetic/ionic transmission (such as described in U.S. Pat. No. 4,987,897 "Body Bus Medical Device Communication System" to Funke) or acoustic transmission (such as described in U.S. Pat. No. 5,113,859 "Acoustic Body Bus Medical Device Communication System" to Funke). Monitor/Brain Therapy unit **26** contains an amplifier **725** to amplify and sense EEG signals from a cranially implanted lead **18** and an output stimulator **729** for stimulation of the brain. Monitor **26** may be constructed as substantially described in US Publication No. 20040176817 "Modular implantable medical device" to Wahlstrand et al. or U.S. Pat. No. 5,782,891 "Implantable Ceramic Enclosure for Pacing, Neurological and Other Medi-

cal Applications in the Human Body" to Hassler, et al or U.S. Pat. No. 6,427,086 "Means and Method for the Intracranial Placement of a Neurostimulator" to Fischell, et al. EEG sensing is accomplished by the use of integrated electrodes in the housing of monitor **26** or, alternatively, by cranially implanted leads **18**.

Specifically, CPU **732**, in conjunction with software program in RAM/ROM **730**, integrates the information from the sensed cardiac, respiration and EEG signals, detects the onset of cerebral, cardiac or respiratory anomalies, provides preprogrammed stimulation therapy to the patient's brain via lead **18** and to the phrenic nerve via respiration lead **28**, formats and stores diagnostic data for later retrieval by the patient's clinician and, optionally, may warn or alert the patient, patient caregiver or remote monitoring location. Optionally, lead **28** may connect to the diaphragm to provide direct diaphragmatic stimulation. See flow diagram and description as described below in association with FIG. **56**.

FIG. **50** is a block diagram of the electronic circuitry that makes up full Monitor/Brain and Respiration Therapy device **460** with a brain lead **18**, phrenic nerve lead **28** and sensor stub **20** (FIG. **17**) in accordance with the presently disclosed alternative embodiment of the invention. As can be seen from FIG. **50**, Monitor/Brain and Respiration Therapy device **460** comprises a primary control circuit **720** and MV circuit **722** whose function was described herein above in conjunction with FIG. **28**. In addition, the full Monitor/Brain and Respiration Therapy device **460** of FIG. **50** also includes an amplifier **725** to amplify and sense EEG signals from a cranially implanted lead **18**. Additionally, the full Monitor/Brain Therapy device **340** of FIG. **44** also includes a stimulator **729** for providing stimulation to the brain through cranially implanted lead **18** and phrenic nerve stimulation via respiration lead **28**. The CPU **732**, in conjunction with a software program resident in RAM/ROM **730**, integrates the information from the sensed cardiac, respiration and EEG signals, detects the onset of cerebral, cardiac or respiratory anomalies, provides preprogrammed stimulation therapy to the patient's brain via lead **18** and stimulation of the patient's phrenic nerve via respiration lead **28**, formats and stores diagnostic data for later retrieval by the patient's clinician and, optionally, may warn or alert the patient, patient caregiver or remote monitoring location. See flow diagram and description as described below in association with FIG. **56**.

The circuitry and function of the device **460** shown in FIG. **50** and described herein above may also be used for the full Monitor/Brain and Respiration Therapy device **480** with integrated electrode **24** brain lead **18** and phrenic nerve lead **28** (FIG. **18**). As described above in association with Monitor/Brain and Respiration Therapy device **460**, thoracic impedance via impedance/voltage converter as measured from the case of monitor **480** to the integrated electrode **24** using a sampling frequency of approximately 16 Hz as substantially described in U.S. Pat. No. 4,596,251 "Minute Ventilation Dependant Rate Responsive Pacer" to Plicchi, et al. The Monitor/Brain and Respiration Therapy device **480** of this alternative embodiment utilizes the same circuitry of Monitor/Brain and Respiration Therapy device **460** but connected to the integrated electrode **24** on brain lead **18** instead of the sensor stub **20** of Monitor/Brain and Respiration Therapy device **340**.

Upon detection of either/or a cardiac or respiration anomaly, CPU **732**, under control of firmware resident in RAM/ROM **730**, will initiate recording of the appropriate diagnostic information into RAM of RAM/ROM **730**, provides preprogrammed stimulation therapy to the patient's brain via lead **18** and stimulation of the patient's phrenic

nerve via respiration lead **28**, formats and stores diagnostic data for later retrieval by the patient's clinician and, optionally, may warn or alert the patient, patient caregiver or remote monitoring location. See flow diagram and description as described below in association with FIG. **56**.

The circuitry and function of the device **460** shown in FIG. **50** and described herein above may also be used for the full Monitor/Brain and Respiration Therapy device **500** with brain lead **18** and integrated electrode **24** phrenic nerve lead **28** (FIG. **19**). As described above in association with Monitor/Brain and Respiration Therapy device **460**, thoracic impedance via impedance/voltage converter as measured from the case of monitor **500** to the integrated electrode **24** using a sampling frequency of approximately 16 Hz as substantially described in U.S. Pat. No. 4,596,251 "Minute Ventilation Dependant Rate Responsive Pacer" to Plicchi, et al. The Monitor/Brain and Respiration Therapy device **500** of this alternative embodiment utilizes the same circuitry of Monitor/Brain and Respiration Therapy device **460** but connected to the integrated electrode **24** on phrenic nerve lead **28** instead of the sensor stub **20** of Monitor/Brain and Respiration Therapy device **340**.

Upon detection of either/or a cardiac or respiration anomaly, CPU **732**, under control of firmware resident in RAM/ROM **730**, will initiate recording of the appropriate diagnostic information into RAM of RAM/ROM **730**, provides preprogrammed stimulation therapy to the patient's brain via lead **18** and stimulation of the patient's phrenic nerve via respiration lead **28**, formats and stores diagnostic data for later retrieval by the patient's clinician and, optionally, may warn or alert the patient, patient caregiver or remote monitoring location. See flow diagram and description as described below in association with FIG. **56**.

Monitor+Treatment (Brain+Cardiac)

FIG. **51** is a block diagram of the electronic circuitry that makes up full Monitor/Brain and Cardiac Therapy device **520** (FIG. **24A**) in accordance with the presently disclosed alternative embodiment of the invention. As can be seen from FIG. **51**, Monitor/Brain and Cardiac Therapy device **520** comprises a primary control circuit **720** and MV circuit **722** whose function is described herein above in conjunction with FIG. **28** and U.S. Pat. No. 5,271,395 "Method and Apparatus for Rate Responsive Cardiac Pacing" to Wahlstrand et al. In addition, the Monitor/Brain and Cardiac Therapy device of FIG. **51** also includes an amplifier **725** to amplify and sense EEG signals from a cranially implanted lead **18** and an output stimulator **729** to provide brain stimulation. The CPU **732**, in conjunction with software program in RAM/ROM **730**, integrates the information from the sensed cardiac, respiration and EEG signals, detects the onset of cerebral, cardiac or respiratory anomalies, provides preprogrammed stimulation therapy to the patient's brain via lead **18** and stimulation to the patient's heart via cardiac lead(s) **16**, formats and stores diagnostic data for later retrieval by the patient's clinician and, optionally, may warn or alert the patient, patient caregiver or remote monitoring location. See flow diagram and description as described below in association with FIG. **54**.

FIG. **52** is a block diagram of the electronic circuitry that makes up full Monitor/Brain and Cardiac Therapy device **521** (FIG. **24B**) in accordance with the presently disclosed alternative embodiment of the invention. As can be seen from FIG. **52**, Monitor/Brain and Cardiac Therapy device **521** in combination with a cranially implanted Monitor/Brain Therapy unit **26** in a patient **10** includes a primary control circuit **720** and MV circuit **722** that are described herein above in conjunction with FIG. **28**. A 2-way wireless telemetry communication link **30** connects the Monitor/Therapy unit **26** and

Monitor/Brain and Cardiac Therapy unit **521** via antennas **736**. The wireless communication link **30** may consist of an RF link (such as described in U.S. Pat. No. 5,683,432 "Adaptive Performance-Optimizing Communication System for Communicating with an Implantable Medical Device" to Goedeke, et al), an electromagnetic/ionic transmission (such as described in U.S. Pat. No. 4,987,897 "Body Bus Medical Device Communication System" to Funke) or acoustic transmission (such as described in U.S. Pat. No. 5,113,859 "Acoustic Body Bus Medical Device Communication System" to Funke). Monitor/Brain Therapy unit **26** contains an amplifier **725** to amplify and sense EEG signals from a cranially implanted lead **18** and an output stimulator **729** for stimulation of the brain. Monitor **26** may be constructed as substantially described in US Publication No. 20040176817 "Modular implantable medical device" to Wahlstrand et al. or U.S. Pat. No. 5,782,891 "Implantable Ceramic Enclosure for Pacing, Neurological and Other Medical Applications in the Human Body" to Hassler, et al or U.S. Pat. No. 6,427,086 "Means and Method for the Intracranial Placement of a Neurostimulator" to Fischell, et al. EEG sensing is accomplished by the use of integrated electrodes in the housing of monitor **26** or, alternatively, by cranially implanted leads **18**.

Specifically, CPU **732**, in conjunction with software program in RAM/ROM **730**, integrates the information from the sensed cardiac, respiration and EEG signals, detects the onset of cerebral, cardiac or respiratory anomalies, provides preprogrammed stimulation therapy to the patient's brain via lead **18** and cardiac stimulation via cardiac leads **16**, formats and stores diagnostic data for later retrieval by the patient's clinician and, optionally, may warn or alert the patient, patient caregiver or remote monitoring location. See flow diagram and description as described below in association with FIG. **56**.

Alternatively, the device as described above in connection to the Monitor and Treatment (Brain and Cardiac) system of FIG. **52** may include a pacemaker/cardioverter/defibrillator (PCD) to enable the termination of cardiac arrhythmias during, or prior to, neurological events. The PCD may be of the type as substantially described in U.S. Pat. No. 5,545,186 "Prioritized Rule Based Method and Apparatus for Diagnosis and Treatment of Arrhythmias" to Olson; U.S. Pat. No. 5,354,316 "Method and Apparatus for Detection and Treatment of Tachycardia and fibrillation" to Kiemel or U.S. Pat. No. 5,314,430 "Atrial Defibrillator Employing Transvenous and Subcutaneous Electrodes and Method of Use" to Bardy. In one embodiment of the present invention, the PCD arrhythmia detection circuitry/algorithms are enabled upon the sensing of the onset or impending onset of a seizure. Upon seizure termination, the arrhythmia detection circuitry/algorithms are turned off.

FIG. **53** is a block diagram of the electronic circuitry that makes up full Monitor/Brain and Cardiac Therapy device **540** (FIG. **22**) in accordance with the presently disclosed alternative embodiment of the invention. The system as shown in FIG. **53** is used for patients temporarily at risk of sudden death, for example, while the patient's physician is trying different epileptic drugs and titrating dosages to eliminate/minimize seizures or their severity. As can be seen from FIG. **53**, Monitor/Brain and Cardiac Therapy device **540** comprises patient worn vest defibrillator **34** containing primary control circuit **720** whose function is described herein above in conjunction with FIG. **26** and in more detail in U.S. Pat. No. 6,280,461 "Patient-Worn Energy Delivery Apparatus" to Glegyak, et. In addition the Monitor/Brain and Cardiac Therapy device connects via a 2-way wireless communication link **30** to a cranially implanted brain stimulator **540**. The

wireless communication link **30** may consist of an RF link (such as described in U.S. Pat. No. 5,683,432 "Adaptive Performance-Optimizing Communication System for Communicating with an Implantable Medical Device" to Goedeke, et al), an electromagnetic/ionic transmission (such as described in U.S. Pat. No. 4,987,897 "Body Bus Medical Device Communication System" to Funke) or acoustic transmission (such as described in U.S. Pat. No. 5,113,859 "Acoustic Body Bus Medical Device Communication System" to Funke). EEG sensor and brain stimulator **540** contains an amplifier **725** to amplify and sense EEG signals from a cranially implanted lead **18** and an output stimulator **729**. The CPU **732**, in conjunction with software program in RAM/ROM **730**, integrates the information from the sensed cardiac, respiration and EEG signals, detects the onset of cerebral, cardiac or respiratory anomalies, provides preprogrammed stimulation therapy to the patient's brain via lead **18** and defibrillation therapy via patient worn vest **34**, formats and stores diagnostic data for later retrieval by the patient's clinician and, optionally, may warn or alert the patient, patient caregiver or remote monitoring location. See flow diagram and description as described below in association with FIG. **56**.

The circuitry and function of the device **540** shown in FIG. **53** and described herein above may also be used for the full Monitor/Brain and Cardiac Therapy device **560** with a cranially implanted stimulator in 2-way communication with an leadless subcutaneous implantable defibrillator **36** (ie, "lifeboat", FIG. **23**). The system described in connection with this embodiment is used for patients temporarily at risk of sudden death, for example, while the patient's physician is trying different epileptic drugs and titrating dosages to eliminate/minimize seizures or their severity. As described above in conjunction with FIG. **53**, Monitor/Brain and Cardiac Therapy device **560** comprises a leadless defibrillator **36** containing primary control circuit **720** whose function is described herein above in conjunction with FIG. **26** and in more detail in U.S. Pat. No. 6,647,292 "Unitary Subcutaneous only Implantable Cardioverter-Defibrillator and Optional Pacer" to Bardy.

The Monitor/Brain and Cardiac Therapy device connects via a 2-way wireless communication link **30** to a cranially implanted brain stimulator **560**. The wireless communication link **30** may consist of an RF link (such as described in U.S. Pat. No. 5,683,432 "Adaptive Performance-Optimizing Communication System for Communicating with an Implantable Medical Device" to Goedeke, et al), an electromagnetic/ionic transmission (such as described in U.S. Pat. No. 4,987,897 "Body Bus Medical Device Communication System" to Funke) or acoustic transmission (such as described in U.S. Pat. No. 5,113,859 "Acoustic Body Bus Medical Device Communication System" to Funke). EEG sensor and brain stimulator **560** contains an amplifier **725** to amplify and sense EEG signals from a cranially implanted lead **18** and an output stimulator **729**. The CPU **732**, in conjunction with software program in RAM/ROM **730**, integrates the information from the sensed cardiac, respiration and EEG signals, detects the onset of cerebral, cardiac or respiratory anomalies, provides preprogrammed stimulation therapy to the patient's brain via lead **18** and defibrillation therapy via implanted defibrillator **36**, formats and stores diagnostic data for later retrieval by the patient's clinician and, optionally, may warn or alert the patient, patient caregiver or remote monitoring location. See flow diagram and description as described below in association with FIG. **56**.

Monitor+Treatment (Brain+Respiration+Cardiac)

FIG. **54** is a block diagram of the electronic circuitry that makes up full Monitor/Brain, Respiration and Cardiac

Therapy device **580** (FIG. **25A**) in accordance with the presently disclosed alternative embodiment of the invention. As can be seen from FIG. **54**, Monitor/Brain, Respiration and Cardiac Therapy device **580** comprises a primary control circuit **720** and MV circuit **722** whose function was described herein above in conjunction with FIG. **28**. In addition the Monitor/Brain, Respiration and Cardiac Therapy device of FIG. **54** also includes an amplifier **725** to amplify and sense EEG signals from a cranially implanted lead **18** and an output stimulator **729** to provide brain stimulation via cranially implanted lead **18** and phrenic nerve stimulation via respiration lead **28**. The CPU **732**, in conjunction with software program in RAM/ROM **730**, integrates the information from the sensed cardiac, respiration and EEG signals, detects the onset of cerebral, cardiac or respiratory anomalies, provides preprogrammed stimulation therapy to the patient's brain via lead **18**, stimulation of the patient's phrenic nerve via respiration lead **28** and stimulation of the patient's heart via cardiac leads **16**, formats and stores diagnostic data for later retrieval by the patient's clinician and, optionally, may warn or alert the patient, patient caregiver or remote monitoring location. Optionally, lead **28** may connect to the diaphragm to provide direct diaphragmatic stimulation. See flow diagram and description as described below in association with FIG. **56**.

FIG. **55** is a block diagram of the electronic circuitry that makes up full Monitor/Brain, Respiration and Cardiac Therapy device **581** (FIG. **25B**) in accordance with the presently disclosed alternative embodiment of the invention. As can be seen from FIG. **55**, Monitor/Brain, Respiration and Cardiac Therapy device **581** in combination with a cranially implanted Monitor/Brain Therapy unit **26** in a patient **10** includes a primary control circuit **720** and MV circuit **722** that are described herein above in conjunction with FIG. **28**. A 2-way wireless telemetry communication link **30** connects the Monitor/Therapy unit **26** and Monitor/Brain, Respiration and Cardiac Therapy unit **581** via antennas **736**. The wireless communication link **30** may consist of an RF link (such as described in U.S. Pat. No. 5,683,432 "Adaptive Performance-Optimizing Communication System for Communicating with an Implantable Medical Device" to Goedeke, et al), an electromagnetic/ionic transmission (such as described in U.S. Pat. No. 4,987,897 "Body Bus Medical Device Communication System" to Funke) or acoustic transmission (such as described in U.S. Pat. No. 5,113,859 "Acoustic Body Bus Medical Device Communication System" to Funke). Monitor/Brain Therapy unit **26** contains an amplifier **725** to amplify and sense EEG signals from a cranially implanted lead **18** and an output stimulator **729** for stimulation of the brain. Monitor **26** may be constructed as substantially described in US Publication No. 20040176817 "Modular implantable medical device" to Wahlstrand et al. or U.S. Pat. No. 5,782,891 "Implantable Ceramic Enclosure for Pacing, Neurological and Other Medical Applications in the Human Body" to Hassler, et al or U.S. Pat. No. 6,427,086 "Means and Method for the Intracranial Placement of a Neurostimulator" to Fischell, et al. EEG sensing is accomplished by the use of integrated electrodes in the housing of monitor **26** or, alternatively, by cranially implanted leads **18**.

Specifically, CPU **732**, in conjunction with software program in RAM/ROM **730**, integrates the information from the sensed cardiac, respiration and EEG signals, detects the onset of cerebral, cardiac or respiratory anomalies, provides preprogrammed stimulation therapy to the patient's brain via lead **18**, to the phrenic nerve via respiration lead **28** and to the heart via cardiac leads **16**, formats and stores diagnostic data for later retrieval by the patient's clinician and, optionally,

may warn or alert the patient, patient caregiver or remote monitoring location. Optionally, lead 28 may connect to the diaphragm to provide direct diaphragmatic stimulation. See flow diagram and description as described below in association with FIG. 56.

FIG. 56 is a flow diagram 850 showing operation of a full monitor/therapy sensing and monitoring cardiac, respiration and electroencephalogram parameters for the detection of neurological events as shown and described in embodiments in FIG. 11-25 above. The blocks 802-808 relating to the identification of cardiac activity, and blocks 816-822 relating to identification of respiratory activity, may be activated or deactivated according to the determination of whether they improve the detection of the neurological disorder (see for example the discussion regarding determining concordance). It is noted that the particular detection scheme used for each of the physiologic signals (brain, heart, respiratory) is not restricted to the examples provided here.

In one embodiment, beginning at block 802, the interval between sensed cardiac signals are measured. At block 804, a rate stability measurement is made on each cardiac interval utilizing a heart rate average from block 806. At block 808, a rate stable decision is made based upon preprogrammed parameters. If YES (heart rate is determined to be stable), the flow diagram returns to the HR Measurement block 802. If NO, the rate stability information is provided to Determine Therapy and Duration block 830.

At block 816, thoracic impedance is continuously measured in a sampling operation. At block 818, a MV and respiration rate calculation is made. At block 822, a pulmonary apnea decision is made based upon preprogrammed criteria. If NO (no apnea detected), the flow diagram returns to MV Measurement block 816. If YES, the occurrence of apnea and MV information is provided to Determine Therapy and Duration block 830.

At block 824, the electroencephalogram is sensed and measured. An EEG calculation is performed at block 826. The seizure detection algorithm is executed at block 826. At block 828, a seizure episode is determined. If NO (no seizure detected), the flow diagram returns to EEG Measurement block 824. If YES, the occurrence of a seizure is provided to Determine Therapy and Duration block 830.

Based upon the data presented to it, Determine Therapy and Duration block 830 determines the type of therapy and the duration to block 832, which controls the start of the therapy by evaluating the severity and ranking of each event (i.e., maximum ratio, duration of seizure detection, spread, number of clusters per unit time, number of detections per cluster, duration of an event cluster, duration of a detection, and inter-seizure interval) per co-pending U.S. patent application Publication No. 20040133119 "Scoring of sensed neurological signals for use with a medical device system" to Osorio, et al incorporated herein by reference in its entirety. Block 834 monitors the completion of the determined therapy. If the therapy is not complete, control returns to block 834. If the therapy is determined to be complete, block 834 returns the flow diagram to blocks 802 (Measure HR), 816 (Measure Impedance) and 824 (Measure EEG) to continue the monitoring of cardiac, respiratory and brain signal parameters.

Therapy may consist of neural stimulation, cardiac pacing, cardioversion/defibrillation, and drug delivery via a pump, brain cooling, or any combination of therapies.

When block 830 determines that a therapy is to be initiated Format Diagnostic Data block 812 formats the data from the cardiac, respiration and EEG monitoring channels, adds a time stamp (ie, date and time), type and duration of therapy

and provides the data to block 814 where the data is stored in RAM memory for later retrieval by a clinician via telemetry. Optionally, block 812 may add examples of intrinsic ECG, respiration or EEG signals recorded during a sensed episode/seizure.

The physician may program the devices shown above in relation to FIGS. 11-25 and 41-55 to allow the ECG/respiratory detectors be enabled to trigger the delivery of therapy (i.e., stimulation or drug delivery) to the patient's brain, with goal of aborting seizures earlier or limiting their severity than if using EEG signal detection alone. Either EEG, respiratory or ECG detections may trigger therapy to the brain, depending on which occurs first. The physician may choose the type of ECG or respiratory event to use for triggering therapy to the brain.

Application of Therapy to the Brain Based on Cardiac or Respiratory Signals and Termination of Such Therapy

In the present invention of the devices shown above in relation to FIGS. 11-25 and 41-55, the device is able to terminate or change the cardiac/respiratory initiated treatment, directed at the brain, if a neurological event is not entered within an expected time frame following cardiac detection. This feature allows the device to begin treating a patient's neurological event before its detection in the brain signal. These termination conditions are defined at block 990 of FIG. 40A and 890 of FIG. 40B.

If the cardiac/respiratory initiated brain therapy has been ongoing for some time, and polling of the brain signal (i.e., processing the brain signal with a neurological event detection algorithm) has indicated the patient is not in a neurological event, then the following may be true: 1. Cardiac/respiratory triggered therapy was successful in aborting the neurological event, and therefore, the neurological event is not detectable in the brain signal. 2. The cardiac/respiratory event was not associated with a neurological event.

In either case, it would be appropriate to change (adjust or terminate) cardiac/respiratory initiated therapy directed specifically at aborting a neurological event. FIG. 57A is a flow chart illustrating the processing steps executed by a processor (e.g., CPU 732 or any other processor). At block 1000 the processor monitors the cardiac or respiratory signals. At block 1002, the processor detects a cardiac or respiratory event in the cardiac or respiratory signals. Based upon a cardiac or respiratory event detection at block 1002, the processor activates the therapy module to provide therapy to the brain at block 1004. The brain signal is monitored at block 1006. This may be a continuation of monitoring of the brain that was already ongoing or it may be initiation of brain monitoring. Once the therapy has been initiated from a cardiac or respiratory detection, the therapy may be changed at block 1008 based on the monitoring of the brain signal.

One embodiment of the process of FIG. 57A is illustrated in FIG. 57B. The processor receives the cardiac or respiratory signals at block 1050. A cardiac or respiratory event is detected at block 1052. The therapy module is activated at block 1054 to provide therapy to the brain based on a cardiac or respiratory detection. Once therapy has been initiated from a cardiac/respiratory detection, the device monitors the amount of time therapy has been delivered at block 1056. This time period is programmable. The processor continues to receive a brain signal at block 1058. At decision block 1060 the processor determines when the programmed time period has been exceeded without detection of a neurological event in the brain signal. If the answer is "Yes" (i.e., the cardiac or respiratory initiated brain therapy has been ongoing for the programmed time period without the occurrence of a neurological event in the brain signal), then therapy to the brain is

discontinued at block 1062. If the patient has entered a neurological event while receiving cardiac/respiratory initiated therapy, control of therapy is transferred to the monitoring of the brain by the neurological event detection algorithm, and therapy decisions are made using the brain signals at block 1064. At this point therapy may continue until the EEG detection algorithm determines that the neurological event has ended. Then therapy may be terminated based on the detected end of the neurological event based on the EEG detection algorithm output.

FIG. 40A discussed above shows a process 971 for determining whether to enable the cardiac or respiratory detectors for neurological event detection and treatment. Once the cardiac or respiratory signals have been enabled for neurological event detection monitoring and treatment at block 986 and the neurological event detection algorithm has been enabled for modulation or other input into cardiac or respiratory therapy, the cardiac/respiratory parameters for ictal/post-ictal treatment options are defined at block 987. At block 988, cardiac/respiratory events to treat when in a neurological state are defined. At block 989, cardiac/respiratory events to treat when outside a neurological event are defined. At block 990, therapy termination conditions (i.e., turn over control of brain therapy to the neurological event detection algorithm and terminate if a neurological event is not entered in a programmable period of time) are defined and the monitor starts monitoring or treatment at block 985.

If the matching test of the flow diagram of FIG. 40A shows that one type of cardiac event (type 1) is associated with neurological event onset while other types of cardiac events (type 2) occur frequently, but have no temporal relationship to the neurological event, then the physician may choose to direct therapy to the Brain (or Brain and Heart) upon type 1 event detection or direct therapy to the Heart on type 2 detection.

In the present invention as described in relation to the devices shown above in FIGS. 11-25 and 41-55, the physician is able to selectively choose which cardiac and respiratory events to treat in seizure and non-seizure states. For example, the device may be programmed to treat incidences of tachycardia in non-seizure states, but not in seizure states, where this type of cardiac behavior is expected and considered normal. Also, the patient may experience certain ECG or respiratory abnormalities, which are seizure induced, but cause no complications or increased health risk to the patient. In such cases, the physician may decide to suppress treatment for these events if detected during a seizure. This cannot be accomplished with existing pacemaker technology, which operates on ECG signals only.

There are other instances in which a detected ECG or respiratory abnormality does pose a health risk, regardless of when it occurs and how it was induced. For these events, the physician may choose a mode of operation that treats the ECG/respiratory abnormality in both seizure and non-seizure states (i.e., asystole, apnea).

Additionally, the physician may choose to treat the same ECG/respiratory event in both seizure and non-seizure states, but may define different thresholds (i.e., duration or intensity) for treating the event. For example, during a seizure state, a higher heart rate or sustained occurrence of tachycardia may be required before cardiac treatment is initiated, relative to a non-seizure state. This feature would enable cardiac therapy during status epilepticus, which is a prolonged condition, but suppress it for typical seizure behaviors.

If the matching test of the flow diagram of FIG. 57 shows that the ECG or respiratory signals do not improve seizure detection, but patient is at cardiac risk, the physician may

choose to enable the ECG/respiratory detector to deliver therapy to the heart or diaphragm.

If the matching test of the flow diagram of FIG. 57 shows that the ECG or respiratory signals improves seizure detection, but the patient is also at cardiac risk, the physician may choose to treat the brain (for seizures) with EEG, ECG or respiratory detection, and heart (for cardiac problems) with ECG detection.

Preventative Pacing Therapy

Optionally, the therapy systems of FIGS. 11-25 and 41-55 may also have pre-emptive or preventative pacing capabilities. For example, upon EEG detection of seizure onset or imminent seizure onset, the pacing systems described in conjunction with FIGS. 11-25 and 41-55 may begin preventative overdrive pacing to prevent or mitigate sleep apnea such as described in U.S. Pat. No. 6,126,611 "Apparatus for Management of Sleep Apnea" to Bourgeois. The '611 patent detects sleep apnea and begins to pace the heart at a rate of 70-100 PPM (overdrive pacing the sleep intrinsic rate of typically 30-55 BPM) causing arousal and elimination/prevention of sleep apnea. The herein described invention uses the detection of the onset or impending onset of a seizure to trigger sleep apnea overdrive pacing to preemptively prevent the initiation of apnea. Upon the sensing of seizure termination or a preprogrammed timeout, the sleep apnea prevention overdrive pacing is terminated/inactivated.

Alternatively, the pacing systems may begin ventricular pacing overdrive upon sensing a ventricular premature contraction to prevent the initiation of ventricular arrhythmias such as described in U.S. Pat. No. 4,503,857 "Programmable Cardiac Pacemaker with Microprocessor Control of Pacer Rate" to Boute, et al and U.S. Pat. No. 5,312,451 "Apparatus and Methods for Controlling a Cardiac Pacemaker in the Event of a Ventricular Extrasystole" to Limousin, et al. Upon detection of the onset or impending onset of a seizure ventricular extrasystole overdrive pacing may be initiated, and subsequent to the programmed number of cycles, a slowing of the ventricular rate until either the programmed base rate is reached or a sinus detection occurs. Upon the sensing of seizure termination or a preprogrammed timeout, the sleep apnea prevention overdrive pacing is terminated/inactivated.

Additionally, the pacing systems described in conjunction with FIGS. 11-25 and 41-55 may include AF preventative pacing therapies as described in U.S. Pat. No. 6,185,459 "Method and Apparatus for Prevention of Atrial Tachyarrhythmias" to Mehra, et al or U.S. Pat. No. 6,650,938 "Method and System for Preventing Atrial Fibrillation by Rapid Pacing Intervention" to Boute. The '459 and '938 patents describe systems that sense premature atrial events and initiate overdrive pacing algorithms to prevent the initiation of atrial arrhythmias. In the present invention, upon detection of the onset or impending onset of a seizure, ventricular extrasystole AF overdrive pacing may be initiated, and subsequent to the programmed number of cycles, a slowing of the ventricular rate until either the programmed base rate is reached or a sinus detection occurs. Upon the sensing of seizure termination or a preprogrammed timeout, the sleep apnea prevention overdrive pacing is terminated/inactivated.

Signal Processing

The signal processing of cardiac, respiration or electroencephalogram signals of the above-described embodiments may include analog, continuous wave bandpass filtering as is well known in the art. Additionally, digital signal processing techniques as substantially described in U.S. Pat. No. 6,029,087 "Cardiac Pacing System with Improved Physiological Event Classification Based Upon DSP" to Wohlgenuth and U.S. Pat. No. 6,556,859 "System and Method for Classifying

Sensed Atrial Events in a Cardiac Pacing System” to Wohlge-muth, et al may be used. Additionally, fuzzy logic processing techniques as described in U.S. Pat. No. 5,626,622 “Dual Sensor Rate Responsive Pacemaker” to Cooper and U.S. Pat. No. 5,836,988 “Rate Responsive Pacemaker with Exercise Recovery Using Minute Volume Determination” to Cooper, et al. may be used to determine/detect the occurrence or onset of seizures, respiratory or cardiac anomalies.

The devices of the above-described systems that contain 2 individual units in 2-way communication (e.g., the systems of FIG. 20-23) may optionally transmit events via the communication channel by one of several ways including, but not limited to, individual event logic signal, marker channel or processed signal.

Power Saving and Clock Synchronization

The devices of the above-described systems that contain 2 individual units in 2-way communication (e.g., the systems of FIGS. 20-23, 43, 45-47, 49, 52, 53, 55) may optionally have a reduced power capability during communication. The devices may communicate at a predefined specific time interval with clocks in each unit of the system updated/resynchronized on each communication (as described in U.S. Pat. No. 6,083,248 “World Wide Patient Location and Data Telemetry System for Implantable Medical Devices” to Thompson. Optionally, a receiving unit may open a window at a period interval (e.g., 1 second) for a brief window (e.g., 100 mSec) to look for an incoming transmission from the other system unit.

Drug Pump

The therapy device in above devices as described in systems as described in conjunction with FIGS. 11-25 and 41-55 may optionally contain a drug pump to deliver liquid medicants in lieu of stimulation or in combination with stimulation. Medicants used could include epileptic drugs (examples of such drugs include, but are not limited to intrathecal delivery of CGX-1007 or Baclofen), mental health and mood disorder related drugs, cardiac drugs (examples of such drugs include, but are not limited to, pharmaceutical compositions comprising beta-adrenergic blocking agents, protein emide, type I antiarrhythmic agents such as disopyramide, class II agents such as propafenone, alphaagonists such as ephedrine and midodrine, and other antiarrhythmic agents such as amiodarone, and combinations thereof) or respiratory drugs (examples of such drugs include, but are not limited to diuretics).

Remote Monitoring

The present invention also allows the residential, hospital or ambulatory monitoring of at-risk patients and their implanted medical devices at any time and anywhere in the world (see system 900 FIG. 58). Medical support staff 906 at a remote medical support center 914 may interrogate and read telemetry from the implanted medical device and reprogram its operation while the patient 10 is at very remote or even unknown locations anywhere in the world. Two-way voice communications 910 via satellite 904, cellular via link 32 or land lines 956 with the patient 10 and data/programming communications with the implanted medical device 958 via a belt worn transponder 960 may be initiated by the patient 10 or the medical support staff 906. The location of the patient 10 and the implanted medical device 958 may be determined via GPS 902 and link 908 and communicated to the medical support network in an emergency. Emergency response teams can be dispatched to the determined patient location with the necessary information to prepare for treatment and provide support after arrival on the scene. See for example, U.S. Pat. No. 5,752,976 “World Wide Patient Location and Data Telemetry System for Implantable Medical Devices” to Duffin et al. An alternative or addition to the remote monitoring system as described above in conjunction with FIG. 58 is

shown in the system 950 of FIG. 59, which shows a patient 10 sleeping with an implantable Monitor 958 or optional therapy device as described above in connection with the systems of FIG. 1-57. The implantable device 958, upon detection of a neurological event (such as a seizure), respiratory apnea or cardiac conduction anomaly (ie, heart rate variability, QT extension, arrhythmia) may alert a remote monitoring location via local remote box 952 (as described in U.S. Pat. No. 5,752,976 “World Wide Patient Location and Data Telemetry System for Implantable Medical Devices” to Duffin, et al.) telephone 954 and phone lines 956 or the patient’s care provider via an RF link 32 to a pager-sized remote monitor 960 placed in other locations in the house or carried (ie, belt worn) by the care provider 962. The remote caregiver monitor 960 may include audible buzzes/tones/beeps, vocal, light or vibration to alert the caregiver 962 of patient’s monitor in an alarm/alert condition. The RF link may include RF portable phone frequencies, power line RF links, HomeRF, Bluetooth, ZigBee, WIFI, MICS band (medical implant communications service), or any other interconnect methods as appropriate. Often the care provider 962 may be able to take some action to help the patient 10. For example, the care provider may arouse the patient 10 from a neurological event (such as a SUDEP episode) by shaking them, arousing them, repositioning the patient, or the like.

Patient Alert

The monitor (and optionally therapy) devices as described in systems described above in conjunction with FIG. 1-57 may optionally allow a patient alert to allow the patient an early warning of impending seizure, respiratory or cardiac anomalies via vibration (e.g., piezo buzzer in implanted device, a vibrator as used in a cell phone or pager in a “silent ring” mode in vest, patch or patient activator), audible buzzing or tones (e.g., audible in cranial implant, audible via external patch, patient activator or vest), light (e.g., external vest or patient activator) or vocal (e.g., spoken word in cranial, vest, external patch, or patient activator) indicators of the monitor in an alarm/alert condition.

It will be apparent from the foregoing that while particular embodiments of the invention have been illustrated and described, various modifications can be made without departing from the spirit and scope of the invention. Accordingly, it is not intended that the invention be limited, except as by the appended claims.

What is claimed is:

1. A medical device system comprising:
 - a brain monitoring element for sensing activity of a brain of a patient and outputting a brain signal;
 - a cardiac monitoring element for sensing activity of a heart of the patient and outputting a cardiac signal; and
 - one or more processors configured to communicate with the brain monitoring element and the cardiac monitoring element, the one or more processors configured to:
 - receive the brain signal;
 - identify one or more brain events in the brain signal, each of the brain events having a start time and an end time defining a brain event time period;
 - receive the cardiac signal and store cardiac signal information in one or more data buffers;
 - identify one or more Inter-event portions of the cardiac signal, each of the one or more Inter-event portions corresponding in time to a period that is not a brain event time period;
 - calculate an Inter-event heart-rate variability (HRV) based on the cardiac signal information stored for the one or more Inter-event portions of the cardiac signal but not based on the cardiac signal information cor-

responding in time to the brain event time period of each of the one or more identified brain events; and modify an output of the medical device system based upon the Inter-event HRV.

2. The medical device system of claim 1 wherein the cardiac monitoring element is a leadless ECG electrode.

3. The medical device system of claim 1 wherein the cardiac monitoring element is an implantable cardiac lead.

4. The medical device system of claim 1 wherein the cardiac signal information includes R-R intervals and the Inter-event HRV is a periodic value representative of variability of the R-R intervals in the inter-event portions of the cardiac signal over a defined period.

5. The medical device system of claim 4 wherein the periodic value is representative of variability of the R-R intervals over a one day period.

6. The medical device system of claim 1 wherein the brain events are identified by a seizure detection algorithm.

7. The medical device system of claim 1 wherein the brain events are identified by an algorithm that detects changes in EEG signals indicative of a psychiatric condition.

8. The medical device system of claim 1 wherein the psychiatric condition is a depressive state, and wherein the changes in EEG signals include EEG asymmetry and/or reduced EEG amplitudes.

9. The medical device system of claim 1 wherein the psychiatric condition is an anxiety or panic state, and wherein the changes in EEG signals include increased EEG amplitudes and/or frequency.

10. The medical device system of claim 1 wherein the brain events are identified by the patient indicating an occurrence of symptoms.

11. The medical device system of claim 1 wherein the output being modified is a warning of a patient condition.

12. The medical device system of claim 1 further comprising a therapy module, wherein the output of the medical device system is a therapy delivered by the therapy module to the brain of the patient.

13. The medical device system of claim 12 wherein the one or more processors are configured to modify the output of the therapy module by changing a programmable setting that determines when the therapy module delivers therapy.

14. The medical device system of claim 12 wherein the one or more processors are configured to modify the output of the therapy module by changing a programmable setting that determines a type of therapy to be delivered by the therapy module.

15. The medical device system of claim 1 further comprising a therapy module, wherein the output of the medical device system is a therapy delivered by the therapy module to the heart of the patient.

16. The medical device system of claim 15 wherein the one or more processors are configured to modify the output of the therapy module by changing a programmable setting that determines when the therapy module delivers therapy.

17. The medical device system of claim 1 wherein the one or more processors are configured to modify the output of the therapy module by changing a programmable setting that determines a type of therapy to be delivered by the therapy module.

18. The medical device system of claim 1 wherein the one or more brain events are epileptic seizures, and wherein the brain event time periods corresponding to the seizures define ictal portions of the cardiac signal during the seizures, and inter-ictal portions of the cardiac signal between the seizures.

19. The medical device system of claim 1 wherein the Inter-event HRV is calculated based on Inter-event portions of the cardiac signal corresponding to sleep periods of the patient.

20. The medical device system of claim 1 wherein the Inter-event HRV is a night-time value calculated based on Inter-event portions of the cardiac signal corresponding to defined night-time periods.

21. The medical device system of claim 1 wherein the Inter-event HRV is a day-time value calculated based on Inter-event portions of the cardiac signal corresponding to defined day-time periods.

22. The medical device system of claim 1 wherein the Inter-event HRV is calculated and recorded once every 24 hours.

23. The medical device system of claim 1, wherein the one or more processors are further configured to modify the output of the medical device system only based upon the Inter-event HRV.

24. A medical device system comprising:

a brain monitoring element for sensing activity of a brain of a patient and outputting a brain signal;

a cardiac monitoring element for sensing activity of a heart of the patient and outputting a cardiac signal; and

one or more processors configured to communicate with the brain monitoring element and the cardiac monitoring element, the one or more processors configured to:

receive the brain signal;

identify one or more brain events in the brain signal, each of the brain events having a start time and an end time defining a brain event time period;

receive the cardiac signal and store cardiac signal information in one or more data buffers;

identify one or more Inter-event portions of the cardiac signal, each of the one or more Inter-event portions corresponding in time to a period that is not a brain event time period;

calculate an Inter-event heart-rate variability (HRV) based on the cardiac signal information stored for the one or more Inter-event portions of the cardiac signal; and

modify an output of the medical device system based upon the Inter-event HRV,

wherein the cardiac signal information includes R-R intervals and the Inter-event HRV is a periodic value representative of variability of the R-R intervals in the inter-event portions of the cardiac signal over a defined period, and

wherein the one or more processors are further configured to record a series of the periodic value of the Inter-event HRV to identify a trend.

25. The medical device system of claim 24 wherein the output is modified when the trend meets a threshold criterion.

26. The medical device system of claim 25 wherein the trend meets the threshold criterion when the periodic value changes by more than a certain amount.

27. The medical device system of claim 25 wherein the trend meets the threshold criterion when the periodic value changes by more than a certain percentage.

28. The medical device system of claim 27 wherein the threshold criterion is met when the periodic value changes by more than a certain percentage within a specified period of time.

29. A medical device system comprising:

a brain monitoring element for sensing activity of a brain of a patient and outputting a brain signal;

a cardiac monitoring element for sensing activity of a heart of the patient and outputting a cardiac signal; and one or more processors configured to communicate with the brain monitoring element and the cardiac monitoring element, the one or more processors configured to:

- 5 receive the brain signal;
- identify one or more brain events in the brain signal, each of the brain events having a start time and an end time defining a brain event time period;
- 10 receive the cardiac signal and store cardiac signal information in one or more data buffers;
- identify one or more Inter-event portions of the cardiac signal, each of the one or more Inter-event portions corresponding in time to a period that is not a brain event time period;
- 15 calculate an Inter-event heart-rate variability (HRV) based on the cardiac signal information stored for the one or more Inter-event portions of the cardiac signal; and
- 20 modify an output of the medical device system based upon the Inter-event HRV,
- wherein the cardiac signal information includes R-R intervals and the Inter-event HRV is a periodic value representative of variability of the R-R intervals in the inter-event portions of the cardiac signal over a defined period, and
- 25 wherein the one or more processors are configured to modify the output when the periodic value of the Inter-event HRV meets a threshold criterion.

30. The medical device system of claim 29 wherein the output is modified when the periodic value of the Inter-event HRV decreases below a threshold value.

31. The medical device system of claim 29 wherein the output is modified when the periodic value of the Inter-event HRV decreases by more than a threshold percentage.

32. The medical device system of claim 29 wherein the one or more processors are configured to modify the output when the periodic value of the Inter-event HRV increases a predetermined amount.

33. A medical device system comprising:

- a brain monitoring element for sensing activity of a brain of a patient and outputting a brain signal;
- a cardiac monitoring element for sensing activity of a heart of the patient and outputting a cardiac signal; and
- one or more processors configured to communicate with the brain monitoring element and the cardiac monitoring element, the one or more processors configured to:
- 35 receive the brain signal;
- identify one or more brain events in the brain signal, each of the brain events having a start time and an end time defining a brain event time period;
- receive the cardiac signal and store cardiac signal information in one or more data buffers;
- 40 identify one or more Inter-event portions of the cardiac signal, each of the one or more Inter-event portions corresponding in time to a period that is not a brain event time period;
- calculate an Inter-event heart-rate variability (HRV) based on the cardiac signal information stored for the one or more Inter-event portions of the cardiac signal; and
- 45 modify an output of the medical device system based upon the Inter-event HRV,
- wherein the cardiac signal information includes R-R intervals and the Inter-event HRV is a periodic value
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representative of variability of the R-R intervals in the inter-event portions of the cardiac signal over a defined period, and

wherein the one or more processors are further configured to calculate an unadjusted HRV based on cardiac signal information stored for both Inter-event and Event portions of the cardiac signal, and wherein the output of the medical device system is modified based upon both the Inter-event HRV and the unadjusted HRV.

34. A medical device system comprising:

- a brain monitoring element for sensing activity of a brain of a patient and outputting a brain signal;
- a cardiac monitoring element for sensing activity of a heart of the patient and outputting a cardiac signal; and
- one or more processors configured to communicate with the brain monitoring element and the cardiac monitoring element, the one or more processors configured to:
- 5 receive the brain signal;
- identify one or more brain events in the brain signal, each of the brain events having a start time and an end time defining a brain event time period;
- receive the cardiac signal and store cardiac signal information in one or more data buffers;
- 10 identify one or more Inter-event portions of the cardiac signal, each of the one or more Inter-event portions corresponding in time to a period that is not a brain event time period;
- calculate an Inter-event heart-rate variability (HRV) based on the cardiac signal information stored for the one or more Inter-event portions of the cardiac signal;
- 15 calculate an Event HRV based on the cardiac signal information corresponding in time to each of the one or more brain event time periods; and
- modify an output of the medical device system based upon a comparison between the Inter-event HRV and the Event HRV.
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35. The medical device system of claim 34 wherein the Inter-event HRV is based on a long-term value, and wherein the output of the medical device system is modified when the Event HRV differs from the Inter-event HRV by more than a specified amount.

36. The medical device system of claim 35 wherein the output of the medical device system is modified when the Event HRV is more than a specified percentage less than the Inter-event HRV.

37. The medical device system of claim 34 wherein the one or more processors are further configured to assign a weighting measure to the comparison between the Inter-event HRV and the Event HRV based upon an Inter-event interval.

38. The medical device system of claim 37 wherein the Inter-event interval is the duration of all of the inter-event portions of the cardiac signal on which the Inter-event HRV is based.

39. The medical device system of claim 37 wherein the Inter-event interval is the time elapsed between two successive brain event time periods.

40. A medical device system comprising:

- a brain monitoring element for sensing activity of a brain of a patient and outputting a brain signal;
- a cardiac monitoring element for sensing activity of a heart of the patient and outputting a cardiac signal; and
- one or more processors configured to communicate with the brain monitoring element and the cardiac monitoring element, the one or more processors configured to:
- 5 receive the brain signal;
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identify one or more brain events in the brain signal,
each of the brain events having a start time and an end
time defining a brain event time period;
receive the cardiac signal and store cardiac signal infor-
mation in one or more data buffers; 5
identify one or more Inter-event portions of the cardiac
signal, each of the one or more Inter-event portions
corresponding in time to a period that is not a brain
event time period;
calculate an Inter-event heart-rate variability (HRV) 10
based on the cardiac signal information stored for the
one or more Inter-event portions of the cardiac signal;
and
modify an output of the medical device system based 15
upon the Inter-event HRV,
wherein the Inter-event HRV is calculated based on
Inter-event portions of the cardiac signal correspond-
ing to sleep periods of the patient, and
wherein a sleep sensor is employed to determine the 20
sleep periods of the patient.

41. The medical device system of claim 40 wherein the
sleep sensor determines sleep periods based on body position.

42. The medical device system of claim 40 wherein the
sleep sensor determines sleep periods based on respiration 25
rate.

43. A medical device system comprising:
a brain monitoring element for sensing activity of a brain of
a patient and outputting a brain signal;
a cardiac monitoring element for sensing activity of a heart 30
of the patient and outputting a cardiac signal; and
one or more processors configured to communicate with
the brain monitoring element and the cardiac monitoring
element, the one or more processors configured to:
receive the brain signal; 35
identify one or more brain events in the brain signal,
each of the brain events having a start time and an end
time defining a brain event time period;
receive the cardiac signal and store cardiac signal infor-
mation in one or more data buffers; 40
identify one or more Inter-event portions of the cardiac
signal, each of the one or more Inter-event portions
corresponding in time to a period that is not a brain
event time period;
calculate an Inter-event heart-rate variability (HRV) 45
based on the cardiac signal information stored for the
one or more Inter-event portions of the cardiac signal;
and
modify an output of the medical device system based 50
upon the Inter-event HRV,
wherein the Inter-event HRV comprises both a day-time
and a night-time Inter-event HRV calculated and
recorded once every 24 hours.

44. A medical device system comprising:
a brain monitoring element for sensing activity of a brain of 55
a patient and outputting a brain signal;
a cardiac monitoring element for sensing activity of a heart
of the patient and outputting a cardiac signal; and
one or more processors configured to communicate with
the brain monitoring element and the cardiac monitoring 60
element, the one or more processors configured to:
receive the brain signal;
identify one or more brain events in the brain signal,
each of the brain events having a start time and an end
time defining a brain event time period; 65
receive the cardiac signal and store cardiac signal infor-
mation in one or more data buffers;

identify one or more Inter-event portions of the cardiac
signal, each of the one or more Inter-event portions
corresponding in time to a period that is not a brain
event time period;
calculate an Inter-event heart-rate variability (HRV) 5
based on the cardiac signal information stored for the
one or more Inter-event portions of the cardiac signal;
and
modify an output of the medical device system based 10
upon the Inter-event HRV,
wherein the Inter-event HRV is calculated and recorded
once every 24 hours, and
wherein the one or more processors are further config-
ured to calculate a Therapy HRV based on cardiac 15
signal information corresponding in time to periods of
therapy delivery to the patient.

45. The medical device system of claim 44 wherein the
therapy delivered to the patient includes electrical stimulation
therapy to the brain of the patient.

46. The medical device system of claim 44 wherein the
therapy delivered to the patient includes electrical stimulation
therapy to the heart of the patient.

47. The medical device system of claim 44 wherein the
therapy delivered to the patient includes drug delivery to the 20
patient.

48. A method of treating a patient, the method comprising:
receiving a brain signal from the patient;
identifying one or more brain events in the brain signal,
each of the one or more brain events having a start time
and an end time defining a brain event time period for
each of the one or more brain events;
receiving a cardiac signal from the patient and storing 25
cardiac signal information in one or more data buffers;
identifying one or more Inter-event portions of the cardiac
signal, each of the one or more Inter-event portions
corresponding in time to a period between two of the one
or more brain event time periods;
calculating, with processing circuitry, an Inter-event heart-
rate variability (HRV) based on the cardiac signal infor-
mation stored for the one or more Inter-event portions of
the cardiac signal but not based on the cardiac signal
information corresponding in time to the brain event
time period of each of the one or more identified brain
events; and
modifying a therapy delivered to the patient based upon the
calculated Inter-event HRV.

49. The method of claim 48 wherein the cardiac signal
information includes R-R intervals and the Inter-event HRV
is a periodic value representative of variability of the R-R
intervals in the inter-event portions of the cardiac signal over
a defined period, and
further comprising modifying the therapy when the peri-
odic value of the Inter-event HRV meets a threshold
criterion.

50. The method of claim 49 further comprising modifying
the therapy when the periodic value of the Inter-event HRV
decreases below a threshold value.

51. The method of claim 49 further comprising modifying
the therapy when the periodic value of the Inter-event HRV
decreases by more than a threshold percentage.

52. The method of claim 49 further comprising modifying
the therapy when the periodic value of the Inter-event HRV
increases a predetermined amount.

53. The method of claim 48 further comprising calculating
an Event HRV based on the cardiac signal information cor-
responding in time to each of the one or more brain event time

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periods and further comprising modifying the therapy based upon a comparison between the Inter-event HRV and the Event HRV.

54. The method of claim **53** wherein the Inter-event HRV is based on a long-term value, and further comprising modifying the therapy when the Event HRV differs from the Inter-event HRV by more than a specified amount.

55. The method of claim **54** further comprising modifying the therapy when the Event HRV is more than a specified percentage less than the Inter-event HRV.

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56. The method of claim **53** further comprising assigning a weighting measure to the comparison between the Inter-event HRV and the Event HRV based upon an Inter-event interval.

57. The method of claim **56** wherein the Inter-event interval is the duration of all of the inter-event portions of the cardiac signal on which the Inter-event HRV is based.

58. The method of claim **56** wherein the Inter-event interval is the time elapsed between two successive brain event time periods.

* * * * *

专利名称(译)	用于监测神经系统疾病患者的心脏信号活动的系统和方法		
公开(公告)号	US8112148	公开(公告)日	2012-02-07
申请号	US11/767054	申请日	2007-06-22
[标]申请(专利权)人(译)	美敦力公司		
申请(专利权)人(译)	美敦力公司, INC.		
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IPC分类号	A61B5/00		
CPC分类号	A61B5/0402 A61B5/0452 A61B5/0476 A61B5/4094 A61N1/365 A61N1/36064 A61N1/3611 A61B5/0031 A61B5/02 A61B5/0245 A61B5/053 A61B5/08 A61B5/0816 A61B5/1135 A61N1/36082 A61N1/36521 A61N1/36585 A61N1/37288 A61N1/3962 A61N1/36592 A61N1/39622 A61B5/0205		
优先权	60/636929 2004-12-17 US		
其他公开文献	US20070260147A1		
外部链接	Espacenet USPTO		

摘要(译)

一种用于监测神经系统疾病患者的心脏信号活动的医疗设备系统和方法。在一些实施例中,处理器接收脑信号和心脏信号,在脑信号中识别脑事件,并且脑事件用于识别心脏信号的部分。在一些实施例中,对应于脑事件时间段识别心脏信号的事件部分,并且识别对应于脑事件之间的时间段的事件间部分。使用心脏信号的事件间部分执行事件间心率变异性(HRV)计算,并且根据本发明的某些实施例,基于计算的事件间HRV修改医疗设备系统的输出。还可以根据某些实施例计算事件HRV,并且例如基于事件HRV与事件间HRV的比较来修改输出。

