Title: DETECTION OF ISCHEMIA

Abstract: An ischemia detector comprises a workload sensor for sensing the workload of a patient, an ejection fraction, EF, determining means (2,4,6,8,10,12), a storing means for storing a predetermined reference relation between EF and workload for the patient, and an analysing means for detecting a state of ischemia of the patient from deviations in determined EF for various workloads from said stored reference relation. A heart stimulator comprises such a detector and stimulation controlling means for controlling the delivery of stimulation pulses to a patient’s heart in response to the detection of an ischemia. In a method of detecting ischemia of a patient a parameter indicative of ejection fraction, EF, and a variable indicative of the workload of the patient are measured, and a state of ischemia of the patient is detected from deviations in EF for various workloads from a predetermined reference relation between EF and workload for the patient in question.
DETECTION OF ISCHEMIA

Technical Field

The present invention relates to an ischemia detector comprising a workload sensor for sensing the workload of a patient. The invention also relates to a heart stimulator comprising such a detector and a method of detecting ischemia.

Background

Cardiac ischemia is a condition related to lack of blood flow and oxygen to the heart muscle. Such a condition arises when a coronary artery is narrowed or occluded for a short time such that flow of oxygen-rich blood to the heart is reduced or prevented. If the ischemia is severe or lasts for too long time, it can cause a heart attack (myocardial infarction) and can result in heart tissue death.

A temporary blood shortage to the heart causes, in most cases, pain or angina pectoris, but in some cases the patient feels nothing. The latter case is called silent ischemia.

Angina usually occurs when the heart’s need of blood exceeds the supply of blood. For example, running to catch a bus could trigger an attack of angina while walking might not. An angina might occur during exercise, strong emotions or extreme temperatures. Persons having a coronary artery spasm may have angina even when resting.

For persons suffering from an unstable angina, the chest pain is unexpected and usually occurs while the persons are resting. Inflammation, infection and secondary causes can also give rise to unstable angina. The cause of a form of unstable angina called variant or Printzmetal’s angina is coronary artery spasm. Unstable angina is an acute coronary syndrome and should be treated as an emergency.

Persons having angina in addition may have also undiagnosed episodes of silent ischemia. Silent ischemia may also cause disturbances in the heart rhythm. Abnormal rhythms, like ventricular tachycardia or ventricular fibrillation, can interfere with the heart’s pumping ability and cause fainting or even sudden cardiac death. A silent ischemia can lead to a heart attack without any prior warning. Detection of silent ischemia is consequently very important. Heart muscle
disease (cardiomyopathy) caused by silent ischemia is among the more common causes of heart failure.

Silent ischemia is very common. The American Heart Association estimates, for instance, that 3 to 4 million Americans have episodes of silent ischemia. Especially persons who have had previous heart attacks and those who have diabetes are in the danger zone for developing silent ischemia.

Angina is a signal from the heart muscle of insufficient oxygen supply to the heart tissue due to diminished blood supply. A heart attack is the most extreme state of oxygen deprivation, in which whole regions of heart muscle cells begin to die because of lack of oxygen. The ejection fraction is often very low in the acute stage.

Even a heart attack may not be unbearably painful at first, permitting its victim to delay seeking treatment for as much as 4 to 6 hours after onset of the attack. By then the heart may have suffered irreversible injuries.

The longest running heart study, the Framingham Heart Study in United States, indicates that about one heart attack of four produces no symptoms, or at least no symptoms which the victim associates with a heart problem.

So-called silent heart attacks are only the most extreme case of the still more prevalent condition silent ischemia described above. The prevalence of silent heart attacks is high for elderly and diabetic patients.

US 6 016 443 describes an ischemia detector including a detecting unit which identifies a state of ischemia as existing upon the occurrence of a predetermined relation between sensed repolarization and sensed workload of the patient.

US 6 233 486 discloses an ischemia detector, wherein an ischemia is detected from an established relation between the systolic pressure of a subject and the subject’s heart rate. It is mentioned that the described technique is useful for detecting also so-called silent ischemia.

In US 6 256 538 an implantable heart stimulator with an ischemia detector is described, wherein the stimulation rate is reduced in response to the detection of ischemia. It is suggested to detect ischemia in one of the following ways, by analysis of recorded IEGMs or ECGs, by analysis of ST segments and T-waves, by analyzing measured AC impedance in a ventricle, by measuring sound absorption in heart tissue, by comparing measured differences between systolic
and diastolic pressures from consecutive heartbeats, or by measuring cardiac output. The possibility to detect silent ischemia with these techniques is also mentioned.

US 6 264 606 discloses an ischemia detector wherein an ischemia is identified upon the occurrence of a predetermined relation between sensed workload and sensed breathing activity, said predetermined relation meaning a sensed low workload and a simultaneously sensed high breathing activity.

The purpose of the present invention is to provide a new improved technique for detecting ischemia.

Disclosure of the Invention

This purpose is obtained by an ischemia detector according to claim 1, a heart stimulator according to claim 18 and by a method according to claim 21.

The present invention is thus based on the fact that the ejection fraction, EF, of a patient drops suddenly when a certain patient dependent workload level is reached. A high cardiac rate then causes the diastolic phase to shorten, which decreases the flow of oxygen and energy to the myocardial cells as this flow is supplied during diastole. The lack of oxygen, energy etc. results in decreased cardiac performance – some cells fail to participate in the cardiac contraction – and EF decreases. The invention is based on the idea to track EF as a function of the workload of the patient and detect sudden drops of EF when increasing the workload level as compared to a stored predetermined reference relation between EF and workload. This reference relation which is patient specific has been determined previously, when the patient did not yet have signs of ischemia. The invention is also well suited for detecting silent ischemia which is an important advantage, since silent ischemia is extremely common as mentioned above.

A surrogate of EF can be obtained by different methodologies, and several different kinds of EF sensors can be used for sensing a parameter suitable for EF determination. Thus according to an advantageous embodiment of the detector according to the invention the EF sensor comprises a CMES sensor. A CMES-sensor, Cardio Mechanical Sensor, is a piezoelectric sensor, the output signal of which contains both electric and pressure information. The pressure information thus received includes several components. In a certain frequency range the sensor is sensible to e.g. sound, i.e. it works as a microphone. The signal also
contains the true pressure, pressure changes or the time derivative of the pressure. By suitable filtration of the sensor signal valve openings and closings can be detected, since a valve closing is associated with a significant pressure increase and sounds. An ordinary pressure sensor can be used as EF sensor or the EF sensor can comprise a photo-plethysmograph as well according to other advantageous embodiments of the detector according to the invention.

According to yet other advantageous embodiments of the detector according to the invention the EF sensor comprises impedance measuring means for measuring the impedance across the patient's heart. These impedance measuring means preferably comprise leads intended for implantation into the patient's heart. Since blood and tissue have different conduction properties, the impedance measured across the heart will be different depending on the blood filling of the heart. The amplitude of an impedance signal measured in this way can consequently be used as an EF surrogate.

According to still other advantageous embodiments of the detector according to the invention the workload of the patient is measured by a sensor comprising an accelerometer, or a minute ventilation determining means, or a means for determining P-wave rate, or a means for determining metabolic demand of the patient. Also combinations of measurements by these measuring means can be used for determining the workload. To be able to determine the workload from the measured P-eave rate a healthy SA (sinoatrial) node is required.

According to another advantageous embodiment of the detector according to the invention a derivation means is provided to determine the derivative of EF with respect to workload, and a derivative comparison means is provided for comparing said derivative with a predetermined derivative reference value. This is an efficient way of finding sudden drops of EF.

According to still other advantageous embodiments of the detector according to the invention the EF determining means is adapted to determine onset of QRS and opening and closing of the aortic valve, and the EF determining means is preferably adapted to determine left ventricular ejection fraction LVEF from one of the following equations

\[
LVEF = 0.84 - 0.64 \times \frac{PEP}{LVET}
\]

\[
LVEF = 1.125 - 1.25 \times \frac{PEP}{LVET}
\]
where PEP denotes the pre-ejection period from onset of QRS to opening of the aortic valve, and LVET the left ventricular ejection time from opening to closing of the aortic valve. Onset of QRS and opening and closing of the aortic valve can be determined with the above-mentioned CMES-sensor, other pressure sensors, or from the impedance signal.

According to another advantageous embodiment of the detector according to the invention alerting means are provided for alerting a physician or clinic or the patient himself or herself in response to detection of an ischemia. For this purpose telemetry means are needed. For patient’s having silent ischemia and consequently do not feel anything from his or her disease it is of great value to be warned in this way.

The invention also relates to a heart stimulator, comprising a detector according to the invention and stimulation controlling means for controlling the delivery of stimulation pulses to a patient’s heart in response to the detection of an ischemia. A patient experiencing ischemia needs to prolong the period of diastole to increase the flow of blood to the cardiac cells. Appropriate actions could therefore be to decrease the stimulation base rate, decrease the maximum tracking rate, making the rate responsiveness less aggressive, etc. The changes could either be permanent or reset after a certain period of time. In an implantable cardioverter defibrillator parameters of ventricular tachycardia and ventricular fibrillation detection could also be changed to make it more sensitive, as ischemia sometimes precedes arrhythmic events.

**Brief Description of the Drawings**

To explain the invention in greater detail embodiments of the invention will now be described with reference to the drawings on which figure 1 is a block diagram of an overview of detecting ischemia and performing actions upon detection, figure 2 is a diagrams showing qualitatively the ejection fraction, EF, as a function of workload for a healthy subject and for a patient suffering from ischemia respectively, figure 3 shows qualitatively different measured signals as a function of time which signals can be used for determining EF, and figures 4 and 5 illustrate impedance measurements for determining a surrogate of EF according to two embodiments of the invention.
Description of Preferred Embodiments

Figure 1 is a block diagram of an overview of detecting ischemia and performing actions upon detection. Thus an ischemia is looked for, at 42, If an ischemia is detected, at 44, suitable actions are performed, at 46. These actions can be alerting a physician, a clinic or simply storing the detected event in a database storing patient diagnostics, at 48. Suitable actions can also include alerting the patient him- or herself to come under medical treatment as soon as possible, and maybe also instruct the patient not to drive him- or herself to the emergency room. This is a very important feature for patients suffering from a silent ischemia, viz. patients who are not feeling anything of the detected ischemia.

Another type of actions could be to change parameters of a heart stimulator of the patient, at 50 in figure 1. A patient experiencing ischemia needs to prolong the period of diastole to increase the flow of blood to the cardiac cells. Appropriate actions could therefore be to decrease the stimulation base rate, decrease the maximum tracking rate, making the rate responsiveness less aggressive, etc. The changes could either be permanent or reset after a certain period of time. In an implantable cardioverter defibrillator parameters of ventricular tachycardia and ventricular fibrillation detection could also be changed to make it more sensitive, as ischemia sometimes precedes arrhythmic events. If such parameters are changed - permanently or temporarily – this must be recorded and communicated to the physician by means of the programmer at next follow-up.

According to the invention the detection of ischemia is based on the fact that EF of the patient drops suddenly when a certain workload level is exceeded by the patient. The high cardiac rate reached then causes the diastolic phase to shorten and this results in a decreased flow of oxygen and energy to the myocardial cells, as this flow is supplied during diastole. The lack of oxygen, energy, etc decreases the cardiac performance, i.e. some cells fail to participate in the cardiac contraction, and EF decreases.

Figure 2 shows qualitatively EF as a function of the workload, represented by the heart rate, for a normal subject and for a patient experiencing ischemia. The
sudden drop in EF shown in the figure is an indication of an ischemia of the patient in question.

The invention is based on the idea to track EF as a function of workload and detect sudden drops of EF at sufficiently high workload levels. The development of EF as a function of workload is then compared with a stored predetermined reference relation between EF and workload for the patient, which reference relation has been determined before the patient was affected by ischemia, cf. figure 2. It should be emphasized that this reference relation is specific for each patient and must be determined separately for each individual patient. Workload level and EF are stored in a memory as a digital signal. A quotient forming means is provided to form from this stored signal the quotient between a change in EF and corresponding change in the workload, and a quotient comparison means is provided for comparing said quotient with a predetermined quotient reference value for the detection of an ischemia.

Alternatively a differentiating means is preferably provided to determine the derivative of EF with respect to workload by differentiating these stored signals to detect sudden drops of EF. If the derivative exceeds a predetermined limit value occurrence of ischemia is indicated.

Since a patient may experience, especially silent ischemia, under conditions for which no ischemia was detected e.g. a week ago, the oldest stored values should be discarded when new values of EF and workload are supplied to the memory. This is realized by a circular buffer of a fixed size, capable of storing a predetermined number of values.

Suitable threshold values for deviations from “normal” EF values, obtained for a healthy subject, for indicating an ischemia could be as follows.

1) Measured EF value deviates from the “normal” EF value by 3 times the standard deviation for EF;

2) A sudden drop of 5 – 10% in the measured EF when the workload is increased;

3) The measured absolute level of EF has dropped to 25 - 30%.

In practice all three conditions above are checked and a detection of ischemia is detected if e.g. at least one of them is satisfied, or alternatively if more than one or all three conditions are fulfilled.
A heart attack is detected as a large decrease in the EF which is present even during rest conditions. If normal EF equals 60%, a relatively small heart attack can cause a mildly lowered EF to e.g. 40 – 45%. A moderate or strong heart attack can cause the EF to decrease to 30 – 40%, and a massive heart attack, or, more commonly, several smaller heart attacks may result in an EF in the range of 10 – 25%.

The workload of the patient can be measured by several different kinds of workload sensors. Thus the workload can be measured by e.g. an accelerometer, minute ventilation means, means for determining the intrinsic P-wave rate for patients having a healthy SA node, means for determining metabolic demand of the patient, or by any combination of these examples.

A surrogate of EF can be obtained according to the invention by using several different methodologies. One example of such a methodology is to detect the cardiac events the onset of QRS and the opening and closing of the aortic valve in order to calculate EF according to one of the following equations

\[
\text{LVEF} = 0.84 - 0.64 \times \frac{\text{PEP}}{\text{LVET}}
\]

\[
\text{LVEF} = 1.125 - 1.25 \times \frac{\text{PEP}}{\text{LVET}}
\]

where PEP denotes the pre-ejection period from onset of QRS to opening of the aortic valve, and LVET the left ventricular ejection time from opening to closing of the aortic valve.

The onset of ejection can be detected from the IEGM. The opening and closing of the aortic valve – and thereby PEP and LVET – can be detected in several ways, e.g. by a CMES-sensor as discussed above. The CMES-sensor is a piezoelectric sensor, wherein the indifferent ring on the lead is coated by piezoelectric material, such that a signal received from this sensor contains both electric and pressure information. The pressure information thus received includes several components. In a certain frequency range the sensor is sensible to e.g. sound, i.e. it works as a microphone. The signal also contains the true pressure, pressure changes or the time derivative of the pressure. By suitable filtration of the sensor signal valve openings and closings can be detected, since a valve closing is associated with a significant pressure increase and sounds. This is illustrated in figure 3.
Figure 3 thus shows the signal, on an arbitrary scale, obtained from a CMES-sensor in a cardiac vein on the left side of the heart as a function of time, together with measured left ventricular pressure, LVP, and a surface ECG. As appears from the indicated figures on the time axis the length of the shown diagram is 1 sec. The asterisks in the diagram mark the opening and the closing respectively of the aortic valve.

Another way to obtain a surrogate of EF is to use the amplitude of a cardiac impedance signal obtained from implanted leads. For a heart stimulator according to the invention ordinary leads for sensing and stimulating can preferably be used for this purpose. Since blood and tissue have different conduction properties, the impedance measured across the heart will depend on the blood filling of the heart.

Figures 4 and 5 show two examples of electrode configurations suitable for obtaining a left ventricular volume surrogate which can be used as an EF surrogate.

Figure 4 thus illustrates an example of impedance measurements between left and right ventricles 1, 3 of a patient's heart. A current is supplied between the pacemaker case, schematically shown at 2, and the tip electrode 4 of a right ventricular lead 6, and the resulting voltage is measured between the ring electrode 8 of the ventricular lead 6 and the tip electrode 10 of a unipolar coronary sinus or left ventricular lead 12.

Figure 5 illustrates another embodiment wherein current is supplied between the tip electrode 26 of a bipolar right ventricular lead 28 and the ring electrode 30 of a bipolar coronary sinus lead 32, and the resulting voltage is measured between the ring electrode 34 of the right ventricular lead 28 and the tip electrode 36 of the coronary sinus or left ventricular lead 32.

If no left ventricular lead is present - which would be rare for the heart stimulators for the population of patients in question - a surrogate of EF can be obtained by using only the right ventricular lead.

If an ischemia is detected actions must be taken, like alerting a physician or a clinic or simply storing the event in a database storing patient diagnostics. Such actions require communication with systems like Housecall and consequently means for telemetry communication. Means could also be provided for alerting the patient him- or herself to come under medical treatment as soon as
possible. Such an alerting function is of special importance for patients suffering from a silent ischemia, viz. patients who are not feeling anything of the detected ischemia. The patient could then also be instructed not to drive to the emergency room him- or herself.

Another kind of actions is to change operation parameters of the heart stimulator which includes the ischemia detector. A patient experiencing ischemia needs to prolong the period of diastole to increase the flow of blood to the cardiac cells. Appropriate actions could therefore be to decrease the stimulation base rate, decrease the maximum tracking rate, making the workload sensor less sensitive, etc. The heart stimulator according to the invention therefore comprises stimulation controlling means for automatically controlling the delivery of stimulation pulses to the patient’s heart in response to the detection of an ischemia. The changes could either be permanent or reset after a certain period of time. In an implantable cardioverter defibrillator parameters of ventricular tachycardia and ventricular fibrillation detection could also be changed to make it more sensitive, as ischemia sometimes precedes arrhythmic events. If such parameters are changed - permanently or temporarily – this must be recorded and communicated to the physician by means of the programmer at next follow-up.
CLAIMS

1. An ischemia detector comprising a workload sensor for sensing the workload of a patient, characterized in that it comprises an ejection fraction, EF, determining means (2,4,6,8,10,12; 26,28,30,32,34,36; 42), a storing means for storing a predetermined reference relation between EF and workload for the patient, and an analysing means for detecting a state of ischemia of the patient from deviations in determined EF for various workloads from said stored reference relation.

2. The detector according to claim 1, characterized in that said EF determining means comprises an EF sensor for sensing a parameter suitable for EF determination and calculating means for calculating EF from said parameter.

3. The detector according to claim 2, characterized in that said EF sensor comprises a CMES sensor.

4. The detector according to claim 2, characterized in that said EF sensor comprises a pressure sensor.

5. The detector according to claim 2, characterized in that said EF sensor comprises a photo-plethysmograph.

6. The detector according to claim 2, characterized in that said EF sensor comprises impedance measuring means (2,4,6,8,10,12; 26,28,30,32,34,36;) for measuring the impedance across the patient’s heart.
7. The detector according to claim 6, characterized in that said impedance measuring means comprise leads (6,12; 28,32) intended for implantation into the patient's heart.

8. The detector according to any of the preceding claims, characterized in that said workload sensor comprises an accelerometer.

9. The detector according to any of the claims 1 - 7, characterized in that said workload sensor comprises a minute ventilation determining means.

10. The detector according to any of the claims 1 - 7, characterized in that said workload sensor comprises a means for determining P-wave rate.

11. The detector according to any of the claims 1 - 7, characterized in that said workload sensor comprises a means for determining metabolic demand of the patient.

12. The detector according to any of the preceding claims, characterized in that a quotient forming means is provided to form the quotient between a change in EF and corresponding change in the workload, and a quotient comparison means is provided for comparing said quotient with a predetermined quotient reference value.

13. The detector according to any of the claims 1 - 11, characterized in that a derivation means is provided to determine the derivative of EF with respect to workload, and a derivative comparison means is provided for comparing said derivative with a predetermined derivative reference value.

14. The detector according to any of the preceding claims, characterized in that a circular buffer is provided for storing a predetermined number of results from said analysing means.
15. The detector according to any of the preceding claims, characterized in that said EF determining means is adapted to determine onset of QRS and opening and closing of the aortic valve.

16. The detector according to claim 15, characterized in that said EF determining means is adapted to determine left ventricular ejection fraction LVEF from one of the following equations

\[
\text{LVEF} = 0.84 - 0.64 \times \text{PEP/LVET}
\]
\[
\text{LVEF} = 1.125 - 1.25 \times \text{PEP/LVET}
\]

where PEP denotes the pre-ejection period from onset of QRS to opening of the aortic valve, and LVET the left ventricular ejection time from opening to closing of the aortic valve.

17. The detector according to any of the preceding claims, characterized in that alerting means are provided for alerting a physician or clinic or the patient himself or herself in response to detection of an ischemia.

18. A heart stimulator, characterized in that it comprises a detector according to any of the preceding claims and stimulation controlling means (46,50) for controlling the delivery of stimulation pulses to a patient’s heart in response to the detection of an ischemia.

19. The heart stimulator according to claim 18, comprising a bipolar right (6) ventricular lead and a left ventricular lead (12), characterized in that said impedance measuring means of said detector comprise a current source for applying a current between the tip electrode (4) of the right ventricular lead (6) and the case (2) of the heart stimulator, and voltage measuring means for measuring the resulting voltage between the ring electrode (8) of the right ventricular lead (6) and the tip electrode (10) of the left ventricular lead (12).
20. The heart stimulator according to claim 18, comprising bipolar right (28) and left ventricular leads (32), characterized in that said impedance measuring means of said detector comprise a current source for applying a current between the tip electrode (26) of the right ventricular lead (28) and the ring electrode (30) of the left ventricular lead (32), and voltage measuring means for measuring the resulting voltage between the ring electrode (34) of the right ventricular lead (28) and the tip electrode (36) of the left ventricular lead (32)ui.

21. A method of detecting ischemia of a patient, characterized in that a parameter indicative of ejection fraction, EF, and a variable indicative of the workload of the patient are measured, and in that a state of ischemia of the patient is detected from deviations in EF for various workloads from a predetermined reference relation between EF and workload for the patient in question.

22. The method according to claim 21, characterized in that a quotient is formed between a change in EF and corresponding change in the workload, and in that said quotient is compared with a predetermined quotient reference value.

23. The method according to claim 21, characterized in that a derivative of EF with respect to workload is determined, and compared with a predetermined derivative reference value.

24. The method according to any of the claims 21 - 23, characterized in that onset of QRS and opening and closing of the aortic valve are determined, and in that left ventricular ejection fraction LVEF is calculated from one of the following equations

\[
\text{LVEF} = 0.84 - 0.64 \times \frac{\text{PEP}}{\text{LVET}}
\]

\[
\text{LVEF} = 1.125 - 1.25 \times \frac{\text{PEP}}{\text{LVET}}
\]
where PEP denotes the pre-ejection period from onset of QRS to opening of the aortic valve, and LVET the left ventricular ejection time from opening to closing of the aortic valve.

25. The method according to any of the claims 21 – 24, characterized in that detection of an ischemia is stored in a database for patient diagnostics for later analysis, e.g. at a follow-up.
Fig. 1

1. Look for ischemia

No

42

Yes

44

Ischemia detected?

Perform actions

46

50

Change device parameters

48

Alert physician, clinic or other
Figure 2:

- Healthy subject
- Ischemia patient

Sudden drop in ejection fraction

Figure 3:

- LVP
- ECG
- CMES
- Filtered CMES

Time (s)
# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/SE 2004/001444

## A. CLASSIFICATION OF SUBJECT MATTER

**IPCC**: A61B 5/0205, A61N 1/365  
According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

**IPCC**: A61B, A61N  
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE, DK, FI, NO classes as above  
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

## EPO-INTERNAL, WPI, PAJ

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

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[ ] Further documents are listed in the continuation of Box C.  
[ ] See patent family annex.

* Special categories of cited documents  
**A**: Document defining the general state of the art which is not considered to be of particular relevance  
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Date of the actual completion of the international search: 9 May 2005  
Date of mailing of the international search report: 12-05-2005

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