METHOD AND APPARATUS FOR ADMINISTERING DIGITALIZING MEDICATIONS

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Filed: Oct. 24, 1969

Appl. No.: 869,136

U.S. Cl. 128/214 E, 128/2.06 R, 128/DIG. 13

Int. Cl. A61m 05/00

Field of Search 128/213-218, DIG. 1, 128/2, 2.05, 2.06, DIG. 13

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A method and apparatus for infusing digitalizing medication to a patient at a controlled rate. The apparatus including first detection means for recognizing an electrical event originating in the muscle of the heart, electrical stimulation means responsive to the electrical event for stimulating the heart with an electrical stimulating signal, second detection means for detecting an electrical signal indicative of the response of the heart to the electrical stimulating signal, and infusion means including means responsive to said last mentioned electrical signal to control the amount of medication administered to the patient.

11 Claims, 5 Drawing Figures
FIG. 1

FIG. 2

FIG. 3

FIG. 4

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Digitalis preparations are among the most commonly utilized pharmaceutical agents (i.e., Acetylstrophanthin, Ouabain and Digoxin). Under usual conditions these drugs are used to increase cardiac output in patients with mild to moderate degrees of congestive heart failure. In this situation it is possible for the physician to prescribe a minimal dose of digitalis with significant improvement in the patient's condition. However, in cases of acute onset of congestive heart failure, as with myocardial infarction, large or almost toxic doses of digitalis preparations are often required. In this situation, it may be extremely difficult for the physician to optimize drug dose while avoiding toxic or lethal drug levels.

However, with the discovery of repetitive ventricular response (RVR) to digitalis administration, it has been possible to develop an automated system to control blood levels of digitalis preparations.

In 1967, researchers reported that digitalization, while not changing the diastolic excitability threshold for single responses, would lower the threshold for RVR which followed the initial ventricular contraction. See the following articles "Electrical Stimulation and Digitalis Drugs: Repetitive Response in Diastole", Proceedings of the Society For Experimental Biology and Medicine 1967, vol. 126,698-701 and "Electrical Stimulation to Estimate the Degree of Digitalization", The American Journal of Cardiology, Aug., 1967, vol. 22, no. 2, pages 251-259.

A most important aspect of this phenomenon was the observed widening of the zone of diastolic sensitivity as a function of the degree of digitalization.

In almost all cases, about half the toxic dose of digitalis preparations produced RVR with stimuli placed in about the midpoint of the Q—Q or somewhat earlier in the R—R cardiac interval. With increasing doses RVR could be obtained with stimuli placed further and further into diastole. With toxicity approaching 100 percent, RVR could be elicited just before the P wave of the next cardiac cycle.

Because of this consistent phase relationship between the degree of toxicity and the percentage of diastole during which RVR could be produced, it is now possible to precisely control digitalis infusion for optimum dosage while avoiding serious side effects (i.e., toxicity).

In accordance with this invention, controlled infusion of digitalizing medications to patients, is achieved by detecting a repetitive electrical event originating in the muscle of the heart, generating an electrical stimulatory signal and applying it to the heart a predetermined time interval after the onset of the electrical event, and then detecting the response of the heart to the electrical stimulatory signal to set the amount of medication being administered to the patient depending on the indicated toxicity of the patient.

An object of this invention is to provide a new and improved method and device for administering digitalizing medications.

A further object of this invention is to provide a method and apparatus for controlling the administration of digitalizing preparations to patients.

The invention accordingly comprises the several steps and the relation of one or more of such steps with respect to each of the others, and the apparatus embodying features of construction, combinations of elements and arrangements of parts which are adapted to effect such steps, all as exemplified in the following detailed description, and the scope of the invention will be indicated in the claims.

For a fuller understanding of the nature and objects of the invention, reference should be had to the following detailed description taken in conjunction with the accompanying drawings, in which:

FIG. 1 is an electrocardiogram illustrating the usual electrical events (signals) generated by the heart of a patient.

FIG. 2 is an electrocardiogram illustrating the sequence of electrical events (signals) showing the electrical stimulatory signal applied to the heart and the (RVR) wave response to the stimulatory signal.

FIG. 3 is a graph illustrating the percent toxicity of a patient as an approximate function of the percent of the R — R wave interval during which the electrical stimulatory signal is applied to the patient, which elicits an RVR response.

FIG. 4 is a block diagram illustrating the apparatus of the invention, and

FIG. 5 is a more detailed diagram illustrating the apparatus of the invention.

In FIG. 1, there is shown an electrocardiogram illustrating the electrical signals associated with the contraction of the normal heart. The P wave illustrates the atrial wave, the Q, R and S waves illustrates the electrical signals associated with ventricular contraction and the T wave illustrates the electrical signal associated with ventricular repolarization.

In FIG. 2, there is shown an electrocardiogram illustrating the RVR stimulatory wave form applied to the heart of a patient at a predetermined time interval after the initial contraction of the heart along with RVR response wave of a patient having between about 46 percent to about 100 percent of a toxic dose of a digitalizing medication in the body.

FIG. 3 illustrates in graph form the relationship of percent toxicity of a digitalized patient as an approximate percentage of the R — R or other appropriate interval in which a stimulatory signal will cause an RVR wave to occur.

Reference should now be had to FIGS. 1-4. FIG. 4, in particular illustrates in block diagram form the principals of the invention.

To apply this invention to a patient, a catheter containing an open lumen, together with an electrode wire 11 is advanced through an appropriate vein into the Superior Vena Cava. The electrode wire 11 is then further advanced into the right ventricular myocardium. It should be understood that an electrode plate in the myocardium is only one way to stimulate the heart muscle with electrical signals. Electrical stimulating signals can also be applied by external electrodes attached to the patient, via wires placed in the esophagus or implanted in the patient as with a pacemaker.

An infusion pump 12 comprising an electrical motor driven syringe, of the type commonly used and publicly available, is then connected to the catheter. At 13 there is shown an EKG (Electrocardiograph) device such as sold by Hewlett Packard and many others for monitoring electrical signals from the heart.

The EKG provides electrical signals to a R wave filter 14 and an RVR wave filter 15. These detected signals are then transmitted to a control unit 16 (shown in greater detail in FIG. 5). The control unit 16 acts as a delay control which preferably seeks RVR signals with the RVR stimulus applied after about 70 to 46 percent (can be varied between 0 up to 100 percent) of the R — R wave interval. Depending upon the position of the RVR electrical stimulus in the R — R interval which elicits an RVR wave, the control unit either increases or decreases the amount of medication being pumped into the patient by the infusion pump 12.

Generally, the control unit will be set to maintain the infusion rate such that about 70 percent of the toxic dose of digitalizing medication is provided to the patient. Thus by detecting when during the R — R interval that an RVR stimulus produces an RVR response wave the toxicity of the patient is determined (the greater the toxicity of the patient, the later that an RVR stimulus may be applied during the R — R interval which will elicit an RVR response). The apparatus in effect determines the toxicity of the patient and then adjusts the infusion rate according to the percent of the toxic dose desired to be maintained in the patient.

Reference should now be had to FIG. 5, which shows in logical block diagram form the apparatus according to this invention. At 10, 11 and 12 are shown the catheter, electrode, and EKG monitor described in FIG. 4. The infusion pump is shown at 12 and includes a motor 20 which drives a gear (not shown).
which moves a rack 21 to force a plunger 22 of the infusion pump forward at a controlled rate in order to dispense medication to the patient. The RVR stimulus is derived from stimulator 17. The stimulator 17 can be the usual type of physiological stimulator, as for example the type made by Grass Instrument Company of Massachusetts. The stimulator is set to preferably provide a 25 microjoule RVR stimulatory wave signal to stimulate the heart. Obviously the amount of energy provided to the heart will vary depending on the patient and the manner in which the heart is stimulated. If the heart is stimulated by external electrodes applied to the body of the patient, higher energy levels are required.

A signal to trigger the stimulator 17 is derived in the following manner; the R wave filter 14 (high pass filter>15 c.p.s.) provides a signal to actuate Schmitt trigger 25. The signal from trigger 25 resets an integrator 26 which is integrating a reference voltage E reference. At the same time, the prior voltage at the output of integrator 26 is gated into a gated sample voltage hold circuit 27. The circuit 27 holds the voltage provided to its input at its output terminal until a gating signal is provided. This type of circuit 27 is available from the following companies: Hybrid Systems of Massachusetts, Philbrick-Nexus of Massachusetts and others. Thus there is provided at a voltage divider network 30 two voltages, one a constant representing a voltage proportional to the R — R wave interval, inverted in inverter 31, and a second voltage increasing during each R — R wave interval. The inverted voltage is provided to a variable plot 32, having a wiper arm 33 which is driven by a DC motor 34 moving at a speed determined by voltage E 1, and the resistance 35. In this manner there is provided a negative voltage at point 36 which is proportional to a percent of the R — R interval and an increasing voltage proportional to elapsed time from the onset of the next R wave. The plot 32 functions so as to gradually reduce the negative voltage at point 36 and therefore to permit the RVR wave stimulator to provide RVR stimuli successively earlier in the R — R interval until a RVR response is detected. Normally the plot 32 starts out so that a voltage proportional to 70 percent of the R — R interval is provided.

When the two wave forms at point 36 cross over, a Schmitt trigger 17 is actuated which in turn triggers the RVR stimulator 17 to produce an RVR stimulatory wave. The stimulator 17 preferably only provides a stimulus every 10 seconds in order to give the heart time to recuperate. This can be controlled by a clock 62 which periodically closes a relay contact 63 through a solenoid. In the alternative the output from trigger 37 can be periodically gated using an AND gate controlled by a clock.

The output from Schmitt trigger is also fed to two coupled monostable multivibrator circuits 39 and 40, the circuit 40 being triggered by the delayed negative going portion of circuits 39 wave form, to provide a window gating voltage at AND gate 41. The window being such that AND gate 41 is permitted to open for a predetermined interval about 46 to 70 percent of the R — R interval.

If we now assume that the patient is sufficiently toxic (over about 46 percent), we will now obtain an RVR response wave from filter 15 (low pass filter less than about 10 c.p.s.) which in turn triggers a Schmitt trigger 16. Thus at the output of AND gate 41 we now have a signal indicating that a RVR response is present.

The signal from gate 41 is used in part to set a bistable multivibrator 42 closing relay contact 43 which places resistance 44 in parallel with resistance 35. Resistance 35 is selected such that it is 10 times smaller than resistance 35. Thus motor 34 rapidly turns to reposition wiper 33 at its initial start position as to again provide a negative voltage at point 36 proportional to 70 percent of the R — R interval. As wiper 33 turns a position 45 carried thereon closes switch 46 to trigger circuit 47 to reset bistable 42. In this manner the pot 32 is reset to once again sample the toxicity of the patient.

In order to develop a voltage which is an indication of how far into diastole an RVR stimulus has been applied which elicits an RVR response, there is provided a bistable multivibrator 50 and a resettable integrator 51 and a gated voltage hold circuit 52 of the type previously described. Bistable 50 initially closes a contact 55 of a relay on receipt of an R signal from trigger 25. This causes integrator 51 to integrate reference signal E ref 2 after being reset by a signal from trigger 25. Bistable 50 is reset each time by trigger 37 whenever a RVR stimulatory signal command is given, which opens contact 55. Thus the voltage at the output of integrator 51 is proportional to a voltage, indicating the time between the presence of an R wave and the initiation of the RVR stimulus.

Assuming now that an RVR stimulus has been through push button the patient, gate 41 produces a signal to gate the voltage from integrator 51 to the voltage hold circuit 52. The output from voltage hold circuit 52 is then inverted and combined with a reference signal E ref 3 indicative of the desired medication (toxicity level) to be maintained in the patient. These signals are combined in a differential amplifier circuit to generate an error signal. The error signal is then combined in a servo loop shown at 60, with the amplifier being a long time constant integrator, to develop a motor control signal in a manner well known to the art to set the speed of motor 20.

The initial speed setting for the motor is provided by a reference voltage E ref 4 on closure of contact 61.

In order to set the initial voltage for a voltage hold circuit 52 there is provided a voltage E 5 which passes through push button switch 65 sets an initial voltage in circuit 52. The voltage E 5 is preferably selected so that it represents a voltage level that could be expected if a patient was 50 percent toxic.

What is claimed:

1. In the method of administering digitalizing medications to a patient which includes automatically administering a digitalizing medication to a patient, the steps of applying an electrical stimulus to the heart of the patient, detecting the response to the stimulus to then determine the toxicity of the patient, and then adjusting the amount of digitalizing medication being automatically administered to the patient in accordance with the determined toxicity of the patient in order to maintain a predetermined percentage of toxic dosage of digitalizing medication in the patient.

2. The method according to claim 1 in which the digitalizing medication is administered to the patient by infusion.

3. The method according to claim 2 in which the stimulus is applied between an interval of heart contraction in order to elicit a response indicative of the toxicity of the patient.

4. The method according to claim 3 in which the stimulus is applied during the latter half of the interval between heart contractions, the portion of time in the R — R interval that the stimulus is applied, between contractions, which elicits a response indicates the toxicity of the patient.

5. The method according to claim 4 in which the presence of a response to the stimulus is converted to an error signal for controlling the rate of medication being provided to a patient using infusion means.

6. In a system for infusing digitalizing medications to a patient comprising means for infusing digitalizing medication into a patient, first means for detecting an electrical event originating in the muscle of the heart, second means responsive to the electrical event for providing an electrical stimulus to stimulate the heart a predetermined time interval after the onset of said electrical event, and third means for detecting the response to said electrical stimulus from said heart and set the amount of medication administered to the patient by said means for infusing.

7. In a system according to claim 6 wherein said first means detects the presence of an R wave produced by the muscle of the heart, wherein said second means produces an RVR electrical stimulus a predetermined time after the R wave is detected, wherein said third means detects the RVR response to the RVR electrical stimulus and also determines the position of the RVR electrical stimulus with respect to the normal R —
R interval produced by the heart of the patient so as to determine the toxicity of the patient and set the rate of infusion.

8. In a system according to claim 6 wherein said third means includes means which provides an indication of the toxicity of the patient which is then used to maintain the amount of medication being administered to the patient at a predetermined desired rate.

9. In a system according to claim 8 including means for only permitting the response to be used to control the infusion of medication during a predetermined interval of the R — R wave interval.

10. In a system according to claim 6 including means for varying the time at which the heart is stimulated.

11. In the method of automatically administering digitalizing medication to a patient which comprises the steps of applying an electrical stimulatory signal to the heart of a patient, detecting if a response occurs to said stimulus, and then controlling the automatic administration of the digitalizing medication after the toxicity of the patient has been determined, depending upon where in the R — R interval the electrical stimulus is applied and a response is detected.
CERTIFICATE OF CORRECTION

Patent No. 3,651,806 Dated MARCH 28, 1972

Inventor(s) PHILIP I. HERSHBERG

It is certified that error appears in the above-identified patent and that said Letters Patent are hereby corrected as shown below:

Please correct the spelling of the inventor's name in the following places: On the front page of the patent, (just after the sheet 1 of 2 of the drawings, and directly under the words "UNITED STATES PATENT" to the left of the bracketed numerals [45]) delete "Hirshberg" and substitute ---- Hershberg----therefor. Also, (to the right of the bracketed numerals [72] after "Inventor: Philip I. Hirshberg," ) please correct inventor's name to ----Hershberg----.

Signed and sealed this 10th day of October 1972.

(SEAL)
Attest:

EDWARD M. FLETCHER, JR. ROBERT GOTTSCALK
Attesting Officer Commissioner of Patents