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A transistorised impulse generator for recording the heart rate from intact and isolated preparations

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A method for presenting the heart rate from intact and isolated preparations as a kymographic record is described. A transistorised impulse generator with either an integral or independent power supply is used to activate a Thorp impulse counter. The ability of the instrument to follow a wide range of heart rate changes and to measure rates in the usually encountered laboratory species is demonstrated.

THE interpretation of routine experimental blood pressure measurements is assisted by simultaneously recording the heart rate to provide a fuller analysis of the observed responses. Heart rate may be determined by simple observation, which is often tedious, or else mechanically, and it is often convenient to present the record in the form of a kymograph tracing (Beakley & Findlay, 1949; de Burgh Daly & Schweitzer, 1950; Dawes, 1951; Griffith, Innes & Kosterlitz, 1953; Perry & Wilson, 1956; and Glaser, Griffin & Knight, 1960). The methods of Beakley & Findlay, of Dawes and of Glaser & others possess the advantage of utilising the components of the electrocardiogram to determine heart rate and do not interfere with adjacent blood pressure recording apparatus.

Techniques to record the heart rate from isolated preparations have also been described (Thorp, 1948; Azarnoff & Burn, 1961).

A transistorised method for heart rate counting which is of low cost, compact and suitable for both teaching and research purposes, is now described.

Experimental

METHODS

The electrocardiogram from anaesthetised, spinal and pithed animals, was obtained from needle electrodes placed beneath the skin on either side of the thorax and fed into the input side of the impulse generator.

The electrical changes from Langendorff isolated perfused heart preparations were obtained by means of two electrodes, one attached to the metal perfusion cannula inserted into the aorta and the other from a heart clip attached to the myocardium and connected to the input stage of the counter through flexible screened leads.

In order to minimise hum pick up, connections from supporting metal structures, including the venous cannula stand, were made to the main earth source.

Kymographic records of heart rate were obtained using a Thorp impulse counter (Thorp, 1948).

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APPARATUS

A schematic diagram of the impulse generator is shown in Fig. 1 and details of the circuit in Fig. 2.

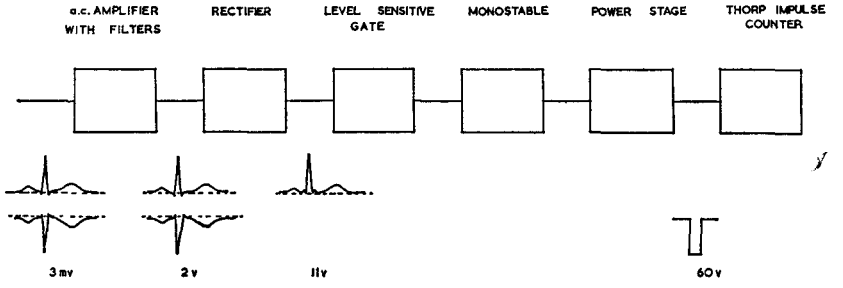

FIG. 1. Schematic diagram of impulse generator.

The AC amplifier comprises three shunt stabilised stages using close gain tolerance transistors with the consequent elimination of the need for feedback loops to stabilise the amplifier gain against production spreads. Low frequency rejection filtering (at approximately 12 db/octave) is provided for by switching interstage coupling capacitors. This is particularly advantageous when using small animals with fast heart rates, so that hum level can be reduced without affecting the QRS complex. At the lowest settings of the low frequency filter the response of the amplifier is flat down to input frequencies of 8 c/sec and the instrument will satisfactorily respond to all ranges of heart rate encountered in laboratory conditions. The upper frequency response of the amplifier is filtered by simple resistance capacitance 6 db/octave filters with options at 1, 5 and 15 Kc/sec as the corner frequencies, and mitigates against high frequency interference due to electric motors or brushes, for example. A jack plug socket at the output stage of the amplifier enables the use of low gain pre-amplifier oscilloscopes to display and check that undistorted

FIG. 2. Circuit diagram of transistorised impulse generator. R1, 10 K Log. R2, 100 K. R3, 100 K. R4, 15 K. R5, 10 K. R6, 100Ω 1 W. R7, 100 K. R8, 100 K. R9, 10 K. R10, 39 K. R11, 39 K. R12, 1 K. R13, 3·3 K. R14, 5 K Lin. R15, 330 K. R16, 8·2 K. R17, 33 K. R18, 4·7 K. R19, 5 K Lin. R20, 50 K Lin. R21, 3·3 K. R22, 1·5 K. R23, 3·3 K 1 W. R24, 39 K. R25, 1 K. R26, 100 K. R27, 100Ω 3 W. R28, 10 K 1 W. R29, 22 K. All resistors ½ W 10% unless otherwise stated. C1, 5 μF 60 V Polyester. C2, 0·5 μF. C3, 50 μF 25 V Electrolytic. C4, 1 μF. C5, 0·05 μF Paper. C6, 0·1 μF Paper. C7, 8 μF. C8, 0·001 μF Paper. C9, 1 μF. C10, 0·05 μF Paper. C11, 0·1 μF Paper. C12, 8 μF. C13, 8 μF. C14, 500 μF 50 V Electrolytic. C15, 0·005 μF Paper. C16, 0·03 μF Paper. C17, 0·002 μF Paper. C18, 8 μF. C19, 25 μF 50 V Electrolytic. C20, 5 μF. C21, 25 μF 50 V Electrolytic. C22, 500 μF 50 V Electrolytic. C23, 500 μF 50 V Electrolytic. Condensers may be Polyester or Electrolytic unless otherwise stated. VT1, ZT 44 Ferranti. VT2, ZT 44 Ferranti. VT3, ZT 44 Ferranti. VT4, ZT 44 Ferranti. VT5, ZT 44 Ferranti. VT6, ZT 44 Ferranti. VT7, ZT 1484 Ferranti. D1, OA 81 Mullard. D2, OA 81 Mullard. D3, OA 81 Mullard. D4, OA 81 Mullard. D5, OA 81 Mullard. D6, ZS 70 Ferranti. D7, ZS 70 Ferranti. D8, ZS 70 Ferranti. D9, ZS 70 Ferranti. D10, ZS 70 Ferranti. T1, TMT 12 1:6 Richard Allen Radio. T2, Mains Transformer TMT 12 6:1 Richard Allen Radio. F1, 500 mA.

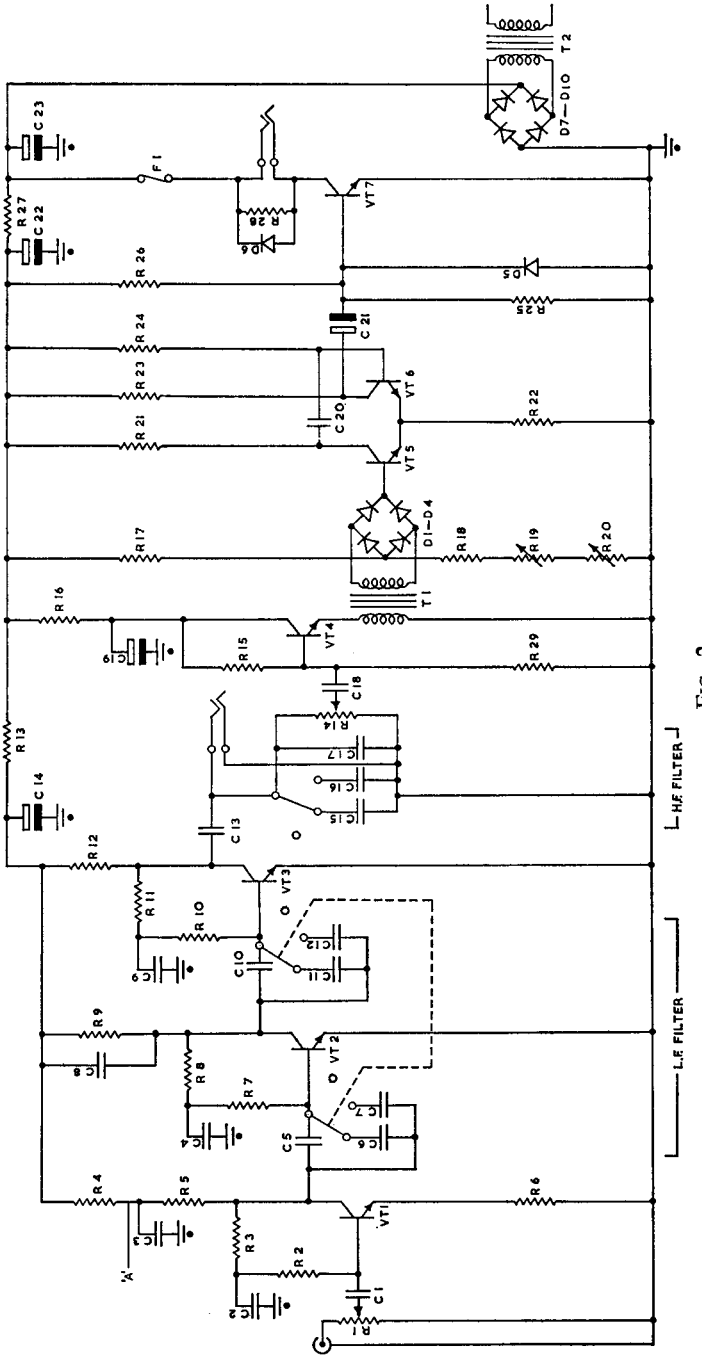
T2
D7—D10
C23
F1
R27
C22
VT7
R26
D6
D5
R25
C21
R24
R23
VT6
C20
R22
R21
VT5
D1—D4
R17
R18
R19
R20
T1
R16
C19
VT4
R15
R29
C18
R14
C17
C16
C15
R13
C14
C13
R12
VT3
R11
R10
C12
C10
C11
R9
C9
R8
VT2
R7
C7
C8
C5
C4
R4
R5
R6
VT1
R3
R2
C3
C2
C1
R1
H.F. FILTER
L.F. FILTER

FIG. 2

amplification of the QRS complex is being applied to the rectifier stage. Assuming the amplifier is functioning correctly, distortion will only be present when overloading occurs on the first stages of the amplifier, and it is recommended that the waveform be monitored at the amplifier output jack plug. The input sensitivity control can then be operated to prevent overloading which, in extreme cases, can result in random firing of the trigger.

The rectifier stage consisting of an emitter follower driving a transformer gives voltage step up and isolates the bridge rectifier on the output from the emitter follower drive. The latter is used to obtain a good low frequency response. Inclusion of a bridge rectifier in the circuit ensures that a positive pulse is always presented to the level sensitive gate in order to fire the trigger circuit. Without this arrangement it would be necessary in some cases to carry out electrode adjustment together with oscilloscope monitoring to ensure the correct sense of the pulse. An alternative method of avoiding this disadvantage has been to use a manually operated reversing switch, but the system still requires monitoring, a feature which is avoided by the adoption of a bridge circuit.

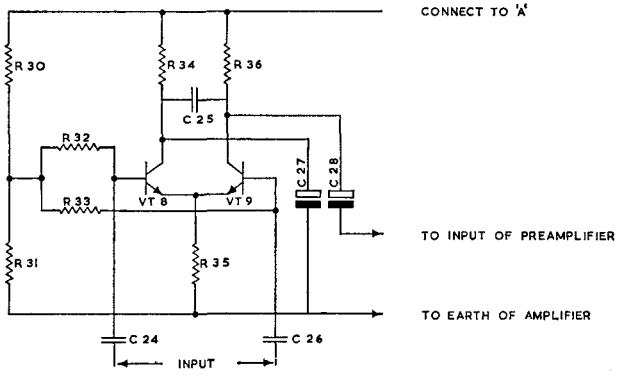

FIG. 3. Circuit diagram of differential pre-amplifier for use in conditions of limited screening. R30, 22 K. R31, 18 K. R32, 39 K. R33, 39 K. R34, 4·7 K. R35, 2·7 K. R36, 4·7 K. All resistors ½ W 10%. C24, 5 μF Polyester. C25, 0·005 μF Paper. C26, 5 μF Polyester. C27, 25 μF 50 V Electrolytic. C28, 25 μF 50 V Electrolytic. VT8, ZT 2270 Ferranti. VT9, ZT 2270 Ferranti.

The output from the rectifier actuates a monostable trigger circuit delivering a pulse into the output stage. The pulse from the output of the trigger circuit is used to drive a common emitter power stage, having a Thorp impulse counter as its load, and which in its quiescent state is held off, but is biased hard on when the base receives the trigger pulse. In order to prevent ringing due to the inductance of the Thorp impulse counter, a damping resistor and diode are used in parallel with the counter.

As the total number of transistors is small, commercial silicon transistors have been chosen on account of their greater thermal stability and reliability. Care has been taken to reduce the amount of stray noise

and hum pick up induced at the input by entirely enclosing the equipment in a metal case and having a single branched earth which is connected to the case from the earthed cable via the input jack plug. The apparatus is compact, portable and robust and the current drawn by the generator from the power supply is very low (<100 mA); thus a small power supply and simple filter is all that is required. Where AC mains are not available the generator may be driven by a battery.

In conditions where only a limited amount of screening is possible due to size of experimental subject, i.e. human heart rate, a differential pre-amplifier has been designed (Fig. 3) for use at the amplifier input, but for the laboratory conditions usually encountered, this is unnecessary.

OPERATING INSTRUCTIONS

1. The generator is more conveniently set up with the aid of a low gain oscilloscope, which may also be used to display changes occurring in the electrocardiogram as a result of experimental procedure, but it can be set up without one. The following procedure should be routinely adhered to.

(*a*) Use the oscilloscope to observe the AC amplifier output by tapping the appropriate jack plug socket.

(*b*) Adjust the input sensitivity until a suitable output is obtained from the amplifier, 5 V peak to peak. If this value is exceeded the amplifier will be overdriven and will in excessive conditions result in the possibility of unreliable counting.

(*c*) If the background noise is considerable, say more than 25% of the ECG signal, try to reduce this component of the amplifier output with the aid of the filters. (Inevitably the first stage of the amplifier generates some noise but a level of 5% of the total output should cover this adequately.)

(*d*) If hum level obscures the signal (when very large it may look like a square wave due to overdriving the AC amplifier) the object under investigation is either insufficiently screened, or else the earthing is incomplete or duplicated, causing induced hum in the resulting loops.

Note: The impulse generator itself is earth free along its mains input wire and should be earthed via the input jack plug to the table.

2. Reduce the gain control to zero.

3. Set the bistable stability control such that it just fails to actuate the Thorp impulse counter. With the setting above a certain level the the bistable runs freely as a square wave generator. The threshold between the two conditions corresponds to maximum sensitivity of the gate.

4. Gradually increase the gain control until the Thorp impulse counter starts to fire regularly. If the oscilloscope is a double beam instrument, the regular firing of the counter can be verified by observing the ECG waveform on one tract simultaneously with the output pulses to the counter on the other.

Note: Increasing the gain too much will cause the bistable to fire from the background noise of the environment and or the amplifier. If the apparatus is correctly adjusted removal of the input jack plug should cause the Thorp impulse counter to stop counting. If this is the case the amplifier noise is failing to fire the counter, and the impulse generator is functioning correctly.

GENERAL

It should be appreciated that the pulse forming and delivery circuits actuating the counter are level sensitive and fire when the amplified ECG

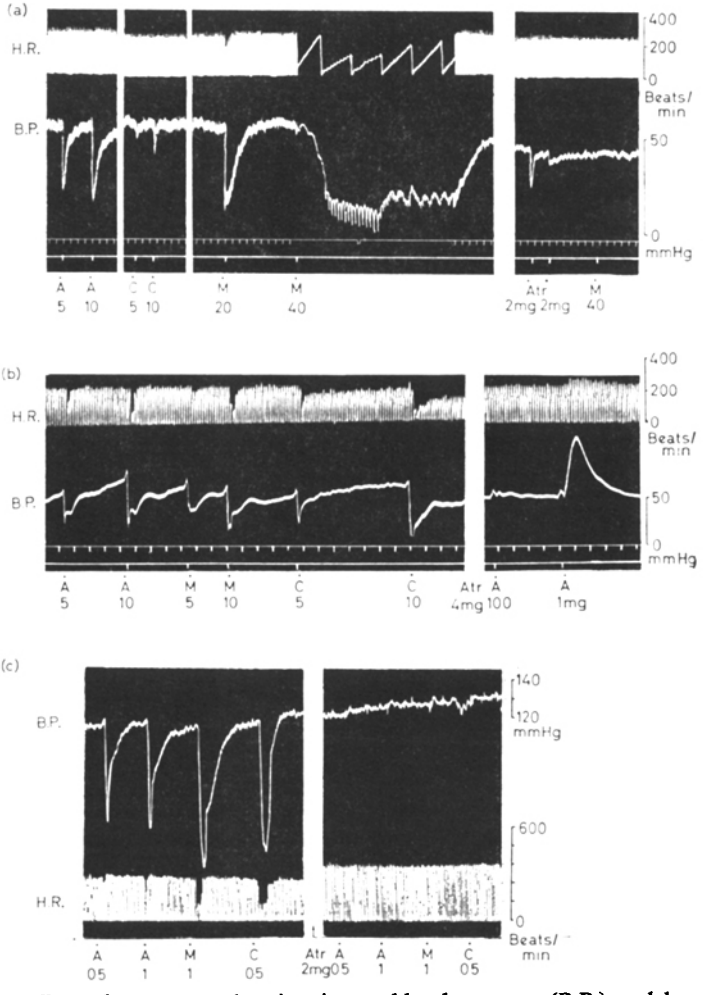

FIG. 4. Effect of parasympathomimetics on blood pressure (B.P.) and heart rate (H.R.). (a) Rabbit, 3·1 kg, anaesthetised sodium pentobarbitone 45 mg/kg intravenously; (b) Cat, 2·6 kg, spinal; (c) Rat, 220 g, anaesthetised sodium pentobarbitone 60 mg/kg intraperitoneally. Time = 30 sec. Acetylcholine (A), Carbachol (C), Methacholine (M), Atropine (Atr). Doses in μg unless otherwise stated.

reaches a suitable level of approximately 2 V. As the AC amplifier has a high gain over a selected frequency range and is typically $\times 10^4$, the background hum and noise level (often as high as 25% of the peak ECG voltage) can easily be made to fire the pulse forming circuits and thus the counter will be incorrectly actuated. This occurs when the gain control is too high.

The object of the above instructions is to adjust the amplified input signal level relative to the firing level such that only the ECG pulses are consistently used to actuate the counter.

Results

INTACT PREPARATIONS

Satisfactory heart rate counts using this apparatus have been made from anaesthetised rat, guinea-pig, rabbit, cat, spinal cat and pithed rat preparations.

Typical responses to parasympathomimetic drugs are shown in Fig. 4 and for sympathomimetic drugs in Fig. 5.

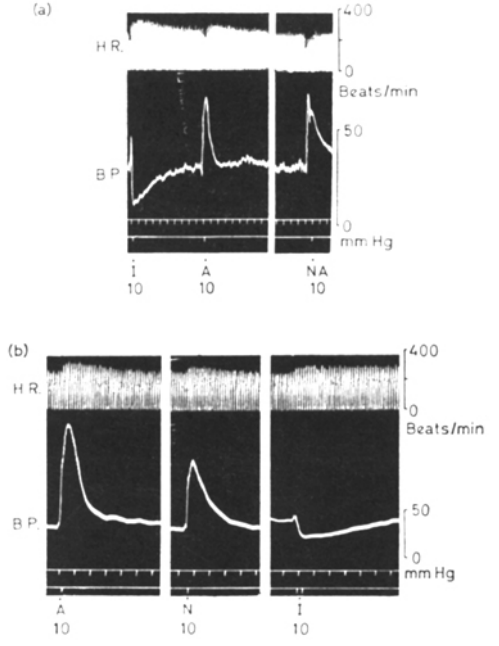

FIG. 5. Effect of sympathomimetics on blood pressure (B.P.) and heart rate (H.R.). (a) Rabbit, 3·1 kg, anaesthetised sodium pentobarbitone 45 mg/kg intravenously; (b) Cat, 2·6 kg, spinal. Time = 30 sec. Adrenaline (A), Noradrenaline (NA), Isoprenaline (I). Doses in μg.

It can be seen that in the spinal cat small doses of parasympathomimetics (5 μg) sufficient to produce a moderate lowering of the blood pressure are also able to bring about a slowing of the heart, Fig. 4 (b), whereas in

the anaesthetised rabbit and rat, Fig. 4 (a) and (c) the doses required to appreciably slow the heart produce a dramatic lowering of the blood pressure. The greater persistence of action of parasympathomimetics whose actions are terminated by cholinesterase hydrolysis is well shown in Fig. 4 (b) in which the evanescent action on the heart rate of 5 μg of acetylcholine is compared with the more prolonged action seen after 5 μg of carbachol, despite the fact that little difference can be observed in their effects on the blood pressure. Fig. 4 (a) also shows on a fast drum the ability of the counter to accurately follow heart rate changes associated with the injection of methacholine 40 μg. The blood pressure lowering effects of parasympathomimetics are completely blocked after atropine, Fig. 4 (a), (b) and (c).

The responses of the spinal cat to sympathomimetic amines, Fig. 5 (b), show that isoprenaline 10 μg and adrenaline 10 μg produce an increase in heart rate although noradrenaline 10 μg has less effect. On the anaesthetised rabbit, Fig. 5 (a), isoprenaline 10 μg produces a marked increase in heart rate; the responses to noradrenaline 10 μg and adrenaline 5 μg are complicated by the initial slowing which presumably arises from reflex vagal discharge associated with the raised blood pressure.

ISOLATED PREPARATIONS

The apparatus has also been used to record the rate of isolated Langendorff perfused heart preparations.

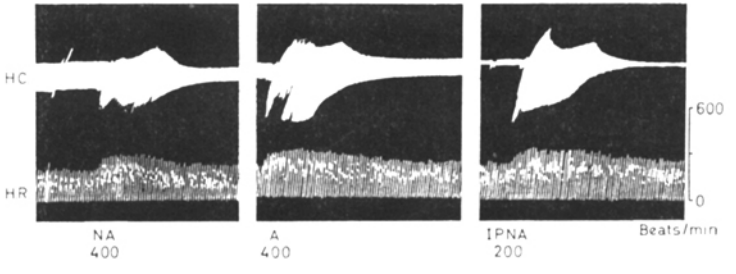

FIG. 6. Effect of sympathomimetics on responses of the isolated Langendorff perfused heart. Guinea-pig. Upper tracing heart contractions (H.C.), lower tracing heart rate (H.R.). Noradrenaline (NA), adrenaline (A), isoprenaline (IPNA). Doses in ng.

A typical record from an isolated guinea-pig heart and its responses to sympathomimetic amines is seen in Fig. 6. Isoprenaline 200 ng is seen to have a more marked stimulating action on the heart than 400 ng of noradrenaline or adrenaline. The chronotropic responses in all cases appear to last appreciably longer than the inotropic ones, and are seen to be greatest with isoprenaline.

Discussion

The need for a reliable, reasonably cheap and compact device to monitor the heart rate from either intact animal or isolated preparations

has been recognised by all experimental physiologists and pharmacologists. In this paper an apparatus is described which reasonably fulfils the above criteria, and will satisfactorily follow changes in heart rate.

In selecting the electrical changes associated with the heart contraction to actuate the recording system, the advantages of flexibility, and independence from other recording systems that may be used simultaneously, have to be weighed against the disadvantages reported by Dawes (1951) of artifacts arising from electrode movement and changes occurring in the QRS complex used to trigger the electrical circuit. In our experience the electrode movement does not constitute a problem but alterations in the character of the QRS waves as a result of drug action have proved to be a problem of real consequence. In choosing the action of parasympathomimetic and sympathomimetic drugs on the heart rate to demonstrate the ability of the counter to follow changes, these are the ones most likely to produce the maximal contrast between induced alterations of the QRS complex that are likely to be experimentally encountered (Goodman & Gilman, 1955), and provide a measure of its usefulness.

Another feature incorporated in the design of this counter is its versatility with respect to the range of species with which it will maintain a satisfactory performance. The difference in the time constants of the QRS complex obtained from a rat and a cat, which presumably is a measure of the total conduction time and size of the heart, is considerable, and the inclusion of adequate low frequency filters enables the apparatus to faithfully follow the electrical changes derived from the heart beat free from distortion and hum.

The apparatus is convenient to use and is suitable for use in both research investigations and for purposes of student demonstrations and teaching.

Difficulties encountered in operation arise from three main sources.

1. It is necessary to ensure good electrode contact by inserting the needles subdermally into the area on either side of the thorax.

2. Provision of adequate earthing on the supporting metal structures must be made to eliminate hum pick up and artifacts.

3. Random firing of the apparatus can occur if incorrect setting up procedures are adopted.

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