Primary T Wave Abnormalities Caused by Uniform and Regional Shortening of Ventricular Monophasic Action Potential in Dog

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SUMMARY

We correlated primary T wave changes with the changes of monophasic action potentials (MAP) recorded with suction electrodes from the ventricular surface of the dog heart following systemic or intracoronary infusions of small doses of isoproterenol (ISP). The portions of the heart perfused with ISP were excised and weighed to determine the mass of perfused tissue. ISP shortened the ventricular MAP by an average of 12–18 msec in the entire ventricular mass following systemic administration, in 34 ± 6% of the ventricular mass after injection into the left circumflex coronary artery (LCA), in 8.5 ± 2.6% of the ventricular mass after injection into a branch of LCA and in 17 ± 8% of the ventricular mass after injection into the right CA. The MAP changes induced by ISP were similar to the transmembrane action potential changes recorded with microelectrodes from papillary muscles excised from the same dogs. The most important results of this study showed that: 1) the early and the late effects of ISP administration produced opposite effects on the T wave polarity. The early T wave change was associated with nonhomogeneous and the late change with homogeneous MAP shortening; 2) the T wave change was greater after infusion into LCA than after systemic administration; 3) the T wave change was greater after infusion into LCA than after infusion into LCA branch apparently because of greater mass of the ISP-perfused myocardium; 4) the T wave change was greater after infusion into LCA branch than after infusion into RCA, apparently due to the unequal regional repolarization contribution to the T wave; 5) the ventricular gradient did not always reflect the magnitude of the primary T wave change. Our study helps to identify factors contributing to high sensitivity and low specificity of T wave abnormalities.

Additional Indexing Words:
Suction electrodes Isoproterenol systemic administration Isoproterenol intracoronary administration Ventricular transmembrane action potential Ventricular gradient ST segment Q-T interval

We have reported that intravenous administration of isoproterenol (ISP) causes a biphasic effect on the normal T wave in the electrocardiogram (ECG) in man. During the first phase the upright T wave becomes low, or inverted, and during the second phase the T wave becomes again upright, but usually taller than before ISP administration. The Q-T interval remains unchanged during the first phase and shortens during the second phase. We postulated that the first phase was due to a non-uniform and the second phase to a uniform effect of ISP on the repolarization of the ventricular action potentials. In this paper we present the experiments which support this hypothesis. We have correlated T wave changes produced by systemic ISP administration with the changes of monophasic action potentials (MAP) recorded with suction electrode from the ventricular surface of the dog heart. We also have infused ISP into different coronary arteries and correlated regional ISP-induced MAP changes with changes in the morphology of the T wave in the ECG. To our knowledge these studies represent the first quantitative analysis of the relation between the change in the duration of monophasic action potential and the T wave change in an animal with intact circulation. Our findings help to explain the influence of the size and location of the region with altered repolarization on the magnitude of the primary T wave change.
Methods

Studies were done on 29 mongrel dogs weighing 13.5 to 25 kg and anesthetized with sodium pentobarbital (30 mg/kg), administered intravenously. The chest was opened by a midternal incision, and the animals were ventilated with a respirator. To gain access to the posterior wall of the heart an additional lateral incision was made in several dogs.

To slow the heart rate, we performed bilateral upper thoracic sympathectomy, removing the paravertebral sympathetic chain cephalad to the fifth thoracic vertebra, including the stellate ganglia. The heart was suspended in a pericardial cradle and a bipolar Grass E2B platinum electrode was attached to the right atrial appendage. Another bipolar electrode was sutured to the right ventricle. The cardiac surface was covered with sponges soaked in warm saline. These sponges were replaced before each recording.

The exposed sites of the application of suction electrodes were kept as small as possible. The entire cardiac surface was heated by means of two model L510 explosion proof surgical lamps (12 in. diameter) illuminating the site of the incision. The distance between the heat reflecting lamp surfaces and the heart was adjusted to maintain the cardiac surface at a temperature ranging in individual experiments from 34° to 37°C. The temperature was monitored with a tele-thermometer, and the difference between the recording sites in each experiment was less than 1°C.

Two electrocardiographic leads and two monophasic action potentials (MAP) from the epicardial surface of the ventricular myocardium were recorded simultaneously with a multi-channel direct writing recorder on paper moving at 100 mm/sec.

We recorded standard limb lead II and lead aVF in the initial experiments (12 dogs), and the orthogonal X and Y leads of the system designed for the dog by McFee and Parungao in the subsequent 17 dogs. The ventricular complexes in leads II and Y were nearly identical while the complexes in aVF and X differed from each other. We measured the Q-T interval in both leads, and used the value from the lead with the longer interval. The area of the T wave was determined planimetrically in both leads after enlargement and retracing. T wave amplitude was measured at two different points designated aT and bT. The former corresponded to the center of the Q-T interval and the latter to the peak of the T wave (second if the T wave was bifid).

MAPs were recorded with bipolar suction electrodes. One electrode pole was the tip of a stainless steel wire (diameter 0.07 mm) inserted into the lumen of a polyethylene tube (ID, 1.3 mm; OD, 1.8 mm). This wire tip touched the epicardium when suction was applied (negative pressure = 75 mm Hg). The other pole was a cotton thread soaked in saline and wound on the outside of the tube at its tip.

Ventricular MAPs were acceptable if the course of the repolarization was smooth and the record was not distorted by the QRS and T wave deflections. To test the influence of the ventricular ECG complex on the MAP we compared the tracings recorded during atrial pacing with those recorded during ventricular pacing. The MAPs were acceptable if: 1) both atrial and ventricular pacing produced identical tracings (fig. 1), 2) the MAP amplitude exceeded 25 mV, and 3) ten or more consecutive MAPs were identical.

The activation time was measured as the interval from the beginning of the QRS complex to the onset of the steep upstroke of the MAP (MAP1), and the MAP duration as the interval from the MAP, to the end of MAP (MAPp). The latter point represented the intersection of the baseline with the tangent to the steepest part of the MAP downstroke.

The accuracy of the measured intervals was within 5 msec. This was determined by repeated measurements made by the same observer, and by independent measurements made by two different observers.

Isoproterenol (ISP) was administered in 5% aqueous dextrose solution (2 μg ISP/ml) with heparin (10 units/ml) into four different vessels: The pulmonary artery (PA) by hand injection via a 23" hypodermic needle (group I; 2 dogs); the left circumflex coronary artery (LCA) close to its origin via a preshaped 4 French catheter advanced from the right carotid artery and connected to an infusion pump (group II; 13 dogs); the first major ventricular branch of the LCA (BrLCA) via a 23" hypodermic needle connected by polyethylene tubing (I.D. 0.58 mm) to an infusion pump (group III; 8 dogs); the right coronary artery (RCA) 2 cm distal to its origin in the same manner as group III (group IV; 6 dogs). In each experiment the ISP dose was chosen in preliminary trial by gradually increasing the test doses to achieve the maximum change in T wave configuration without inducing ventricular arrhythmia. The atria were paced at the slowest rate required to overdrive the spontaneous rhythm after ISP infusion. This rate was kept con-

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†Wilmont Castle Co., Rochester, N.Y.
‡Yellow Springs Instrument Company, Inc., Yellow Springs, Ohio.
§Hewlett Packard

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stant in each animal during all procedures. The heart rate ranged from 120–160 beats/min. ISP injections into the PA were completed within 2–5 seconds and the doses ranged from 2–4 ?g. The infusions into the coronary arteries were completed within 5–10 seconds and the doses ranged from 0.06 to 0.64 ?g. In each animal ISP was administered only into one site but the procedure was repeated from 3 to 7 times. Each new infusion was made after the ECG pattern had returned to control, i.e., usually within 5–7 minutes. Both sites of suction application for the MAP recordings were changed after each ISP administration. All tracings were recorded continuously during the first minute after the onset of infusion, and subsequently at 15 second intervals until the ECG pattern returned to control. In several experiments contractile force was measured by means of Walton-Brodie strain gauge arches sutured to the epicardium. One of the gauges was attached to the area supplied by the artery into which ISP was infused, and the other gauge to the control area not perfused by ISP solution.

After the termination of experiments, the hearts were excised and indocyanin-green dye was injected into the coronary artery at the site of the previous ISP infusion. The area stained by dye was excised and weighed. The remaining ventricular myocardium was weighed following the excision of the atria and the great vessels. The weight of the stained myocardium was expressed in percent of the total ventricular weight.

In several experiments the MAPs were compared with the transmembrane action potentials (TAP) recorded with standard microelectrode techniques from papillary muscles excised from the same heart and mounted in a tissue bath (temperature 36°C; pH 7.4). These muscles were superfused with oxygenated Krebs-Hanseleit solution and driven at constant rates (1–2.5 c/sec). Isoproterenol solution (1 ?g/ml) was added to the bath. The contractile force of the papillary muscles was measured with a Grass force displacement transducer (FT 03C) sutured to one end of the preparation. The TAP and the contractile force were displayed on a Tektronix 5648 storage oscilloscope and photographed with a Polaroid camera.

Student’s t-test was used to evaluate the significance of the results.

Results

Mass of ventricular myocardium perfused with ISP.

We assumed that ISP reached the entire myocardium after the injections into the PA. The weights of the dye-stained myocardium indicated that the drug reached 23–41 (34 ± 6)% of the ventricular myocardium after the injection into LCA, 6–12 (8.5 ± 2.6)% after the injection into a branch of LCA, and 12–18 (17 ± 8)% after the injection into RCA (fig. 2).

Sites of MAP Recording

We recorded 114 pairs of acceptable MAPs. Of these, 14 pairs were recorded after injection into PA, (group I), 48 after infusion into the LCA (group II), 26 into the LCA branch (group III), and 26 into RCA (group IV). In group I, one of the MAPs was recorded from the right ventricular outflow tract and the other from the apex or the anterior wall of the left ventricle. In the other three groups, one of the MAPs was recorded from the ISP perfused area and the other from the control area in 97 experiments. In eleven experiments in group II, two in group III, and four in group IV, both MAPs were recorded from the ISP-perfused area.

T Wave in Control ECG

In agreement with previous studies, we found that bilateral sympathectomy had only a slight and inconsistent effect on ventricular repolarization. Following the sympathectomy, the Q-T interval was slightly prolonged (average 16 ± 2 msec) but the T wave vector was generally unchanged, and the T wave amplitude was either unchanged, or decreased. The shape of the T wave was similar to that recorded in other studies of anesthetized dogs in the supine position. In leads II and Y, the T wave was inverted, or upright with a single or bifid peak. The average amplitudes of a1T and a2T amplitudes in different groups were not significantly different from each other.

Effect of ISP on the ECG

All ISP infusions induced T wave changes without QRS changes. Since the sequence and the magnitude of changes in both leads were similar, we will describe these changes only in the longitudinal lead. In the evolution of these changes, we have identified an early and a late stage. The early and the late effects of ISP produced nearly opposite changes in the T wave polarity (fig. 3 and two upper rows of fig. 4, panels B and C).

The early change appeared less than 20 seconds after the onset of infusion when the Q-T interval remained unchanged. This change was clearly recognizable in all experiments in group I (onset at 13 ± 3 sec and duration 6 ± 3 sec) and group II (onset at 8 ± 2 sec and duration 5 ± 2 sec) (fig. 3 and two upper rows of fig. 4B) but was less distinct in group III and IV (two lower rows in fig. 4B). The early change affected mainly the ST segment which deviated from the baseline and produced a new proximal nadir of T wave (fig. 3B and first row in fig. 4B). The amplitude of this nadir averaged −0.24 ± 0.17 mV in group I and −0.31 ± 0.21 mV in group II. As a result of this change, the T wave area decreased by an average 22 ?mV sec in group I and 19 ?mV sec in group II. The differences between the early changes in the group I and II were not significant.

The late changes lasted usually 2–5 minutes. The average maximum T wave changes during this period are shown in table 1. During this phase, the ST seg-

*Hynson, Westcott and Dunning, Inc., Baltimore, Md.
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Figure 2

Late (steady state) effect of isoproterenol (ISP) on T wave amplitude in $10^4$ mV (solid line) and T wave area in $\mu$V sec (broken line) in four groups of experiments. The points represent average change from control values. In each panel, the proximal solid dot represents the $a_1$ T amplitude and the distal dot the $a_2$ T amplitude. The lower part shows the percent of the ventricular myocardial mass perfused with ISP. The ISP-perfused area of the ventricles is indicated by the dotted area in the diagram under each number. In each panel the anterior surface of the heart is shown on the left and the posterior surface on the right. The abbreviations are: PA = pulmonary artery (group I), LCA = left circumflex coronary artery (group II), LCA branch = left circumflex coronary artery branch (group III), and RCA = right coronary artery (group IV).

This is reflected in greater Q-$a_2$T shortening in groups I and II (table 1).

Effect of ISP on MAP

During the early stage of T wave changes, slightly less than one third of the MAPs shortened while the remainder did not change (fig. 3B). When both MAPs were recorded simultaneously from the ISP-perfused area the response varied: sometimes both MAPs remained unchanged, sometimes only one MAP shortened, and sometimes both MAPs shortened unequally. Of those MAPs which shortened during this stage, the average shortening was $9 \pm 3$ msec in group I, $11 \pm 5$ msec in group II, and $12 \pm 7$ msec in group III.

During the late stage all MAPs in the ISP-perfused areas shortened by more than 5 msec. All MAPs that had shortened during the early stage underwent...
further shortening. The maximum MAP shortening occurred within 18–30 sec after the onset of infusion and persisted for 1–3 minutes. All values in table 1 and figure 2 represent MAPs recorded during the “steady state” of maximum shortening simultaneously with the analyzed T waves.

The maximum shortening ranged from 7 to 30 msec (average 16 ± 7 msec) in group I, from 7 to 36 msec (average 15 ± 8 msec) in group II, from 6 to 36 msec (average 18 ± 8 msec) in group III, and from 8 to 35 msec (average 12 ± 4 msec) in group IV. The MAP shortening in group III was significantly greater than in group IV. None of the other differences between the MAP shortening in different groups was significant. There was no significant difference between the shortening of MAPs on the right and left ventricular surface following ISP administration into PA (group I). The shortening of 71 MAPs in group II was evaluated separately in three different areas of myocardium perfused by LCA: 20 MAPs at the apex shortened by 16 ± 8 msec, 30 at the posterior middle area by 14 ± 6 msec, and 21 at the posterior base by 14 ± 6 msec. These values were not significantly different from each other.

Table 1

<table>
<thead>
<tr>
<th>Group</th>
<th>No. experiments (dogs)</th>
<th>Amplitude (mV)</th>
<th>Amplitude (μV)</th>
<th>T wave area (μV·sec)</th>
<th>Q-aT interval (msec)</th>
<th>Q-T interval (percent)</th>
<th>MAP duration (msec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>14 (2)</td>
<td>−10 ± 8</td>
<td>+10 ± 14</td>
<td>NS</td>
<td>−12 ± 14</td>
<td>−6.0 ± 3.8</td>
<td>−16 ± 7</td>
</tr>
<tr>
<td>II</td>
<td>48 (13)</td>
<td>−6 ± 11</td>
<td>+37 ± 27</td>
<td>+17 ± 21</td>
<td>−12 ± 17</td>
<td>−2.3 ± 3.0</td>
<td>−15 ± 8</td>
</tr>
<tr>
<td>III</td>
<td>26 (8)</td>
<td>−7 ± 6</td>
<td>+7 ± 12</td>
<td>NS</td>
<td>−8 ± 14</td>
<td>NS</td>
<td>−18 ± 8</td>
</tr>
<tr>
<td>IV</td>
<td>26 (6)</td>
<td>+2 ± 5</td>
<td>−2 ± 4</td>
<td>NS</td>
<td>−2 ± 4</td>
<td>NS</td>
<td>−12 ± 4</td>
</tr>
</tbody>
</table>

All average values are significantly different from the control (P values vary from <0.01 to <0.001).
Effect of isoproterenol (ISP) on the ECG (lead II) and simultaneously recorded monophasic action potential (MAP) in the upper and middle panels, and on the transmembrane potential (TAP) in the lower panel. In A control, in B late ISP effect, and in C return to control. In D superposition of T wave and MAP from A (dashed line), B (heavy continuous line), and C (dotted line). In E and F, TAP at slow speed, upstroke of TAP and dV/dt max of the upstroke (inverted trace) at fast speed. The driving rate is 1 cps. Panel E is the control. In F superimposed TAPs during first 3 minutes after addition of ISP (1 µg/ml) to the bath. The TAP indicated by broken arrow is recorded at the time of the maximal effect of ISP. The resting potential and the dV/dt max remain unchanged, the action potential shortens, and the plateau level becomes more positive. Note the similarity of ISP effect on MAP and TAP.

Relation of MAP Termination to the End of the T Wave

ISP did not alter the relation between the end of the MAP on the ventricular surface and the end of the T wave. Only one MAP after ISP administration terminated later (5 msec) than the end of the T wave.

Effect of ISP on Contractile Force

Increase in the amplitude and the shortening of time to peak in the area perfused with ISP occurred in all experiments. The contractile force did not change in the control area.

Effect of ISP on TAP

Within 2–5 minutes after ISP administration, the TAP shortened in eight papillary muscles from five dogs by 8.0 ± 1.4% (range 6–10%) at the time when the amplitude of contraction increased two to eight fold. This shortening is comparable to the MAP shortening during the stage of late T wave changes (7.0 ± 3.0%) (fig. 5).

Discussion

Critique of the Method

The ventricular MAP in situ and the TAP in excised papillary muscles from the same animals showed identical slopes during both the distal portion of phase 2 and the entire phase 3 repolarization. This confirms the results of previous MAP and TAP comparisons in the rabbit hearts, and indicates that the duration of MAP represents the duration of TAP at the recording site.

It is a reasonable assumption that the ISP-induced changes in the MAP on the surface of the heart during the late stage represent changes occurring within the entire thickness of the ventricular myocardium for the following reasons: 1) in some experiments we
recorded endocardial and intramural MAP. Although the number of such records was not sufficient for statistical analysis, we always found the same ISP effect on the subendocardial and the intramural MAP as on the MAP from the ventricular surface. 2) ISP produced uniform MAP changes on the entire surface of both ventricles during the systemic administration, and on the entire surface of the affected region during infusion into the LCA, and 3) the shortening of the MAP and the Q-T interval during systemic ISP administration was nearly identical. Such response would not be expected if the MAP shortening in the deeper layers of the myocardium was less pronounced than on the surface.

During all intracoronary ISP infusions, the MAP duration and the contractile force changed only in the regions perfused by the ISP-containing blood. This indicates that the ISP effect was confined to the portions of the myocardium supplied by the vessel into which ISP was injected, and that the amount of recirculated ISP was not sufficient to affect the MAP or the contractility.

The Effect of ISP on MAP

ISP consistently shortened the ventricular MAP and the TAP. This shortening was due almost exclusively to the shortening of phase 2. In addition, the intracellular recordings, particularly at slower driving rates, revealed that ISP reset the plateau of the TAP to a more positive potential (fig. 5). This effect, previously observed in cardiac Purkinje fibers, can be detected during the continuous recording in the superimposed TAP, but it may escape recognition in the MAP because the amplitude of MAP depends more on the technique of recording than on the TAP amplitude.

The Effect of ISP on the T Wave

The earliest ISP effect was an alteration of the ST segment and the initial portion of the T wave without change in the terminal T wave portion and the Q-T interval. This suggests that the shift of the plateau to a more positive potential might have preceded the change in the plateau duration. The technique of MAP recording is not suitable for the evaluation of such changes. However, we observed this sequence during continuous TAP recording after ISP application.

Our study shows also that the early ST-T changes which preceded the shortening of the Q-T interval were associated with an asynchronous MAP shortening. This is in accord with the findings of Han and associates who have shown that both epinephrine infusion and left stellate ganglion stimulation cause an early asynchrony of refractory periods in the dog ventricle.

The late effect of ISP consisted predominantly of increased amplitude of the terminal portion of the T wave with some persisting ST-segment depression. A similar pattern has been recorded after ISP infusion into the left anterior descending coronary artery in dogs. In our study the late T wave changes were always associated with uniform MAP shortening induced by ISP, and reflect probably the altered potential gradients during the phase 3 of the ventricular AP.

The Effect of ISP on Q-T Interval

The average shortening of MAP during systemic ISP administration (16 msec) was similar to the average shortening of the Q-T interval (14 msec). This finding is consistent with our previous results which have shown that ventricular AP seldom terminate after the end of the T wave. "Silent repolarization" following the end of T wave was not evident in our experiments because the Q-T interval did not increase in any of the three groups with regional MAP shortening.

After ISP administration into the LCA the average MAP shortened by 15 msec and the average Q-T interval by only 6 msec. Following the ISP infusion into the RCA, or the BrLCA the MAP shortening was not associated with any Q-T shortening. These results indicate that some of the action potentials generated within the regions of the left ventricle supplied by the left anterior descending coronary artery contribute to the genesis of the terminal portion of the T wave.

Characterization of T Wave Changes Induced by ISP

The typical ISP effect alters the polarity of the initial and the terminal T wave portions in an opposite manner. Hence, we have observed conspicuous changes in T amplitude in association with negligible changes in the T wave area. In such cases, the change in ventricular gradient (VG) is not expected to be an accurate indicator of repolarization changes responsible for the primary T wave abnormalities. The limitations of the VG measurement in clinical practice have been discussed previously. A more recent computer analysis of the ECG after exercise demonstrated significant differences in the direction of the T vector between two groups of patients while the changes in VG "lacked comparable sensitivity and specificity." This finding may be explained by opposite deviations of the ST segment and the T wave vectors in some patients with positive exercise test. Harumi and associates have discussed the differences between the components of the ventricular AP responsible for the genesis of the ST segment and the T wave.
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The Site of Altered Repolarization and the T Wave Change

As expected, the MAP shortening in the lateral wall of the left ventricle (groups II and III) and similar MAP shortening in the right ventricle (group IV) were associated with opposite effects on the T wave polarity. Similar opposite changes in the T wave polarity have been shown previously during regional temperature alterations on the ventricular surface. This suggests that systemic ISP administration may be expected to produce partial cancellation of repolarization changes in the left ventricle and right ventricle. This effect may explain our finding that T wave change was greater when ISP affected 34% of myocardium (group II) than when the entire ventricle was affected (group I).

The Mass of Myocardium With Altered Repolarization and the T Wave Change

The T wave change in group II was greater than in group III. We attribute this to the larger mass of myocardium affected by comparable shortening of MAP. However, we cannot explain in the same manner why the MAP shortening in the right ventricle which comprised 17% of ventricular myocardium (group IV) was associated with lesser change in T wave amplitude than the MAP shortening in the portion of the left ventricular wall comprising only 8.5% of ventricular myocardium (group III). We have established that this difference could not be attributed to a lower average MAP shortening in group IV than in group III because when we eliminated the experiments with the greatest MAP shortening in group IV and those with the least MAP shortening in group III, the differences between the MAP shortening in groups III and IV were no longer present but the changes in both amplitude of \( a_T \) and \( a_T \) were significantly greater in group II than in group IV (\( P < 0.001 \)).

We compared the activation times of the MAP in groups III and IV. The Q-MAP, interval averaged 23 ± 6 msec in group III and 16 ± 7 in group IV. The difference between these two activation times was significant (\( P < 0.001 \)). It is reasonable to assume that the cancellation of repolarization is greater in the areas which are depolarized earlier. Therefore, such areas may contribute less to the T wave than the areas depolarized later. However, the uneven contribution of different regions to the T wave may be due to other differences, e.g., shape, orientation of fibers, or ventricular wall thickness.

Conclusions

The average MAP shortening induced by ISP in four groups of experiments ranged from 12–18 msec, and was always associated with T wave changes. This shows that the T wave is a sensitive indicator of small changes in the duration of action potentials, even if these changes are confined to a mass comprising less than 10% of the ventricular myocardium. We have established that certain abnormalities of repolarization at the cellular level may change the amplitude of the T wave without changing the magnitude of the ventricular gradient. We have also shown that the magnitude of the T wave change may not be proportional to the mass of tissue with uniformly altered repolarization. We attribute some of the discrepancies to cancellation, and some to an uneven contribution of different repolarization regions to the T wave. Our present clinical methods are not sufficiently accurate to assess precisely the character and extent of repolarization abnormalities. New methods may be needed to improve the specificity of T wave abnormalities in the electrocardiogram or the vectorcardiogram.

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