Epicardial Excitation Pattern as Observed in the Isolated Revived and Perfused Fetal Human Heart

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In this era of cardiac surgery the opportunity to study epicardial excitation and form of the epicardial complexes in the human heart seems amply present. Conditions in the operating room, however, dictated by the safety of the patient and the character of the surgical procedure, make extensive recording of epicardial electrocardiograms extremely difficult and nearly impossible.

In the course of experiments with the isolated perfused rat’s heart, it became clear that the electrocardiogram during perfusion did not show significant differences from the intra-vitam electrocardiogram. Cardiac standstill for one-half to 2 hours had no appreciable effect on the epicardial leads examined after revival. The same results also apply to the rabbit’s heart revived one-half hour after cardiac standstill. Figure 1 shows the electrocardiograms recorded during life and during perfusion after 40 minutes cardiac arrest; the differences are minimal.

After these experiments it was thought possible to study the excitation pattern of the isolated human fetal heart. The results of Burchell, Essex and Pruitt on the excitation pattern of the ventricular myocardium and ventricular septum of the isolated canine heart also prompted us to use this method for the study of the excitation pattern.

Methods

In 3 fetuses, 30 minutes after cardiac arrest and clinical death, autopsy was performed. The anterior wall of the thoracic cage was opened, the heart and great vessels were freed. The ascending aorta was opened immediately beneath the bifurcation of the innominate artery. A cannula of suitable size was inserted into the aorta, the apex pointing towards the heart. The opening was placed directly above the aortic valves, fixing it at this level with a ligature around the aorta. The cannula was filled with heparin. From insulated wire with a diameter of 1 mm, the tip was bared, slightly broadened and sutured to the epicardial surface of the apex of the left ventricle. The record between this electrode and the peripheral electrode served as a control for the detection of eventual deterioration of the preparation, for example, broadening of the complexes. The connections of the heart with the great vessels and surrounding tissues were severed, the heart was removed from the thoracic cage and connected immediately by means of a Luer lock to the Langendorff perfusion apparatus. After connection, the heart was placed in a cylindrical glass container, of 3,200-ml. capacity, filled with perfusion fluid. In the container 1 large electrode, surface area 24 cm², was used for grounding; another one of the same size at the opposite side was used as the peripheral electrode. Dimensions of the container were: diameter, 18.5 cm.; height, 15 cm. The distance between the heart and the peripheral electrode was at least 8 cm. The container was immersed in a thermostatically controlled water bath. The temperature of the bath was kept constant at 37 ± 0.1 C. The mean perfusion pressure was 90 cm. H₂O. The composition of the perfusion fluid is shown in table 1.

Immediately after reviving the heart, an accurate drawing of the heart surface was made by D. Durrer, who applied the exploring electrode during all experiments. Coronary vessels, including their bifurcations, were carefully drawn since these were used for the localization of the exploring electrode.

After the anterior surface was explored, the heart was rotated, making possible complete exploration of the lateral and posterior surfaces. In many instances, points from the lateral surfaces could be identified on the anterior and posterior
Figure 1
Electrocardiogram of the revived rabbit's heart. \( L \) = electrocardiogram recorded intra vitam. \( B \) = electrocardiogram recorded from the revived heart after 40 minutes of cardiac arrest, sensitivity 10 times greater than in \( L \). The numbers indicate places from the epicardial surface which were explored intra vitam and after revival.

At least 125 epicardial points were explored in each experiment. The connection of the electrodes with the recording apparatus was made in such a way that positivity of the exploring electrode resulted in an upright deflection in the recorded complex. Over large regions of the left ventricle the T wave was positive; it remained unchanged throughout the experiment. In fetal heart 1, the cardiac frequency at the beginning of perfusion was 115 per minute, at the end after 4 hours, 111 per minute. In fetal heart 2, the frequency varied between 122 and 128 per minute, and in fetal heart 3, between 125 and 139 during 4 hours perfusion.

After cardiac arrest a small amount of India ink was injected into the coronary arteries and the hearts were fixed in 10 per cent formalin. After fixation, a wax model was made on which the coronary arteries and small black spots representing the explored epicardial points were drawn. The anterior and posterior attachments of the ventricular septum were determined by injecting both ventricular cavities with radiopaque material (fig. 2). Sections of the heart were made in a direction parallel to the atrioventricular ring, each section at a distance of approximately 2 to 2½ mm. In this way the relation of the epicardial points to the anterior and posterior septal attachment could be studied. Each heart was examined microscopically. Except for slight edema, no abnormalities were observed.

Recordings were made on 36 mm. film, using a 2-channel, high-fidelity cathode ray oscillograph.

*Developed by Dr. L. H. van der Tweel, Laboratory of Medical Physics, University of Amsterdam, Amsterdam, The Netherlands.

at a speed of 2½ inches per second. Time pips occurred every 100 msec., synchronously in both leads. Only those records were used which showed a stable baseline and a constant form of the successive complexes. Each record was enlarged 5 times on millimeter paper to measure time relations and height of deflections. The large thermally controlled water bath in which the container with the fetal heart was placed only allowed one direction of approach for the exploration of the fetal heart. Therefore, the heart was rotated 90 degrees each time the lateral and posterior surfaces of the heart had to be explored. The reference electrocardiogram changed very slightly after each 90-degree rotation of the heart; the major deflections were always clearly visible and did not change. This slight change was caused by small movements of the reference electrode, even if sutured on the epicardial surface. Zero reference point was the beginning of the Q wave in a lead from the posterior ventricular surface, assuming that the beginning of the Q coincides with the beginning of ventricular depolarization. All time relations were corrected to this point.

For determining the arrival time of the excitation wave at the epicardial surface, the intrinsic deflection must be identified. In previous publications, we gave evidence that only the rapid portion of the intrinsic deflection signals the arrival of excitation at the epicardial surface. The duration of this rapid portion is less than 3 msec. Under our experimental conditions the height of the rapid phase of the intrinsic deflection varied from 0.05 to 0.5 mv. When the intrinsic deflection was small, identification was sometimes difficult. The localization of the intrinsic deflection in the ventricular complexes varies. It is not always present at the downstroke of the R or S wave, as commonly accepted, but may occur as a negative going potential on the upstroke of the S. Even at the end of the experiments the rapid portion of the intrinsic deflection remained unchanged.

Three hearts from 28-week-old fetuses were revived 30 minutes after occurrence of clinical death. Fetal hearts 2 and 3 were those of monozygotic twins. At autopsy hyaline membranes in the lungs of the second and third fetuses were found. Microscopic examination of the various organs revealed no abnormalities, except for small areas of bronchopneumonia in the lungs of the third fetus.

Results
Form of Epicardial Complexes (Figures 3 and 4)
We cannot give an exhaustive description of the form of all the epicardial complexes. Corresponding areas of all 3 hearts show great...
EPICARDIAL EXCITATION

Table 1
Composition of Perfusion Fluid

<table>
<thead>
<tr>
<th></th>
<th>Gm.</th>
<th>mOsm./L.</th>
<th>mEq./L.</th>
</tr>
</thead>
<tbody>
<tr>
<td>NaCl</td>
<td>7.5</td>
<td>236.4</td>
<td>149.1</td>
</tr>
<tr>
<td>KCl</td>
<td>0.35</td>
<td>9.4</td>
<td>4.7</td>
</tr>
<tr>
<td>CaCl₂</td>
<td>0.15</td>
<td>3.9</td>
<td>2.6</td>
</tr>
<tr>
<td>NaHCO₃</td>
<td>1.7</td>
<td>40.4</td>
<td>3.9</td>
</tr>
<tr>
<td>Na₂HPO₄</td>
<td>0.05</td>
<td>1.0</td>
<td>40.4</td>
</tr>
<tr>
<td>MgCl₂</td>
<td>0.1</td>
<td>3.0</td>
<td>20.2</td>
</tr>
<tr>
<td>Glucose</td>
<td>2.0</td>
<td>11.0</td>
<td>0.7</td>
</tr>
<tr>
<td>Aqua dest.</td>
<td>1,000 ml.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>325.1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*The chemical composition of the fluid was chosen to match the concentration of the electrolytes of the extracellular fluid; the pH at 37 C. in the perfusion fluid, if saturated with 95 per cent O₂ and 5 per cent CO₂, was 7.35.

It is surprising that in all 3 hearts, at the high right anterolateral region bordering the A-V groove, small Q waves followed by a large well-developed R are seen. In the adjacent area below this, extending roughly one-third the distance from basis to apex, the complexes have a qRS or qrS form. The beginning of these complexes coincides with our zero-point. Therefore, it is unlikely that the first part of the complex is isoelectric.

The complexes in the right laterobasal region resemble those in the precordial leads in right ventricular hypertrophy. In the higher right anteroparaseptal areas rsR complexes are seen, sometimes showing notching of the R.

In the left anteroparaseptal middle region, rS complexes are found. In the middle region of the anterior wall of the left ventricle, rsR or rSr'S' complexes are found in some places. The left anterior region of the atrioventricular border shows in a relatively large area rsr's', RSR'S' or rSr'S' complexes.

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anterior part of the fetal heart, but the distance between the epicardial surface and the heart was at least 8 cm.

In the first fetal heart, the presence of a deep Q on the posterior wall at this low level was unexpected. A mistake in localization was thought possible. Therefore, in a second heart, immediately after restoring cardiac action, this area was investigated directly upon beginning the experiment. The identical complexes were found and in the third heart the same pattern was repeated. It is unlikely that the experimental conditions have caused this peculiar morphology.

The duration of the QRS complex varied from 40 to 50 msec. in the records from the different points, not changing more than 5 msec. from identical points made at different moments during the experiments.

We refrain from a very detailed description of all minor variations present in epicardial records.

**Epicardial Excitation Patterns (Figure 5, Left and Right)**

For the sake of clarity, the times of arrival of excitation at the epicardial surface have been grouped into 5-msec. intervals. In all 3 hearts examined, epicardial breakthrough occurs first in the right lower anteroparasetal region, 10 to 15 msec. after the beginning of ventricular depolarization. Five msec. later the lower and middle part of the right ventricle, a large portion of the ventricular muscle overlying the anterior attachment of the ventricular septum, and a small portion of the adjacent anterior left ventricular muscle are excited. Each successive 5-msec. interval shows an enlargement of this area.
excitation wave moves across the epicardial surface of the left ventricle around the left lateral wall towards the posterobasal region, a second one proceeding simultaneously in the opposite direction, i.e., around the right lateral wall towards the right posterobasal region. The posterobasal regions are activated latest in the cardiac cycle. This is clearly shown in figure 5, right. There is close agreement in the excitation pattern of all 3 hearts.

The ventricular muscle overlying the anterior and posterior attachments of the ventricular septum behaves as the adjacent myocardium. The excitation wave at the epicardial surface moves across these zones without any interruption. Therefore, the epicardial excitation pattern can be very simply described: there is a radial spread in all directions, beginning from the area prepapillaris (trabecularis) proceeding towards the high posterobasal regions. The distances covered in each 5-msec. time interval differ. They are relatively large during the early intervals of epicardial excitation and decrease somewhat in the later intervals.

Discussion

The use of the isolated perfused fetal heart as an experimental tool deserves comment. Is it permissible to use a resuscitated heart, after a cardiac standstill of about 30 minutes, for the study of the excitation pattern of the living heart?

In 1918 Boden and Neukirch, comparing the electrocardiograms of living infants with those obtained post mortem after isolation and perfusion, proved that the electrocardiogram of the perfused isolated human heart can be used for the investigation of cardiac excitation. Their work seems unjustifiably forgotten.

In our experiments on the rabbit and rat's heart intra vitam and revived after a half-hour cardiac standstill, multiple unipolar records from various points on the epicardial surface were made in both conditions. Figure 1 shows the electrocardiograms from an experiment of this type, the complexes intra vitam and after revival are very similar. The voltage during immersion is one-tenth the intra-vitam voltage recorded, due to the short-circuiting effect of the immersion fluid.
During perfusion of the rabbit, rat, and fetal hearts no significant changes in the electrocardiogram occur. In the first fetal heart the anterior side was explored immediately after resuscitation and again 4 hours later. In figure 6, complexes of both series are shown; the differences are minimal. The degree of similarity is great between some complexes recorded in our experiments and those from the human living heart.

The perfusion fluid was matched as closely as possible to the composition of the extracellular fluid, but one drawback was present. It did not possess colloid-osmotic (oncotic) pressure. Immediately after the beginning of perfusion, visible swelling of the heart occurred. The cardiac frequency remained unchanged, however, and no changes in the electrocardiograms were seen. Earlier investigations on the perfusion of the rat’s heart have shown that the concentration of the electrolytes of the intracellular fluid does not change appreciably during 4 hours perfusion. Table 2 shows the electrolyte composition of the isolated rat’s heart after 15 minutes of perfusion.

Several attempts with the isolated rat’s heart to use albumin or narrow-fractionated dextran were unsuccessful, since the heart stopped beating after a half to one hour. We therefore performed our experiments on the fetal heart with a nononcotic fluid, not being completely certain that this did not cause minor changes in the excitatory process.

In all 3 hearts radial spread originating in the area trabecularis was present. The pattern may be described as a double envelopment of both ventricles. The latest activated area was always the posterobasal region of the left and right ventricles. The area covered in each 5-msec. interval was not identical in the different hearts. The same over-all pattern of epicardial excitation was present. In each heart, the area covered in a 5-msec. interval was relatively larger in the early phases of depolarization than in the later phases. One of the reasons for this fact may be a lower Purkinje.
fiber density in the high anterobasal and posterobasal parts of the ventricular walls.

To the best of our knowledge up to now, no analysis has been published of the excitation process which can be observed at the epicardial surface of the isolated human fetal heart.

Boden and Neukirch did not use leads comparable with "unipolar" recordings, because of the inconsistency of these records.

The complexes in the corresponding areas of the 3 different hearts show a close similarity. The lower anterior portion of the right ventricle, corresponding part of septum, and paraseptal lower anterior part of the left ventricle show a rS pattern. The regions of the lower lateral part of the right ventricle show the "classical" left ventricular pattern. From this we must conclude that no typical right ventricular or left ventricular pattern can be found, since in the fetal heart a left ventricular pattern may also be found over the right lateral portion of the right ventricle near the atioventricular ring and the posterobasal regions of the right ventricle.

Initial positivity is present at the anterior side of the right and left ventricles and at the small area of the apical posterior surface.

Q waves appear mainly on the posterior and lateral side on both ventricles. The presence of small Q waves in these regions on the right ventricle is difficult to explain in view of the commonly assumed initial positivity of the right ventricular cavity in the human heart. It is possible that in the fetal heart initial negativity of some parts of this cavity exists. Latour and Puech published a monograph on intracavitary electrocardiography in the adult heart in which records can be found (fig. 10, no. 13 of this monograph) showing initial negativity of the right ventricular cavity in regions near the tricuspid valve.

We cannot explain satisfactorily the presence of deep Q waves and QS complexes at the apical-posterior surface of the heart. The epicardial surface of this area is activated relatively late (30 to 40 msec.), the intrinsic deflection occurring on the upstroke of the QS complex.

Figure 6

Epicardial records from anterior surface of fetal heart 1 at the beginning of perfusion and 4 hours later.

The area showing Q waves is surprisingly large. Differences in excitation pattern between adult human heart and fetal heart may be responsible.

The Q waves from the posterior wall are deepest in the region overlying the posterior attachment of the ventricular septum, one-third the distance from apex to basis.

The beginning of the Q wave is synchronous in all these complexes. It is possible that excitatory forces in the ventricular septum progressing in a basal direction are responsible for the occurrence of this deep initial negativity.

We compared the electrocardiograms of the fetal with those from the exposed human heart.

The first detailed account of the morphology and time relations of the exposed adult human heart appeared in 1930. Barker, MacLeod and Alexander had the opportunity to examine the partially exposed heart of a young man with an extrapleural pericardiotomy. The earliest point to become active was located high on the anterior surface of the right ventricle near the tip of the right auricular appendage (10 milliseconds after the beginning of R in lead II). Other early
points on the right ventricle were located on the conus arteriosus and the anterior surface near the base of the large papillary muscle (14 and 15 milliseconds respectively after beginning of R II). The earliest points on the left ventricle were high on the antero-lateral surface near the left auricular appendage, and on the left apex posteriorly, 16 and 20 milliseconds respectively. The latest point was on the posterior surface of the left ventricle near the atrioventricular groove, becoming active 30 milliseconds after beginning of R II.9

These findings suggested that the excitation of the various points on the surface of the ventricles showed a different time course, as postulated for the human heart by Lewis and Rothschild.10 They thought that the earliest region to become activated was on the anterior surface of the right ventricle near the base of the anterior papillary muscle. From figure 77 in Lewis' book,11 depicting his considered view on total ventricular excitation, a radial spread from this earliest activated point towards the basal parts of the ventricles can be seen.

In the past decades Groedeland Borchardt's monograph12 and an increasing number of papers have appeared on epicardial excitation.13-19 In these publications some areas show a striking correspondence with the fetal complexes, but differences are present, some of which may be mentioned: the QRS complex of a W type in the anterior superior portion of the septum or its neighboring vicinity, and the QR pattern in the left anteroparametal zone.18-20 From the lateral parts of the right ventricle RS and Rs patterns were found regularly. These differences may be caused by differences in excitation of the fetal and adult human hearts or experimental conditions. The pathway of activation of the epicardial surface in the dog's heart as described by Scher 21 is very similar to the pattern found in the fetal heart. Further experiments on intramural and septal excitation will be necessary to explain the form of the epicardial complexes in terms of total ventricular excitation.

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**Table 2**

<table>
<thead>
<tr>
<th>Hearts</th>
<th>Number of analyses</th>
<th>Electropotentials in serum and perfusion fluid (mV, μA)</th>
<th>Solids (%</th>
<th>Muscle water in ml/Kg, fat-free solids</th>
<th>Intracellular Na^+ (mEq/L, intracellular H^+</th>
<th>Na^+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fresh isolated, nonperfused hearts</td>
<td>13</td>
<td>143 ± 0.6</td>
<td>4.9 ± 0.1</td>
<td>103 ± 0.6</td>
<td>22.3 ± 0.1</td>
<td>3860 ± 30.6</td>
</tr>
<tr>
<td>Isolated hearts perfused during 15 min.</td>
<td>17</td>
<td>141 ± 0.2</td>
<td>4.9 ± 0.05</td>
<td>131 ± 0.7</td>
<td>16.7 ± 0.1</td>
<td>5550 ± 57.3</td>
</tr>
</tbody>
</table>

*Assumptions made: (1) chloride is entirely extracellular; (2) solids contain 10 per cent fat; (3) Donnan factor for serum: Na^+, K^+ and Cl^- = 0.96; (4) serum contains 95 per cent H_2O.

\[±SD_m = \text{standard deviation of the mean} = \sqrt{\frac{\sum (x_i - \overline{x})^2}{n(n-1)}}\]

DURBER, BULLER, GRAAFF, LO, MELDIEEE
The resuscitated fetal human heart can be used as an experimental tool for the investigation of the excitatory process in the human heart. During perfusion the configuration of the epicardial electrocardiograms does not change appreciably. For accurate recording permitting a detailed analysis, the use of a high-fidelity oscillograph is absolutely necessary, otherwise no identification of the rapid portion of the intrinsic deflection can be made. The heart is suspended in an homogeneous volume conductor at 37 C. and perfused with fluid matching as closely as possible the composition of the extracellular fluid.

The morphology of the unipolar complexes is difficult to describe adequately. At the anterior side of the right and left ventricles rS complexes are found. Some parts of the left ventricular wall and posterobasal region of the left ventricle show QR complexes. In the area bordering the A-V groove one-third the distance from apex to basis, deep Q waves and even QS complexes are found. The relatively late intrinsic deflection here points to late excitation of this region. In regions neighboring the A-V groove, the Q wave diminishes in size and the R increases. The left posterior part of the left atrium is activated latest in the atrial cycle. The epicardial excitation pattern is surprisingly simple. The excitation wave reaches the region of attachment of the right anterior papillary muscle first, then spreads radially with varying velocity across the left ventricle towards the posterobasal region, while another wave spreads simultaneously across the right ventricle towards the same region. There is, therefore, a double envelopment of the epicardial surface. A comparison of the complexes having an intrinsic deflection occurring at the same time shows conclusively that, even over the same ventricle, the morphology of these complexes may be completely different. Thus the excitation time does not determine the morphology of the complexes. There is no typical right or left ventricular pattern. There appears to be no relationship between thickness of the heart wall and height of the R wave.

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References

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