Experimental Studies

Study on the Genesis of Giant Negative T Wave in Apical Hypertrophic Cardiomyopathy Using a Three-Dimensional Computer Model

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SUMMARY

Apical hypertrophic cardiomyopathy is characterized by a spade-like left ventricular cavity and by both giant negative T waves and tall R waves in the electrocardiogram. However, the mechanisms of these ECG abnormalities have not been satisfactorily clarified. We have recently developed a three-dimensional computer model of ventricular depolarization and repolarization processes. This model has successfully simulated normal QRST waves and changes characterizing some abnormal conditions. A model of apical hypertrophic cardiomyopathy was constructed by adding model units to the endocardium of the left ventricular apex. The surface ECG was then calculated by assuming different gradients of action potential durations and different proportions of the hypertrophic cells in the apical segment. A negative T wave of $-1.45 \text{ mV}$ in lead V4, similar to the clinically reported ECG, was obtained by assuming: (1) diffusely distributed hypertrophic cells at the apex and (2) uniform, long action potential durations of hypertrophic cells. It is suggested that these properties may account for the distinctive ECG abnormalities in apical hypertrophic cardiomyopathy.

Key Words:
Computer simulation Apical hypertrophic cardiomyopathy Giant negative T wave Action potential duration

A PICAL hypertrophic cardiomyopathy (AHC) is a variant form of non-obstructive hypertrophic cardiomyopathy. Initially reported from Japan in the late 1970s, it has been shown to exist throughout the world. The diagnostic features of AHC are (1) a spade-like deformity of the left ventricular cavity at end-diastole, reflecting hypertrophy confined to the apex and (2) giant negative T waves (≥10 mm T wave inversion) with high pre-
cordial QRS voltages in the electrocardiogram. Changes in the recovery process of the hypertrophied myocardium at the left ventricular apex have been considered to play a major role in the genesis of giant negative T wave in AHC.\(^1\),\(^2\) However, the mechanism has not been well-defined because of the difficulties in studying electrophysiologic abnormalities of the hypertrophied myocardium in clinical cases.

We have recently developed a three-dimensional computer model of ventricular depolarization and repolarization processes.\(^2\),\(^3\),\(^4\),\(^5\) This model has successfully simulated normal QRST waves and abnormal waves produced during bundle branch block and myocardial infarction.\(^6\),\(^7\) This simulation model may provide insight into the etiology of the distinctive ECG abnormality in AHC. Thus the giant negative T wave in AHC was simulated by assuming the hypertrophy to be localized to the apex with alterations in the electrical properties of the hypertrophied myocardium.

**METHODS**

The electrocardiographic simulation used in the present study was first developed by Aoki et al.\(^2\),\(^3\) Subsequently, a model editor has been designed to modify the geometry and electrophysiologic properties of the heart model.\(^4\) In brief, the normal ventricular model was composed of approximately 50,000 model units arranged in a close-packed structure. Each unit was in direct contact with the adjacent 12 units with the same distance of 1.5 mm. The specialized conduction system was assumed to have a conduction velocity 5 times greater than the ventricular units of 0.5 m/sec. The system was distributed in both the right and left ventricles so as to obtain an excitation sequence resembling that reported by Durrer et al.\(^8\) (Fig. 1). The ventricular excitation was assumed to be isotropic. It started from the endocardial sites in contact with the Purkinje network and propagated in steps of 3 msec from the activated units to the adjacent resting units toward the epicardium.

The repolarization sequence is determined by both the excitation sequence and the distribution of action potential durations (APDs). The action potential waveforms were given to individual units in such a way that the APDs were shortest on the epicardial site and increased linearly towards the endocardial site (Fig. 1). The APDs of the units located on the epicardium were 255 msec and other units were incremented in steps of 5 msec.

The heart model was mounted in a homogeneous torso model covered with 684 triangles connecting 344 nodes. The surface potentials on the torso model were calculated by means of the boundary element method with the
In brief, the action potential of model unit $i$ at time $T$, $\phi_i(T)$, was given by

$$\phi_i(T) = A_i(T-T_i)$$

where $A_i(t)$ was the action potential of unit $i$ as a function of time and $T_i$ is the initial time of activation of model unit $i$.

The dipole moment of the model unit $i$, $J_i$, was then calculated as

$$J_i = -k \Delta \phi_i$$

where $k$ is theoretically defined using the intracellular and extracellular conductivity, $g_i$ and $g_e$, by

$$k = \frac{g_i g_e}{g_i + g_e}.$$
Fig. 2. Ventricular model of apical hypertrophic cardiomyopathy. The display format is the same as Fig. 1. Apical hypertrophy was constructed by adding the model units on the endocardium of the left ventricular apex. The activation sequence (upper panel) is not significantly changed from the normal ventricular model, except at the apical segment. In the present model, the apical segment was assumed to be occupied diffusely by the hypertrophic cells, which had the longest action potential durations among the normal model cells (lower panel).

was adjusted until the maximum R wave for the normal model equaled 2 mV.

For the simulation of the giant negative T wave in AHC, the ventricular model was modified on the basis of clinical data.1,2) As shown in Fig. 2, a spade-like left ventricular cavity was simulated by adding units on the endocardium of the left ventricular apex. The number of the added units was approximately 3% of the total number of the normal ventricular model. Thus, the left ventricular apex was thickened from 7 normal layers to 15 layers. The thickness of the anterior and inferior wall and the septum of the apical segment was also increased from 10 layers to 15 layers. The ratio of the thickness of the anterior apical wall to the anterior free wall at the point of the median transverse diameter thus became approximately 1.5, in good agreement with the ratio described previously.1,2) The modified endocardium was also covered with the Purkinje network distributed in the position corresponding to the normal heart model. As a result, changes in the ventricular activation sequence were not significant, except in the apical por-
There have been few studies on the distribution and the electrophysiologic properties of the hypertrophied muscle cells in AHC. Pathological findings suggested that the hypertrophied cells are distributed diffusely at the apex with extensive disarray of myocardial fibers indistinguishable from those of classic hypertrophic cardiomyopathy. The electrophysiologic properties of hypertrophied cells in human hearts have not been studied in detail. It is likely that the action potential of hypertrophied cells show prolongation of duration without significant alterations in resting potential, amplitude and upstroke velocity.

Thus, in the present model for apical hypertrophy, it was postulated that the left ventricular apex contained a diffuse array of hypertrophic cells from endocardium to epicardium. The hypertrophic cells were set to have a uniform APD of 310 msec, equal to that of the endocardial cells and longest among the normal ventricular cells. The remaining area of the ventricular model was assumed to have the same APD distribution as the normal model. A gradual transition of APD was set between the hypertrophied
Fig. 4. Body surface isopotential maps at 6 instants of time during ventricular activation and recovery in the AHC model. The timing of each map is indicated by a vertical line intersecting the reference electrocardiogram. In each map, the left side represents the anterior and the right side the posterior aspect of the chest surface. Solid lines indicate isopotential lines. The positions of the extrema are indicated by the plus and minus signs. Note that the left anterior chest was covered with strongly negative potentials throughout the T wave.

and the normal regions.

Conditions such as different gradients of APDs and different proportions of hypertrophic cells were simulated to see which condition is necessary to obtain giant negative T wave. Each condition was specified by the use of a model editor which can create and modify the geometry and electrophysiological properties of the heart model.14)

RESULTS

Figure 3 shows the simulated ECG and VCG from the AHC model. The QRS voltages increased markedly as the sum of the R wave in lead V_{4} and the S wave in lead V_{1} became 3.9 mV from 2.7 mV of the normal model. The T wave was negative in leads I, aV_{L}, and V_{3} to V_{6}. The negative T wave can be defined as "giant", because it was \(-1.45\) mV in V_{4}, deeper than \(-1.0\) mV in leads V_{3} and V_{4}.

As in the simulation of normal subjects, the QRS loop presented counterclockwise rotation in the horizontal plane and was oriented to the left, posteriorly and inferiorly on the VCG. In contrast, the T loop was markedly abnormal because it was oriented to the right and posteriorly with clockwise rotation and the maximum T vector was \(+160^\circ\) in the horizontal plane.

The isopotential maps obtained from the AHC model showed a normal distribution of positive and negative potentials over the thorax during the
QRS complex (Fig. 4). The positive potentials covered the left anterior chest with the negative potentials over the right upper anterior chest and the left upper back in the early and mid QRS maps. On the other hand, the isopotential maps during the T wave were distinctively abnormal, since the left anterior chest was widely occupied by deep negative potentials (Fig. 4). These features of the wave forms and the potential distribution during the QRST complex strikingly resemble those seen in human subjects (Fig. 5).
Table I. Effect of Different APD Gradients and Different Proportions of Hypertrophic Cells on T Wave

<table>
<thead>
<tr>
<th>APD gradient (msec)</th>
<th>5.0</th>
<th>3.75</th>
<th>2.5</th>
<th>1.25</th>
<th>0</th>
</tr>
</thead>
<tbody>
<tr>
<td>T wave in V₄ (mm)</td>
<td>+2.5</td>
<td>-3.2</td>
<td>-8.0</td>
<td>-12.0</td>
<td>-14.5</td>
</tr>
<tr>
<td>Distribution (%)</td>
<td>0</td>
<td>39</td>
<td>50</td>
<td>67</td>
<td>100</td>
</tr>
<tr>
<td>T wave in V₄ (mm)</td>
<td>+2.0</td>
<td>-1.5</td>
<td>-7.6</td>
<td>-11.5</td>
<td>-14.5</td>
</tr>
</tbody>
</table>

Distribution: % of hypertrophic cells (assumed APD=310 msec).

The time integral area of the QRST complex was calculated for each lead as the algebraic sum of all potentials from the onset of the QRS complex to the offset of the T wave, multiplied by the sampling interval, and was displayed as an isointegral map. Figure 6 shows the QRST area maps from the model (a) and a patient with AHC (b). These two maps were quite similar, characterized by strongly negative isointegral values over the left anterior chest.

The effect of the different gradients of APDs and proportions of hypertrophic cells on the T waves was also investigated (Table I). The T wave in lead V₄ increased progressively in negativity as the APD gradients of the hypertrophic cells were decreased; an APD gradient ≤1/4 of normal gradient (5 msec) was necessary to produce giant negative T waves. Similarly, the depth of the T waves in V₄ was proportional to the percentage of the hypertrophic cells (uniform APD of 310 msec) distributed in the apical segment. The apical segment needed to contain at least 67% hypertrophic cells to obtain giant negative T waves.

**DISCUSSION**

The computer simulation model does not necessarily provide the electrophysiologic basis for the ECG waveforms under normal and abnormal heart conditions. However it may be valuable for a better understanding of the ECG if certain QRST waveforms are appropriately simulated based on assumptions from experimental or clinical data. Further, it permits a direct comparison between the electrophysiologic properties of the heart and the resulting ECG waveforms.

At this time, it is unclear if any current model is satisfactory for simulation of the heart. In our three-dimensional model, there are limitations such as ignorance of inhomogeneity of the volume conductor and the use of an isotropic myocardium. However, since the simulated ECGs were in good agreement with those from human subjects, it is unlikely that the errors introduced by these factors had a significant effect on the resulting surface
potentials. In addition, the present model has an advantage over those reported in the past\textsuperscript{20} in that the geometry of the heart and the electrophysiologic parameters can be arbitrarily modified.\textsuperscript{14} The electrocardiographic features of AHC are as deep negative T waves in the left chest leads and high QRS voltages. In order to simulate these abnormalities, apical hypertrophy was constructed by adding model units on the endocardial side of the left ventricular apex. This approach reconstructed the spade-like deformity of the left ventricular cavity reported in the literature.\textsuperscript{1,2} Pathologic findings have revealed that the heart shows apical hypertrophy with extensive disarray of myocardial fibers near the apex of the left ventricle.\textsuperscript{3,6} Although the electrophysiologic properties of the hypertrophied myocardial cells in human cardiomyopathy have not been reported, experimental studies have suggested that the APD of the hypertrophied myocardium prolongs without alterations in resting potential, amplitude and upstroke velocity.\textsuperscript{17–19} With the assumptions that the apical segment was occupied diffusely by the hypertrophic cells with the longest APD among the normal cells, the simulated ECG, VCG, and body surface maps shown in this study were in good agreement with those of patients with AHC.

The basis for production of giant negative T waves by the model can be explained as follows. Unlike the normal ventricular model, there was no difference in the APDs among the units at the apex. As a result, the early depolarized units repolarize early and the late repolarization follows the late depolarization. The time difference of the recovery process between two adjacent layers is 2 msec in the normal model, while it is 3 msec in the hypertrophied area with the reverse recovery sequence. The potential difference between the two layers is thus greater and the polarity was opposite the normal area during the recovery process. Thus, the dipole moment of the hypertrophied area became about 1.5 times greater than normal (equation (2)), with the opposite polarity of the normal area during the T wave. In addition, the proximity of the left ventricular apex to the anterior chest wall may have contributed to the negativity of the T wave in the chest leads.\textsuperscript{21}

It is possible that the giant negative T waves resulted from alterations in the activation sequence, since the T wave is determined by the excitation sequence as well as the distribution of the action potential waveforms. However, the algebraic sum of the QRST area is largely independent of the ventricular activation sequence and dependent on intrinsic ventricular recovery properties.\textsuperscript{22,23} It is suggested that the changes in the recovery process play a major role in the genesis of giant negative T waves in AHC, since the QRST area map of the model strikingly resembles results from a patient with AHC. This was confirmed by the second part of the present study (Table I).
One necessary condition for the appearance of giant negative T waves was that the APD gradient of the units in the hypertrophied region was no more than 25% of the normal gradient (5 msec). Further, at least 67% of the apical segment needed to be replaced by the hypertrophic cells with an assumed APD of 310 msec. These features are consistent with pathological findings suggesting that the hypertrophic cells are distributed diffusely at the apical segment.

Limitations of the present model are related to simple assumptions regarding the anatomy and physiology of hypertrophied muscle. Actual myocardial hypertrophy is usually accompanied by increases in both the size and the number of muscle fibers. In addition, extensive disarray and whirling of thick myocardial fibers with interstitial fibrosis were shown in the patients with AHC. Thus, a more sophisticated model of the hypertrophied myocardium would be necessary for more accurate simulation.

In conclusion, the giant negative T wave of apical hypertrophic cardiomyopathy was simulated using a three-dimensional computer model. A negative T wave of $-1.45 \text{ mV}$ in lead $V_4$ was obtained by calculating the ECG on the assumptions: (1) that hypertrophy is localized to the left ventricular apex, (2) that hypertrophic cells are distributed diffusely at the apex, and (3) that the APDs of hypertrophic cells are uniform and prolonged. Thus, these changes in geometry and repolarization properties may contribute to the distinctive ECG abnormalities in apical hypertrophic cardiomyopathy.

REFERENCES

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