On the Genesis of the Absolute Ventricular Arrhythmia Associated with Atrial Fibrillation

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ABSTRACT

Genetic factors in the formation of the long R-R interval in ventricular arrhythmia associated with atrial fibrillation were investigated in the isolated rabbit heart which was perfused using Langendorff's technique. The transmembrane action potentials recorded from a single cell within the A-V node or within its vicinity were analyzed, and contiguous bipolar-lead electrograms simultaneously recorded from the right atrium and ventricle. Atrial fibrillation was induced by the combined application of acetylcholine solution and electrical stimulation. Atrial excitation was mainly blocked in the right atrium and in the anterior half of the A-V node.

To clarify further the time-correlation between the right atrial electrogram and the A-V nodal responses, the pattern of atrio-ventricular conduction was studied by applying only the electrical stimulation at high frequency without acetylcholine. The conduction was mainly blocked in the same sites as in the above experiment and the pattern of the conduction block in Wenckebach rhythm was observed. The conduction block within the anterior half of the A-V node may be the most important factor in producing the long R-R interval in atrial fibrillation. It was shown that the pattern of the conduction block can be explained by the Wenckebach rhythm.

ADDITIONAL KEY WORDS

long R-R interval  acetylcholine
transmembrane action potential  electrical stimulation
A-V nodal action potential  A-V conduction delay
conduction block

In 1909, Rothberger and Winterberg (1) reported that atrial fibrillation causes absolute ventricular arrhythmia. Since then, there have been a few reports (2-7) in which this problem has been investigated clinically or experimentally. However, some controversial and obscure points remain unsolved, especially the underlying mechanism of the long R-R interval, which has never been well clarified, although there are several interpretations. It is usually attributed to the pattern of atrio-ventricular (A-V) conduction itself. It is frequently believed that the refractory period of the A-V nodal fiber governs the pattern of rhythm in the ventricular response. As the excitations evoked within the intra-atrial musculature are high in frequency, though irregular in rhythm, the atrial excitation enters the A-V node as
soon as the A-V nodal fiber recovers from its refractory period (5). Consequently, the interval between the effective ventricular responses evoked by such irregular intra-atrial excitatory waves, becomes equal to, or very close to, the interval of the refractory period of the A-V nodal fiber. If these speculations are true, it would be rather difficult to explain why the long interval between the ventricular responses often occurs in absolute ventricular arrhythmia.

Recently, more precise but rather perplexing explanations (5-7) have been postulated for the origin of absolute ventricular arrhythmia. Moe and Abildskov (5) proposed that the occurrence of the long interval between ventricular responses can be explained by assuming that the mechanism of "concealed conduction" is within the A-V node, and that the probable occurrence of a long cycle is a function of the duration of the "concealment zone" and of the atrial input frequency.

Moore (7) recently investigated the pattern of atrio-ventricular conduction, analyzing records of the transmembrane action potential obtained from a single myocardial cell within the A-V node. He used the more refined methods of microelectrode technique and reached the same conclusions proposed by Moe and Abildskov (5).

In the present report, the underlying mechanism of the occurrence of absolute ventricular arrhythmia was investigated. This was done by analyzing patterns of the transmembrane action potential recorded from a single cell within the A-V node or its vicinity, using microelectrode techniques and two contiguous bipolar-lead electrograms simultaneously recorded from the vicinity of the sino-atrial node and from the endocardial surface of the right ventricular septum.

**Method**

Thirty adult rabbits weighing 2.0 to 2.5 kg were used in the experiments. Anesthesia was achieved in each animal with 5% pentobarbital sodium (Nembutal) in intravenous doses of 1 ml/kg of body weight. A left thoracotomy was then performed. Heparin solution containing 2,000 to 3,000 units was injected into the left atrium or into the pulmonary vein to prevent coronary artery embolization. The entire heart was excised. The isolated heart was constantly perfused through the aorta with fully-oxygenated Tyrode's solution at 30°C using the Langendorff technique. After insertion of a polyethylene cannula into the aorta, the specimen was fastened to the shaft of a supporting frame. Then the entire right ventricular septal surface and the right atrial septal surface were exposed for investigation.

A pair of electrodes for artificial electrical driving was placed in the vicinity of the sino-atrial node (S-A node). Two pairs of electrodes were used for contiguous bipolar leads. One pair was placed several millimeters from the site of the stimulating electrode and was used for registering electrical activity of the right atrium (A region). The other pair was placed in the apical region on the right ventricular septal surface (V region). A fine glass capillary microelectrode filled with 3 M KCl was used for registering the change of the intracellular potential of the myocardial cell within the A-V node and its vicinity. The stimulating electrodes were made of fine silver wire 100 μ in diameter. The interpolar distance was adjusted so that the electrodes were 1 mm apart. Similar electrodes were used for the two bipolar contiguous leads.

Artificial electrical driving consisted of square-wave pulses of 0.3 to 0.5 mA and of 5-msec duration.

![Diagram of the heart showing the placement of electrodes and microelectrode.](http://circres.ahajournals.org/doi/fig/10.1161/01.CIR.22.5.708)

**FIGURE 1**

Right atrioventricular specimen of isolated rabbit heart perfused by Langendorff's technique. CS = orifice of the coronary sinus. VCI = inferior vena cava. VCS = superior vena cava.
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The tip of the glass capillary microelectrode was less than 0.5 \( \mu \). The electrical resistance ranged from 10 to 30 megohms. The tip of the microelectrode was mounted on flexible tungsten wire to prevent undue dislodging of the tip from the cell due to movement of the heart.

The location for the penetration of the microelectrode into a myocardial cell within the A-V node, or in the vicinity of the A-V node, was determined by noting the appearance of a characteristic configuration of the transmembrane action potential recorded from that site. In addition, the arrival time of excitation from the site of the applied stimulus to the onset of a sharp upstroke of the transmembrane action potential was analyzed.

First, the site of the A-V node was determined by the above procedure. This was designated the N region. Secondly, a site 1 mm distant toward the orifice of the coronary sinus was defined as the AN region (the transitional region between the right atrium and the A-V node). Thirdly, a site 1 mm distant toward the pars membranacea of the ventricular septum was designated as the NH region (the transitional region between the bundle of His and the A-V node). Paes de Carvalho and de Almeida (8) used these same designations (Fig. 1).

Atrial fibrillation was induced by electrical stimulation at a frequency of 600/min and by the continuous dripping of 0.1% acetylcholine solution at a speed of 10 drops/min onto the right atrial endocardial surface. Special care was taken that the acetylcholine solution did not overflow or leak onto the A-V node or its vicinity or onto the ventricular surface.

In atrial fibrillation it was difficult to find any time-correlation between the deflection of the right atrial electrogram and the A-V nodal response displayed by the transmembrane action potential. Therefore, to check the pattern of the stimulus conduction at the vicinity of the A-V node, similar experiments were carried out using only electrical stimulation of high frequency without using acetylcholine. In these latter experiments, all tracings were continuously registered while the frequency of artificial electrical driving

**FIGURE 2**

Records obtained from the A, AN, and V regions during the combined application of acetylcholine and electrical stimulation. (See text for details.) A = right atrial electrogram. AN = transmembrane action potential from a single cell within the AN region. V = right ventricular electrocardiogram.
Records obtained from the A, N, and V regions during the combined application of acetylcholine and electrical stimulation. (See text for details.)

**FIGURE 4**
Summarized analytical diagrams of Figures 2 and 3, during the combined application of 0.1% acetylcholine and electrical stimulation of 600/min. Ordinate: the ratio, in percentage, of the frequencies of excitation evoked in the A, AN, and N regions, to the number of electrical stimulations applied to the S-A nodal area. Abscissa: Locations of each recording site.
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rate/Min

Elect. Stim. 170

A 170

AN 170

V 170

Elect. Stim. 260

A 260

AN 260

V 180

Elect. Stim. 353

A 340

AN 240

V 200

FIGURE 5

Transmembrane action potential recorded from a single cell within the AN region to which only electrical stimulation was applied, and two contiguous bipolar-lead electrograms simultaneously recorded from the A and V regions. (See text for details.)

waves as the frequency of electrical stimulation reaches 600/min.

The conduction block occurs between the A and AN regions, and between the AN and V regions as the frequency of electrical stimulation reaches 286 to 428/min (center strip) and 600/min (lower strip). This block resulted in a pattern of ventricular arrhythmia, i.e., absolute arrhythmia. It is important to note that the long pause of ventricular arrhythmia, the long R-R interval, does not appear in the tracing of the transmembrane action potential recorded from the AN region (center and lower strips).

Figure 3 illustrates the transmembrane action potential recorded from the N region and two contiguous bipolar-lead electrograms from the A and V regions. In the lower strip, the conduction block is seen to be present between the A and N regions. It is of interest to note that the long R-R interval, absolute arrhythmia, appears in the transmembrane action potential recorded from the AN region (center and lower strips).

Figure 6

Analytical diagram of the center strip of tracings in Figure 5.
Records of the transmembrane action potential obtained from a single cell within the N region and of the two contiguous bipolar-lead electrograms recorded simultaneously from the A and V regions.

The experimental results observed in Figures 2 and 3 are summarized in Figure 4. The abscissas indicate the location of each recording site. As fibrillation occurred (A Fibril. in Figs. 2 and 3), the frequency of excitation evoked in the right atrium (A region) exceeded the frequency of artificial driving by 20%. The frequency of excitation evoked in the AN region decreased to 45%. Further, the frequency of excitation evoked in the N region decreased to 25%. The frequency of excitation evoked in the V region was almost the same as that evoked in the N region. It may therefore be presumed that the conduction disturbance occurred in the right atrium and in the anterior half of the A-V node, i.e., between the A and the AN regions. It may also be reasonably considered that the anterior...
half of the A-V node plays an important role in the occurrence of absolute arrhythmia and especially in the long R-R interval.

In atrial fibrillation, it seems difficult to find a time correlation between the deflection of the right atrial electrogram and the A-V nodal response as displayed by the transmembrane action potential. Therefore, to clarify further the mechanism of the occurrence of the long R-R interval, the pattern of the atrio-ventricular conduction was investigated by applying only electrical stimulation at high frequency.

The conduction times from the site of stimuli applied to the AN and V regions gradually lengthened as the frequency of the applied stimuli was gradually increased from 120/min to 260/min (Fig. 5). In the lower strips, conduction block was observed between the A and AN regions. In the middle strips, there was delayed conduction but no block between the A and AN regions.

Figure 6 is an analytical diagram of the middle row of records in Figure 5, and shows that the pattern of the conduction block in Wenckebach phenomenon began to occur between the AN and V regions as the frequency of electrical stimulation reached 260/min. Additional block occurred between the A and AN regions as the frequency reached 353/min. At this stage, there was ventricular arrhythmia. The long interval between ventricular excita-
Conduction block occurs between the A and N regions at a frequency of 230 to 414/min (Fig. 7, center and lower strips). All excitations reaching the N region were conducted to the V region even at a high frequency of electrical stimulation (414/min) applied to the S-A nodal area (lower strip). The frequency of excitation reaching the N region is 160/min, thus resulting in an irregular long cycle. In Figure 8, the conduction time between the site of electrical stimulation and the N region was markedly prolonged as the frequency of electrical stimulation was gradually increased. The conduction block pattern in Wenckebach phenomenon occurred between the A and N regions at a frequency of 230/min. However, all of the excitations evoked at the N region were conducted to the V region without the appearance of block and as the frequency of electrical stimulation reached 414/min. The frequency of excitation evoked at the N region was 160/min, resulting in irregular excitation. It is important to note that the long interval occurred in the record obtained from the N region, as it did in the previously mentioned case of atrial fibrillation.

Conduction block occurs between the A and NH regions at a frequency of 280 to 360/min (Fig. 9, center and lower strips). All excitations reaching the NH region were conducted to the V region without the appearance of block.

From the experimental results seen in Figures 5 to 9, it can be reasonably assumed that the conduction delay may occur mainly between the A and N regions.

The main location where conduction block can easily occur within the A-V nodal region or its vicinity is shown in the summarized diagram of Figure 10. During electrical stimulation at a frequency of 231 to 286/min (upper diagram), the conduction block is observed between the AN and N regions. As shown in the lower diagram, as the frequency reaches 343 to 353/min, conduction block occurs between the A and AN regions and also between the AN and N regions.

These findings are the same as those observed in atrial fibrillation induced by the combined application of acetylcholine and electrical stimulation.

**Discussion**

It is well known that the absolute irregular rhythm of ventricular excitation occurs in atrial fibrillation. There are several reports explaining its underlying mechanism, but it remains obscure.

Hoffman and Cranefield (9), using the microelectrode technique, reported that conduction delay within the A-V node takes place between nonspecialized atrial fibers and the atrio-ventricular nodal fibers. However, they did not investigate this in relation to atrial fibrillation.

Recently, Moore (7) reported experimental results in which the concealed conduction of impulse occurs within the A-V node in atrial fibrillation. He proposed that this conduction is a genetic factor in the occurrence of ventricular arrhythmia. However, in his report, there are no definite statements concerning which part of the A-V node plays the most
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important role in its occurrence, and as to the A-V nodal conduction delay which could definitely occur when atrial response becomes rapid, as in atrial fibrillation.

The experimental results reported here may validly clarify and explain this mechanism. In the present experiments, transmembrane action potentials were recorded from single myocardial cells in several different sites within the A-V node itself and within its vicinity. It was observed that conduction block occurs in the right atrium and in the area between the AN and N regions. Conduction block in the latter area can be considered to contribute greatly to the formation of a long R-R interval of ventricular response in atrial fibrillation (Fig. 4).

To further investigate the underlying mechanism, similar experiments were performed in which only electrical stimulation at high frequency was utilized. It was observed that conduction block between atria and ventricles also occurs in the right atrium and in the area between the AN and N regions, as the frequency of the given stimulus is increased over 231/min (Fig. 10).

In the progressive change up to the appearance of conduction block as the frequency of the given electrical stimulation is gradually increased, the conduction time of the stimulus from atria to ventricles is prolonged. Its prolongation occurs in the area between the AN and N regions. Also of interest is the finding that conduction block in Wenckebach rhythm occurs in the early stage of development of the block.

From these experimental results, it can be assumed that conduction block in Wenckebach rhythm takes place within the A-V node. The conduction block occurring at the anterior half of the A-V node can be considered to play the most important role in producing ventricular dysrhythmia in atrial fibrillation. The genesis of ventricular dysrhythmia associated with atrial fibrillation is better explained when concealed conduction is considered as an additional factor.

It is well known that the physiological function of the A-V node may be considerably compromised when the coronary circulation is disturbed. In Moore's experiments (7), the entire atrioventricular specimen was isolated and then immersed in a bath of perfusate of Tyrode's solution. The specimen thus prepared may present some difficulties in that the coronary circulation may be compromised to some extent. However, the specimens used in the present experiments were perfused through the aorta by Langendorff's technique, and a better oxygen supply to the A-V nodal region was therefore maintained. As a result, we believe there was a less disturbed coronary circulation.

References

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