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Abstract

[Background] Brugada syndrome is characterized by a J-point (terminal portion of the QRS) elevation on the electrocardiogram (ECG). The electrophysiological mechanism of the ECG morphology is understood based on the physiological conditions and is contributed by vagal stimulation (VS). However, the change in the ordinary ECG morphology due to VS has not been reported. Therefore, we experimentally investigated the effect of the VS. [Methods and Results] In 14 canines, right cervical VS (electrical stimulation) was performed during a standard 12-lead ECG recording. In 6 canines, the J-point amplitude increased in the right precordial leads. In these canines, the RR interval tended to lengthen with the strength of the VS, and the amplitude of the J-point also tended to increase with the strength of the VS, but the QRS interval was unchanged. [Conclusion] VS induced the J-point elevation in the right precordial leads. The electrophysiological mechanism was believed to be an accentuation of the availability of the Ito current due to prolongation of the RR interval and modulation of the current balance in the early phase of the action potential due to the direct effect of the VS.

Key Words
Brugada syndrome, Electrocardiogram, J-point, Vagal stimulation

Background

Transient J-point (terminal portion of the QRS) elevation on the electrocardiogram (ECG) is well-known to represent acute ischemia of the myocardium. It is caused by acute epicardial myocardial damage due to various origins, i.e. coronary arterial disturbance, pericarditis, myocarditis, etc. Recently, severe heart disease with transient J-point modulation, i.e. Takotsubo cardiomyopathy and Brugada syndrome, has been recognized in the clinical setting. The investigation of the electrophysiological mechanism of the J-point modulation remains unclear, but the response to catecholamines and autonomic nervous stimulation is suspected as being one of the origins.

J-point elevation with a right bundle branch block type ECG morphology in the right precordial leads is a characteristic of Brugada syndrome which causes sudden cardiac death in patients without obvious heart disease. This ECG change is generally believed to be caused by the electrical heterogeneity of the action potentials (AP) of the right ventricle, based on the difference in the density of the transient outward current (Ito) between the epicardial and endocardial myocardium. Therefore, the J-point elevation is considered to be related to the occurrence of the ventricular arrhythmias. This J-point elevation is augmented by vagal stimulation (VS), but suppressed by sympathetic stimulation. A prominence of an Ito density in the epicardium, but not in the endocardium of the right ventricle is
a basic characteristic in humans, canines, etc. However, the influence of the VS on the ECG morphology has never been presented. In this study, the effect of the VS on the ECG morphology was experimentally investigated.

**Materials and Methods**

**Materials**

Fourteen canines anesthetized with pentobarbital (30 to 35 mg/kg intravenous injection), weighing 9 to 12 kg (average 10 kg), were used in this study. They were maintained on positive pressure respiration, and while in the supine position, the standard 12-lead ECG was recorded using an EPLab recording system (Quinton Electrophysiology Co., Canada). Bent 18 gauge needles were inserted into the subcutaneous tissue on the chest and limbs of the canines for recording the body surface ECG.

The experiment was carried out according to the Guidelines for Animal Experimentation, Institute of Experimental Animals, St. Marianna University Graduate School of Medicine.

**Vagal stimulation**

Electrical VS was directly delivered to the right cervical vagal nerve. An original bipolar electrode (2 mm interval) was directly attached to the right vagal nerve. Thirty minutes after attaching the electrode, VS was performed. Three different strengths of the stimulation were used; 3.3 Hz–5 V, 5.0 Hz–5 V, and 10.0 Hz–5 V for 20 seconds. Each application was performed after the recovery of the RR interval, which increased due to the preceding VS. A BC-03 Cardiac Stimulator (FUKUDA DENSHI CO., LTD., Tokyo, Japan) was used for the stimulation.

**Measurements and Statistical Analysis**

The RR interval, QRS interval and amplitude of the J-point were measured and the average value of 3 stable beats was obtained. ECGs were recorded using a recording speed of 50 mm/s and amplitude of 1.0 mV/10 mm. The J-point was defined as the terminal portion of the QRS (Fig 1.). The isoelectric line of the ECG was used as the baseline for the amplitude measurements.

The measurements were presented as the mean value±standard deviation. Statistical analysis was performed by using the Student's t-test. A value of p <0.05 was considered statistically significant.

**Results**

During the VS, the RR interval lengthened, but the QRS morphology did not change. The J-point amplitude increased (>0.1 mV) in 6 canines and was accompany by an increase in the T-wave amplitude. The 8 remaining canines did not exhibit J-point or T-wave elevation. An actual case with J-point elevation is shown in Fig 2. This canine exhibited significant J-point elevation (arrow in the Fig 2.), and this ECG change was especially observed in the right precordial leads Fig 3. represents another actual case. J-point elevation (solid arrow in the Fig 3.) and significant T-wave elevation (dotted arrow in the Fig 3.) were also exhibited during VS.

**RR interval change due to vagal stimulation**

Before the VS, the mean RR interval obtained was 356.5±53.2 ms. The RR interval increased during the VS (3.3 Hz–5 V, 5.0 Hz–5V, and 10.0 Hz–5 V), and was 505.0±120.5 ms, 537.2±126.5 ms, and 679.5±202.6 ms, for the respective VSs (p<0.01, respectively).

**QRS interval change due to vagal stimulation**

Before the VS, the mean QRS interval obtained was 75.3±9.9 ms. For each VS strength, 3.3 Hz–5 V, 5.0 Hz–5 V, and 10.0 Hz–5 V, the QRS interval observed was 78.8±10.7 ms, 77.7±9.7 ms, and 81.2±9.1 ms, respectively.

**J-Point amplitude during vagal stimulation**

The relationship between the actual J-point elevation and strength of the VS is shown in Fig 4. The J-point amplitude tended to increase with augmentation of the strength of the VS. The measurements taken in the group (n=6) with an increase in the J-point amplitude are shown in Fig 5. In these canines, the RR interval tended to lengthen with the strength of the VS (p<0.01 or <0.05, respectively), and the amplitude of the J-point also tended to increase with the strength of the VS (p<0.01 or <0.05, respectively), but the QRS interval was unchanged.

An actual case without J-point elevation is shown in Fig 6. In regard to the ECG morphology, the J-point amplitude and T-wave were unchanged for every strength of the VS. The measurements obtained in this group (n=8) are shown in Fig 7. The RR interval tended to lengthen with the
Fig 1. Point of measurements on the electrocardiogram. The QRS interval and amplitude of the J-point were measured. The J-point was defined as the terminal portion of the QRS, and the isoelectric line of the electrocardiogram was used as the baseline for the amplitude measurements.

Fig 2. An actual case with J-point elevation during vagal stimulation. The J-point (arrow in the figure) amplitude increased during vagal stimulation, and this electrocardiographic change was especially observed in the right precordial leads.

Fig 3. An actual case with J-point and T-wave elevation during vagal stimulation. The J-point (solid arrow in the figure) amplitude increased during vagal stimulation, and a significant increase in the T-wave (dotted arrow in the figure) amplitude was also exhibited.
Fig 4. The actual J-point amplitude increase in V1, V2, and V3 for each strength of the vagal stimulation. The J-point amplitude tended to increase with augmentation of the strength of the vagal stimulation.

Fig 5. The RR interval, QRS interval, and J-point amplitude for each strength of the vagal stimulation in canines with an increase in the J-point amplitude. The RR interval and amplitude of the J-point tended to increase with the strength of the vagal stimulation (*p<0.01, **p<0.05), but the QRS interval was unchanged.
strength of the VS, but the QRS interval and amplitude of the J-point were unchanged.

**Discussion**

In our present study, it was demonstrated that VS affected the repolarization phase on the ECG. The modulation of the ECG morphology during the VS resulted in the J-point elevation and T wave elevation. These responses appeared especially in the right precordial leads. However, the changes in the QRS interval and QRS morphology were not accompanied by the aforementioned ECG morphology changes. Therefore, the J-point and T wave changes are considered to be caused by a repolarization abnormality and not a depolarization abnormality.
Recently, the J-point elevation and T-wave changes in the right precordial leads of the 12 lead ECG have been discussed as an electrophysiological mechanism of Brugada syndrome in which the J-point elevation is especially exhibited in the right precordial leads. Antzelevitch et al.9 experimentally discussed the electrophysiological mechanism of Brugada syndrome. They proposed that the mechanism of Brugada syndrome was as follows; (1) The J-point corresponded to phase 1 of the AP of the right ventricle; (2) The morphology of the AP in the epicardium was different from that in the endocardium; (3) The main characteristic of the AP was that it exhibited a deep notch during phase 1 of the epicardium, but not the endocardium. In the epicardium, the morphology had a notch (phase 1) and dome (phase 2–3) shape; (4) That difference originated from the physiological difference in the $I_{Na}$ density (epicardium > endocardium); (5) The amplitude of the J-point in the right precordial leads modulated due to the difference in the phase 1 potential between the AP of the epicardium and that of the endocardium; (6) The amplitude of the early phase, including phase 1, of the AP was mainly regulated due to the inward Na current, inward Ca current, and $I_{Na}$ current; (7) A greater outward current than inward current lead to a gradient of the early phase of the AP, resulting also in J-point elevation on the ECG; (8) A slight increase in the outward current lead to an accentuation of the notch and slow rise of phase 2 in the epicardium, therefore the gradient between the epicardium and endocardium caused an elevation of the J-point, ST-segment, and T wave on the ECG. This morphology is called the saddle-back type ST-elevation; (9) More accentuation of the outward current lead to a greater notch (decrease in the amplitude). Such a current balance occurred with an all or non phenomenon of phase 2, resulting in a diminished AP duration in the epicardium due to the disappearance of the dome. With this current balance, a prominent J-point and negative deflection of the T wave, which is called the coved-type ST-segment elevation, was observed; (10) Based on such a gradient of the AP, reentrant ventricular arrhythmias occurred.

The J-point elevation in our present study was explainable by using the theory of the difference in the amplitude of the APs between the epicardium and endocardium of the right ventricle. The accentuation of the outward current or diminishing of the inward current during the early phase of the AP possibly lead to the J-point elevation. The possible ion channels which modulate the current balance during the early phase of the AP are mainly the $I_{Na}$ current, Na current, and Ca current.

The $I_{Na}$ current was associated with the AP duration and formation of the notch in phase 1 of the AP. The activation and inactivation of the $I_{Na}$ was a relatively rapid voltage dependent process. The activation thresholds ranged from $-40 \text{ mV}$ to $0 \text{ mV}$. A noticeable characteristic was that the recovery from the inactivation was very slow, therefore it caused a frequency dependent modulation of the AP morphology. Namely, the $I_{Na}$ current became more increased with bradycardia.

In our present study, the J-point elevated along with a prolongation of the RR interval. The frequency dependent modulation of the $I_{Na}$ current was believed to be supported by our data (the elevation of the J-point, ST-segment, and T wave). Namely, the bradycardia due to VS was believed to accentuate the $I_{Na}$ current, resulting in the accentuation of the amplitude difference of the early phase of the APs between the epicardium and endocardium.

In the clinical situation with Brugada syndrome, an increase in the vagal tone was possibly associated with the ST-segment elevation and occurrence of ventricular arrhythmias, however, in that description, bradycardia or RR interval prolongation was not detected as a contributing factor to the J-point elevation and ventricular fibrillation occurrence. In contrast, Fujiki et al.10 suggested that the prolongation of the RR interval contributed to the J-point elevation in Brugada syndrome with atrial fibrillation. Further, improvement in the RR interval prolongation using cardiac pacing had an effect on the treatment of ventricular fibrillation in Brugada syndrome10. Consequently, we concluded that the prolongation of the RR interval due to VS was one of the contributing factors in the J-point elevation in the present study.

Litovsky and Antzelevitch12 demonstrated a direct effect of acetylcholine (Ach) on the ventricular myocardium. As another cause for the modulation of the current balance during the early phase of the AP, the direct effect of the VS possibly contributed to the J-point elevation. The chemical transmitter of the VS, Ach, elicited a different response between the epicardium and endocardium. Namely, it had little effect on the endocardium, but had an effect on the epicardium in which it prolonged the AP with
low concentrations and abbreviated the AP with high concentrations of Ach. The prolongation of the AP in the epicardium was caused by slowing of the 2nd upstroke and delayed achievement of peak dome. In the J-point and early phase of the AP, the difference in the amplitude between the epicardium and endocardium became accentuated, resulting in elevation of the J-point, ST-segment, and T wave in the ECG. The abbreviation of the AP at high concentrations of Ach was caused by the disappearance of the dome, due to the all or non repolarization, resulting in the J-point elevation.

The mechanism of the different effects observed with Ach was the inhibition of the Ca current. Ach has no direct effect on the $I_{to}$ channels. The difference in the Ca current between the epicardium and endocardium was also demonstrated to be due to the different response of the Ca channel blockade. The Ca channel blockade caused a greater response in the epicardium than in the endocardium. The Ca current blockade caused a diminishing of the inward current during the early phase of the AP, and was possibly responsible for the J-point elevation in the ECG. The different effects of the Ca channel blockade between the epicardium and endocardium was demonstrated in this experiment, however, in the clinical situation the Ca channel blockade inducing the J-point elevation has never been previously described.

The Na channels have also been considered to be one of the main inward currents during the early phase of the AP. The Na channel blockade inducing J-point elevation was used as an examination method to diagnose Brugada syndrome. Because the Ca channels are also one of the main inward currents during the early phase of the AP, the Ca channel blockade also possibly contributed to the J-point elevation. Although the degeneration of the ECG morphology and occurrence of arrhythmias due to the clinical administration of a Ca channel blocker were not observed, it may be a theoretical degenerative factor.

Consequently, two mechanisms can be proposed for the electrophysiological mechanism of the J-point elevation during VS; the accentuation of the $I_{to}$ current availability caused by a prolongation of the RR interval and the diminishing of the inward current caused by the direct effect of the VS.

Conclusion

VS caused the J-point, ST-segment, and T wave elevation to appear in the right precordial leads. The electrophysiological mechanism of the ECG morphology change was believed to be caused by the direct VS effect and prolongation of the RR interval.

Limitations

Two electrophysiological mechanisms were proposed for the ECG morphology change due to the VS. The discrimination of which mechanism was more related to the change remained unclear. In order to perform that discrimination, an experiment under a fixed heart rate is needed.

The presence or absence of depolarization was determined by the QRS morphology and QRS interval. However, Litovsky and Antzelevitch demonstrated a direct effect of Ach on the ventricles. The measurement of the standard 12-lead ECG may be insufficient for determining whether there is a conduction disturbance.

The observation of the individual data, distribution of the grade of the J-point elevation, and the relation between the grade of the RR interval and that of the J-point elevation, are believed to be caused by the existence of another contributing factor of the J-point elevation. With the aforementioned mechanisms, the most significant factor for the modulation of the amplitude of the J-point was the magnitude of the notch in the epicardium which was associated with the $I_{to}$ density. Although individual differences in the $I_{to}$ density are related to the individual differences in the notch, the individual differences in the $I_{to}$ density should be recognized.

The Na channel blockade administration is an accepted method for unmasking latent substrates of Brugada syndrome. Because the mechanism of this test represents a diminishing inward current during the early phase of the AP that unmasks the J-point and ST-segment elevation, the grade of the $I_{to}$ density can be estimated. If this test had been performed in our subjects in this study, the grade of the contribution of the $I_{to}$ may have been recognized.

References


迷走神経刺激による右側胸部誘導心電図の J 点上昇

抄録

Brugada 症候群は右側胸部誘導心電図の J 点上昇が特徴であり、その機序は生理的に存在する電気生理学的基盤で説明されている。その特徴の一つとして、迷走神経刺激で増幅される性質があるが、迷走神経刺激による心電図波形の変化は一般的に知られていない。そこで、14頭の雑種成犬の右側頚部迷走神経を電気的に刺激した際の心電図変化を記録し、迷走神経刺激の影響を実験的に検討した。その結果、6頭で右側胸部誘導の J 点上昇を認めた。これらの RR 間隔は迷走神経刺激の強度により延長する傾向にあり、J 点も迷走神経刺激の強度により上昇する傾向にあった。しかし、QRS 間隔の変化はなかった。右側迷走神経刺激は右側胸部誘導心電図の J 点上昇を誘発したが、その機序として、迷走神経刺激による徐脈によって Ia 電流が増加したこと、および心筋への直接的な効果として、活動電位早期の内向き電流の減少によって外向き電流 > 内向き電流のバランスになったこと、が考えられた。