Pharmacological and Electrophysiological Characterization of Junctional Rhythm During Radiofrequency Catheter Ablation of the Atrioventricular Node
— Possible Involvement of Neurotransmitters From Autonomic Nervous System —

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Catheter ablation of the atrioventricular node (AVN) with radiofrequency current is closely associated with the short-term onset of a junctional rhythm. The origin of this rhythm was analyzed in Beagle dogs which were anesthetized with pentobarbital sodium. Atrioventricular (AV) conduction block was induced first using a standard catheter ablation technique for the AVN, so that the sinus automaticity could not override the junctional ectopy during the following energy delivery. The ablation catheter was kept in the initial position and the delivery of radiofrequency energy was repeated. The pattern of ECG changes suggests that the dominant pacemaker may shift from the distal portion of the AV junctional area to the proximal portion during the energy delivery. This enhanced junctional automaticity was suppressed by the $\beta$-blocker esmolol, but was not affected by $\M$-antagonist atropine. Moreover, the $\M$-agonist isoproterenol did not induce the same type of junctional tachycardia, but the pacemaker shift was induced by the increased sympathetic tone after transient asystole by ventricular overdrive pacing or acetylcholine administration. These results suggest that proximal portion of the AV junctional area has extremely slow pacemaker activity, but responds to locally released norepinephrine with an abrupt rise and fall in rate, resulting in a typical pattern of junctional tachycardia during the ablation of the AVN. (Circ J 2002; 66: 696–701)

Key Words: Atrioventricular block; Catheter ablation; Junctional rhythm; Neurotransmitters; Pacemaker shift

Methods

All experiments were carried out according to the Guidelines for Animal Experiments of Yamanashi Medical University. Beagle dogs of either sex weighing approximately 10 kg were obtained through the Animal Laboratory for Research of Yamanashi Medical University. The dogs were anesthetized with pentobarbital sodium (30 mg/kg, iv) and artificially ventilated with room air (Shinano, SN-480-3, Tokyo, Japan). Tidal volume and respiratory rate were set at 20 ml/kg and 15 strokes/min, respectively. Heparin calcium (200 UI/kg, iv) was administered to prevent blood clotting. The surface lead II ECG and systemic blood pressure at the right femoral artery were continuously monitored using a polygraph system (Nihon-Kohden, RM-6000, Tokyo, Japan).

Production of Complete AV Block With a RF-CA Technique

A quad-polar electrodes catheter with a large tip of 4 mm (Cordis-Webster, D7-DL-252, CA, USA) was inserted...
through the right femoral vein using the standard percutaneous technique and positioned across the tricuspid valve under the guide of bipolar electrograms from the distal electrode pair. The optimal site for ablation, namely the compact AVN, was determined on the basis of the intracardiac electrogram, of which a very small His deflection was recorded and atrium/ventricular voltage ratio was >2 (Fig 1A). The site was usually found 1–2 cm proximal to the position where the largest His bundle electrogram was recorded. The power source for the AVN ablation was an electrosurgical generator (Mera, MS-1500, Tokyo, Japan), which delivers continuous unmodulated RF energy at a frequency of 500 kHz. After adequate localization, RF energy of 20 W was delivered for 10 s from the tip electrode to an indifferent patch electrode positioned on the animal’s back, and was continued for a further 30 s if junctional ectopic complexes were induced. After each application, the PR interval was measured to determine whether AVN conduction had been affected. The end-point of the procedure was complete AV block with the onset of a stable idioventricular escaped rhythm (VR) (Fig 1B). Our previous experience with this procedure indicates that energy application to this area hardly affects slow pathway conduction, if it is present, of the canine heart.

Experimental Protocol

After an apparently successful ablation of the AVN, each animal was stabilized for at least 10 min before starting the subsequent experiments. Because it was difficult to find the ablation site after the onset of AV block, the catheter was kept in position. Sinus automaticity cannot override the junctional ectopy in this model and so the JR was defined as the occurrence of premature beats without a P wave, in which the QRS complex structure and axis were identical to those seen during sinus rhythm. Three consecutive recordings of the shortest cycle lengths of JR were measured during the energy application to estimate the peak response (peak JR).

Effects of Esmolol and Esmolol Plus Atropine on the Responses of the Automaticities (Experiment 1) The RF energy was delivered for 10 s at control, and its effects on JR and VR were assessed in a drug-treated group (n=6). Five minutes after the initial energy delivery, 0.1 mg/kg of esmolol was intravenously administered and because cardiac β-adrenoceptors are maximally inhibited 3–12 min later and its elimination half-life is 10 min the effects of RF energy on JR and VR were assessed 3 min after drug administration. Five minutes after the second delivery of energy, an additional 1.0 mg/kg of esmolol was administered intravenously and the effects of RF energy were assessed in the same manner 3 min later. Five minutes after the third delivery of energy, 0.1 mg/kg of atropine was intravenously administered to the same animal and again the effects of RF energy on JR and VR were assessed in 3 min later. Reproducibility of the responses of JR and VR to RF energy application was also assessed. The 10 s delivery of RF energy was repeated 4 times with intervals of 8 min in a control group animals (n=6), and its effects on JR and VR were assessed.

Effects of Atropine on the Responses of the Automaticities (Experiment 2) Atropine at a dose of 0.1 mg/kg was intravenously administered to another series of animals with AV block (n=6), and the effects of RF energy on JR and VR were assessed 3 min after drug administration.

Effects of Overdrive Ventricular Pacing on the Automaticities (Experiment 3) This protocol was carried out using the control group animals (n=6). Having assessed the reproducibility of the effect of RF energy in Experiment 1, the electrode catheter was moved to the right ventricle and the heart was electrically driven at a cycle length of 400 ms for 30 s by a cardiac stimulator (SEC-3102; Nihon-Kohden). The stimulation pulses were rectangular in shape and 1–2 V in amplitude (approx twice the threshold voltage) with 1 ms duration. The effects of the overdrive pacing on JR and VR were assessed.

Effects of Intravenous Administration of Acetycholine (ACh) on the Automaticities (Experiment 4) This protocol was also carried out using the control group animals (n=6). After the response to ventricular pacing in Experiment 3 disappeared, 1 μg/kg of ACh was intravenously administered to assess its effects on JR and VR.

Effects of Isoproterenol on the Sinus, Junctional and Idioventricular Automaticities and β-Blocking Action of Esmolol (Experiment 5) This protocol was also carried out using the control group animals (n=6). After the response to ACh in Experiment 4 disappeared, 1 μg/kg of isoproterenol was intravenously administered to assess the effects of systemic β-adrenoceptor stimulation on the sinus automaticity rate (SR), JR and VR. After the response to isoproterenol disappeared, 0.1 mg/kg of esmolol was intravenously administered and 3 min later, 1 μg/kg of isoproterenol was administered to assess the extent of β-blocking action of the low dose of esmolol. Next, an additional dose of 1.0 mg/kg of esmolol was intravenously administered and another 1 μg/kg of isoproterenol was administered in the same manner.

Drugs

The following drugs were used: esmolol hydrochloride (Ono, Osaka, Japan), l-isoproterenol hydrochloride (Nikken, Tokyo, Japan), acetylcholine chloride (Dai-ichi, Tokyo, Japan), atropine sulfate (Tanabe, Osaka, Japan), pentobarbital sodium (Tokyo-Kasei, Tokyo, Japan) and heparin calcium (Mitsui, Tokyo, Japan). Esmolol was dissolved in 0.9% saline, giving concentrations of 1 and 10 mg/ml.
Data are presented as the mean ± SE. The statistical comparisons of mean values within a group were evaluated by one-way repeated-measures ANOVA followed by Contrasts, or assessed by paired t-test, and those between the groups were examined by unpaired t-test. A p value less than 0.05 was considered significant.

Statistics

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Results

Production of AV Block

Ablation of the AVN was performed in 19 dogs and the occurrence of JR during ablation served as an excellent index of success. Radiofrequency ablation was successful in eliminating AV conduction in 18 animals, and in 1 dog ventricular fibrillation was induced during the initial energy application for unknown reasons. The number of radiofrequency applications was 4±1 (range, 1–10). Typical tracings of arterial pressure and ECG before and after the ablation procedure are shown in Fig 1. The junctional tachycardia was observed in all animals during the ablation procedure. Stable idioventricular escaped rhythm always developed within 1 min of the onset of AV conduction block. This automaticity is considered to originate from the distal part of the AV junctional area, most likely a fascicular rhythm because of the relatively 'narrow' QRS width with a right-bundle branch block pattern.1 When the experimental protocol was over, the hearts were excised from 6 dogs of the control group to confirm exactly the ablation. Histological examination indicated that the RF energy had been delivered over, or close to, the compact AVN (data not shown).

Effects of Autonomic Blockade on Peak JR

(Experiments 1 and 2)

Experiment 1 A pacemaker shift from VR to JR was observed during the delivery of RF energy in all animals. Typical tracings of ECG and arterial blood pressure are depicted in Fig 2 and the effects of esmolol and atropine on JR and VR are summarized in Fig 3. JR occurred during the energy application with a steep rising phase and was terminated quickly. The peak rate in JR (beats/min) during the RF application before drug administration was 126±16 in the drug-treated group (n=6) and 130±12 in the control group (n=6) (NS). In the control group, the RF energy was delivered 4 times, but no significant change was detected in the peak response of JR, supporting the reproducibility of this phenomenon (Fig 3). In the drug-treated group, the peak JR decreased in a dose-related manner after the administration of esmolol and this effect was not attenuated by atropine.

Experiment 2 In another series of animals with AV block (n=6), we assessed the effects of atropine alone on the RF energy-induced peak response in JR in the absence of β-blockade (data not shown). The peak JR before and after the administration of atropine was 127±12 and 120±15, respectively (NS), indicating a lack of suppression of locally released ACh on the JR.

Effects of Autonomic Blockade on VR

(Experiments 1 and 2)

Experiment 1 Transient asystole was observed following the junctional tachycardia in all animals. Typical tracings of arterial pressure showing the transient asystole following tachycardia are depicted in Fig 2A and the effects of esmolol and atropine on the VR are summarized in Fig 3. Before drug administration, the VR (beats/min) before the RF energy delivery was 49±4 in the drug-treated group (n=6) and 48±5 in the control group (n=6) (NS). The recovery time of VR (VR-RT) after the cessation of JR was 2.4±0.3 in the drug-treated group (n=6) and 3.2±1.2 in the control group (n=6) (NS). In the control group, the RF energy was delivered 4 times, but no significant change was detected in VR or VR-RT, supporting the reproducibility of this phenomenon. In the drug-treated group, no significant change was detected in the VR and VR-RT after the administration of the lower dose of esmolol. However, after the additional administration of the higher dose of esmolol, the VR decreased and VR-RT was significantly prolonged.
After the additional administration of atropine, no significant change was observed in the VR, but the VR-RT was significantly shortened to the basal control level, indicative of the suppressive effect of locally released ACh on the VR.

Experiment 2 In another series of animals with AV block (n=6), we assessed the effects of atropine on the VR and VR-RT in the absence of ß-blockade (data not shown). The VR before and after the administration of atropine was 41±2 and 38±2, respectively. No significant change was observed in these values. Meanwhile, the VR-RT before and after the administration of atropine was 3.1±0.6 and 2.1±0.1, respectively. Atropine tended to decrease the VR-RT, but this effect did not achieve a statistical significance.

Overdrive Suppression of VR (Experiment 3) The effects of ventricular overdrive pacing on VR are summarized in Fig 4A, and typical tracings of the changes in ECG and arterial blood pressure are shown in Fig 4B. The basal R-R interval was 1,487±90 ms (n=6). Although blood pressure was maintained in the physiological range during the ventricular rapid pacing, transient asystole was induced immediately after the cessation of pacing. The maximum R-R interval was 8,268±2,527 ms. Following 1–2 beats of escaped depolarization, the VR gradually recov-
ered. These transient escaped beats were observed in 3 of 6 experiments, of which the QRS complex morphology and axis were identical to those of the JR.

Effect of ACh on VR (Experiment 4) The effects of intravenous administration of ACh on VR are summarized in Fig 4C, and typical tracings of the changes in ECG and arterial blood pressure are depicted in Fig 4D. The basal R-R interval was 1,882±165 ms (n=6). After the administration of ACh, blood pressure decreased and transient asystole was induced. Atrial fibrillation was transiently induced in all animals. The maximum R-R interval was 8,942±2,575 ms. Following 10–20 beats of escaped depolarization, the VR gradually recovered; these transient escaped beats were observed in 5 of 6 experiments, of which the QRS complex morphology and axis were identical to those of the JR.

Effects of Isoproterenol on the Automaticities and ß-Blocking Action of Esmolol (Experiment 5) The effects of intravenous administration of isoproterenol (Iso) on the sinus automaticity rate (SR) and idioventricular automaticity rate (VR) before and after the esmolol administration are shown in Fig 5A, and typical tracings showing the effects of isoproterenol on VR and ECG are depicted in Fig 5B. The effects of isoproterenol on SR before and after the esmolol treatment are summarized in Fig 5C, and typical tracings showing the effects of isoproterenol on VR and ECG before the esmolol
treatment are depicted in Fig 5B. The basal SR and VR were 202±13 and 44±4 beats/min, respectively. The administration of isoproterenol increased the SR to 245±9 beats/min (peak SR) with a concomitant increment of SR (ΔSR) of +43±5 beats/min. The VR increased to 68±3 beats/min (peak VR), and a pacemaker shift was observed in 5 of 6 experiments. Because the QRS complex morphology and axis of this new automaticity were different from either the JR during the energy application or the VR before the isoproterenol administration, and the QRS width of the new rhythm was wide (Fig 5B-b), the origin of the new rhythm must have been the distal part of the conduction system.

After the administration of the lower dose of esmolol, the SR decreased, but no significant change was detected in the VR. The peak SR, ΔSR and peak VR after the administration of isoproterenol decreased compared with the respective control values. The same type of pacemaker shift of VR as observed before the esmolol administration was induced in 3 of 6 experiments. After the additional administration of the higher dose esmolol, the SR and VR decreased. The peak SR, ΔSR and peak VR all decreased after the administration of isoproterenol compared with the respective control values. The pacemaker shift of VR was induced in 3 of 6 experiments. These responses of the VR to isoproterenol were slower in onset with a longer duration compared with those of JR during the RF energy application, and gradually returned to the control level. These changes of the responses in SR and VR also provided the rationale for the doses of esmolol used in this study.

Discussion

Given the limited information regarding the mechanism of the JR during RF-CA of the AVN, we analyzed the origin of the rhythm using a canine model of complete AV block. As clearly shown by the results, RF ablation of the AVN was associated with the development of a VR that was stable during the experimental period, and this model can elicit the same automaticity response at least 4 times to repeated RF application. The junctional tachycardia occurred with a steep rising phase and was quickly terminated. Although it was difficult to discern exactly the subdivisions of the AV junctional area where the automaticities originated in the current model, the pattern of ECG changes suggests that the dominant pacemaker shifted from the distal part (VR) of the AV junctional area to the proximal part (JR) during the energy delivery. Following the cessation of the junctional tachycardia, severe bradycardia was observed. In the present study, these different foci of automaticities were characterized pharmacologically as well as electrophysiologically for the first time to explain how RF-energy application at the site of the AVN results in the pacemaker shift leading to the development of the junctional tachycardia.

Junctional tachycardia can be seen clinically during ablation of both RF AVN and slow and fast pathways for AVN reentrant tachycardia. The following hypotheses have been proposed for the mechanism of accelerated junctional automaticity.

1. The presence of a heat-sensitive area located over, or very close to, the compact AVN, which is considered to induce the accelerated junctional activity.
2. The second hypothesis is the injury current, which is conducted decrementally through the specialized tissues from the ablation site to the AV junctional area. This depolarizing current enhances the diastolic depolarization of the pacemaker cells in the junctional area.
3. The third hypothesis is the postganglionic release of norepinephrine from sympathetic nerve endings in excess of ACh release from vagal nerve endings by the RF current, which may increase AV junctional automaticity by increasing the rate of diastolic depolarization.

Of these hypotheses, the first is the least probable, because clinically it has been demonstrated that the RF energy-induced AV junctional beats usually originate not from the endocardium in contact with the ablating catheter tip, but appear to exit remotely from the anterior atrial septal region. In addition, a graded response of junctional tachycardia to various frequencies of power has not been reported, and the energy-induced automatic activity is very uncommon during the RF ablation of the ventricular tissue. Therefore, we concentrated on the latter 2 hypotheses using the information obtained from the present study.

We found that the dominant pacemaker shifted from the distal part of the AV junctional area to the proximal part during the energy delivery and this enhanced junctional automaticity was suppressed by esmolol, but was not affected by atropine. Moreover, systemic administration of isoproterenol did not induce the same type of junctional tachycardia observed during the energy application, but the pacemaker shift was induced by the reflex sympathetic excitation after transient asystole induced by overdrive ventricular pacing or ACh administration via severe hypotension. These results suggest that the basic JR may be slow, but preferentially sensitive to locally released norepinephrine and insensitive to ACh, possibly because of a unique distribution of respective receptors, thus supporting the third hypothesis. Moreover, the results of the control group support the third hypothesis. Our result is further supported by a previous in vitro study using a canine isolated blood-perfused AVN preparation without functional sinus nodal activity in which norepinephrine injected into the anterior septal artery, a nutrient artery of the His–Purkinje-ventricular system, increased the frequency of automaticity of the distal AV junctional area, but norepinephrine injected into the AVN artery caused a pacemaker shift from the distal to the proximal part of the AV junctional area.

However, our conclusion differs from a recent clinical report by Chen et al in which they did not find a significant difference in the cycle length of junctional tachycardia and the number of consecutive junctional beats per session between patients with autonomic blockade and a control group, although the cycle length of the junctional tachycardia tended to be longer in the patients with autonomic blockade than in the controls. This contradictory observation might be related to differences in study design. The number of patients in each of their groups (n=10 for each group) is small for a clinical study and/or the dose of propranolol (0.2 mg/kg) might have been inadequate for eliminating the potent β-adrenoceptor stimulatory action of the locally released norepinephrine, because the sympathetic as well as parasympathetic nervous system richly innervates the peri-AVN region. To assess the role of autonomic nervous system more accurately, we used 2 different doses of esmolol; moreover, the effects of the RF application were examined in the same animal before and after pharmacological treatments.

The severe bradycardia observed following the cessation
of junctional tachycardia also deserves a comment. It was potentiated by the administration of esmolol in a dose-related manner and was attenuated by atropine. Systemic administration of isoproterenol enhanced the automaticity, and in some animals shifted the automatic focus transiently to the lower part of the conduction system, whereas ACh, as well as ventricular overdrive pacing, dramatically suppressed the VR. These results indicate that the VR may be sensitive to both locally released norepinephrine and ACh, which is different from the electrophysiological property of the JR, and suggest that the bradycardia observed after the junctional tachycardia may be, in part, a result of the overdrive suppression of VR. A similar observation was reported in another in vitro experiment.14

In conclusion, the present results suggest that there are more than 2 different automatic sites below the ablation site. The dominant pacemaker exists in the distal part of the AV junctional area after the onset of complete AV conduction block, whereas the proximal part has extremely slow pacemaker activity that responds to locally released norepinephrine with an abrupt rise and fall, resulting in a typical pattern of junctional tachycardia during the ablation of the AV junctional area.

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References


