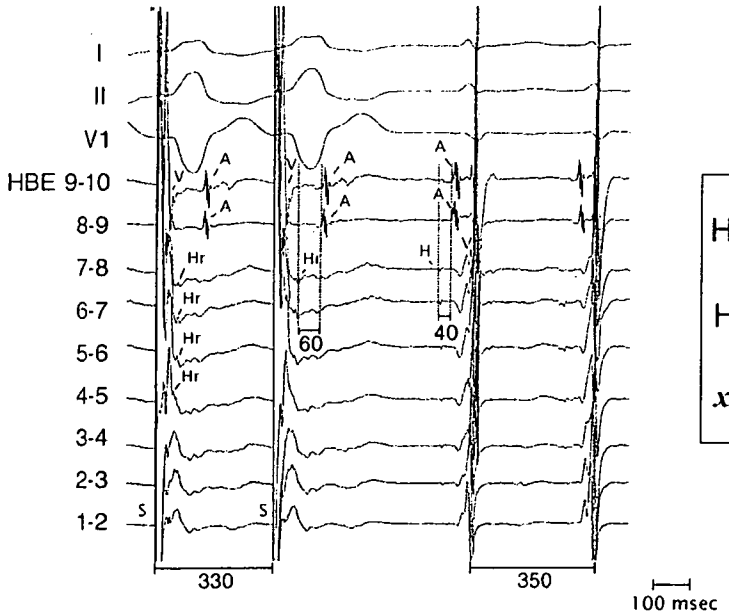

Figure 2 Body surface and intracardiac ECGs recorded during entrainment pacing from the parahisian right ventricular region (pacing cycle length 330 ms) and typical AV nodal reentrant tachycardia (tachycardia cycle length 350 ms) in a patient with adenosine triphosphate-sensitive retrograde fast pathway. HAe (60 ms) exceeds HAt (40 ms) by 20 ms; therefore, x was calculated to be 10 ms. See text for details. A = atrial electrogram; H = anterograde His-bundle potential; Hr = retrograde His-bundle potential; HBE = His-bundle electrogram; V = ventricular electrogram. Other abbreviations as in Figure 1.

ipate in the reentrant circuit as a retrograde limb in most ATP-R patients (Figure 4, right). On the other hand, x was >0 ms in 41 (87%) of 47 ATP-S patients, suggesting that a lower common pathway with a short length was present in most ATP-S patients (Figure 4, left). Twenty-three (92%) of the 25 patients with x <0 ms were classified into the ATP-R group, whereas 41 (95%) of 43 patients with x >0 ms were classified into the ATP-S group (Table 2). Hence, the results obtained from electrophysiologic and pharmacologic evaluations were highly consistent in both groups.

Slow pathway ablation

All 74 patients underwent successful slow pathway ablation with a mean 2 ± 2 applications. No patients had complications related to the procedure. No recurrences were observed after a mean follow-up of 36 ± 30 months, without any antiarrhythmic medications.

Discussion

Major findings

The present study demonstrated that the retrograde fast pathway could be a nondecremental, ATP-resistant, concealed atriohisian tract, and that the lower turnaround of the reentrant circuit might be located within the His bundle in approximately one third of patients with typical AVNRT. Slow pathway ablation was equally effective for AVNRTs with and without participation of the concealed atriohisian tract.

Participation of a concealed atriohisian tract in typical AVNRT

Previous reports showed that 11%[17] to 17%[11] of patients with retrograde fast pathway conduction exhibited a short VA conduction time during ventricular pacing with few

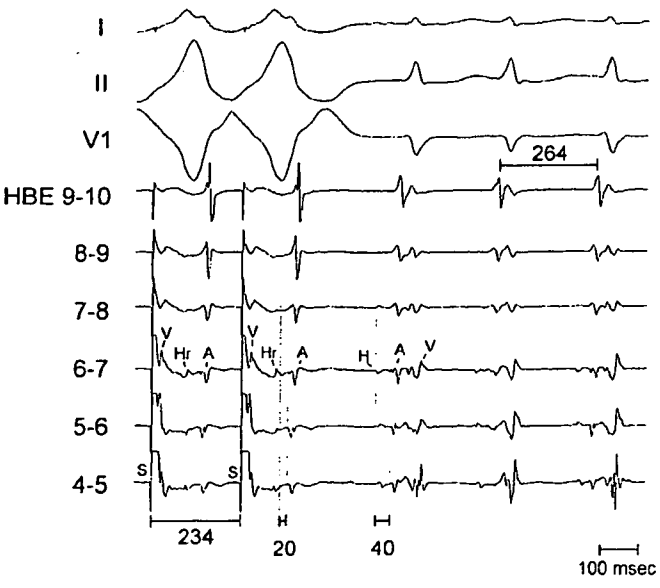

Figure 3 Body surface and intracardiac ECGs recorded during entrainment pacing from the parahisian right ventricular region (pacing cycle length 234 ms) and typical AV nodal reentrant tachycardia (tachycardia cycle length 264 ms) in a patient with adenosine triphosphate-resistant retrograde fast pathway. HAt (40 ms) exceeds HAe (20 ms) by 20 ms; therefore, x was calculated to be −10 ms. See text for details. Abbreviations as in previous figures.

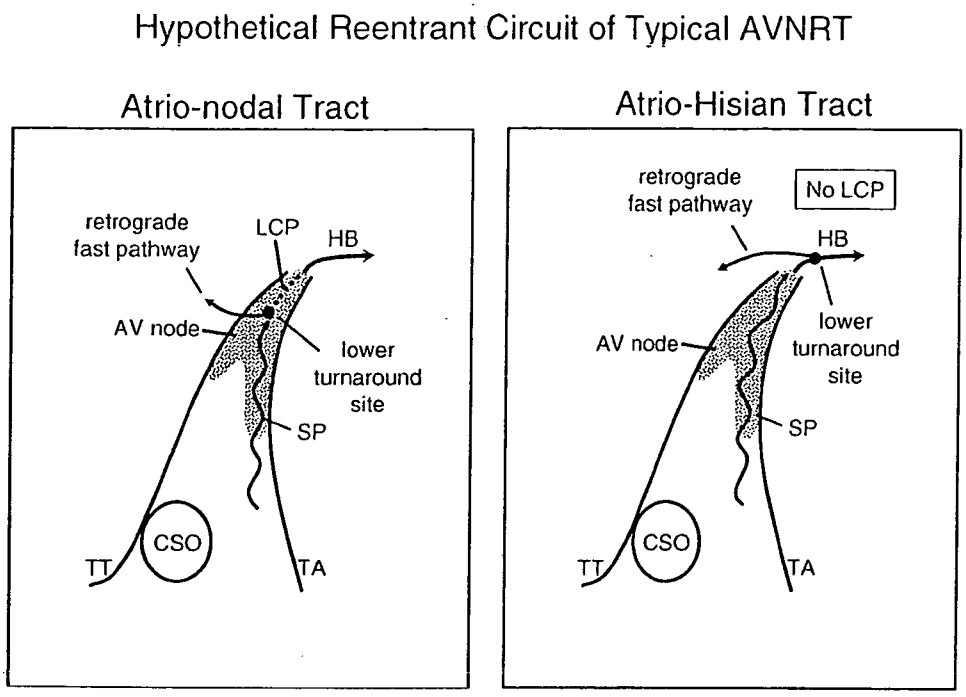

Figure 4 Schematic representation of the hypothetical reentrant circuit of typical AV nodal reentrant tachycardia. An atrionodal tract (left) and atriohisian tract (right) were assumed to constitute the retrograde fast pathway in the reentrant circuit of typical AV nodal reentrant tachycardia for ATP-S and ATP-R patients, respectively. See text for details. CSO = coronary sinus ostium; HB = His bundle; LCP = lower common pathway; SP = slow pathway; TA = tricuspid annulus; TT = tendon of Todaro.

decremental properties and little resistance to adenosine or ATP. Akhtar et al[16] reported that such a retrograde fast pathway did not exhibit VA prolongation after administration of verapamil. Spurrell et al[12] found a nondecremental retrograde fast pathway in 7 (58%) of 12 patients with slow-fast AVNRT. The mechanism responsible for such "Kent bundle-like" behavior of the retrograde fast pathway was considered to be retrograde bypass of the AV node.[11–15,18,19] Evidence suggesting an intrahisian location of the lower turnaround site included a coincidence of a variation in the H-A interval and H-V block or bundle branch block during the tachycardia[28,29] and tachycardia termination with H-A and H-V block.[30] Preservation of retrograde AV nodal conduction in patients with complete heart block also might suggest the prevalence of a retrograde AV nodal bypass tract in some patients.[31] In the present study, most retrograde fast pathways with "Kent bundle-like" behavior exhibited ATP resistance and $x < 0$, suggesting that they consisted of non-AV nodal tissue connecting the proximal His-bundle and right superoseptal area, that is, atriohisian tracts. Because anterograde AV nodal conduction was blocked after an ATP bolus of the same amount, as in the evaluation of the retrograde fast pathway in all ATP-R patients, the atriohisian tracts would be capable of conducting only in the retrograde direction.

Table 2 Sensitivity of retrograde fast pathway to adenosine triphosphate at different x values

Group	$x > 0$	$x = 0$	$x < 0$	Total
ATP-S	41 (95%)	4 (67%)	2 (8%)	47 (64%)
ATP-R	2 (5%)	2 (33%)	23 (92%)	27 (36%)
Total	43 (100%)	6 (100%)	25 (100%)	74 (100%)

Values are given as number of patients, unless otherwise indicated.
$P < .01$ between groups of patients with $x > 0$, $x = 0$, and $x < 0$ by Fisher's exact probability test.

Evaluation of the lower common pathway in typical AVNRT

The hypothesis to evaluate the conduction time over the lower common pathway (Figure 1) would be valid only if the following prerequisites[32] were met: (1) autonomic tone was similar during tachycardia and entrainment pacing; (2) the most proximal His-bundle potential was generated from the proximal end of the His bundle; (3) conduction time over the lower common pathway was the same during anterograde and retrograde conduction; and (4) conduction route and conduction time over the retrograde fast pathway was the same during tachycardia and entrainment pacing. In the present study, the HAe and HAt were measured at the last entrained and first tachycardia beats, respectively, in order to reduce as much as possible the change in autonomic tone possibly induced by ventricular pacing associated with transient blood pressure decrease.[3] The change in autonomic tone during the entrainment, if present, might shorten the HAe and lead to underestimation of the lower common pathway conduction time. The proximal portion of the His bundle was mapped with high spatial resolution using a decapolar catheter with 2-mm interelectrode spacing to record activation of the most proximal portion of the His bundle. Therefore, the possibility that the "most proximal His-bundle potential" was generated from a more distal portion of the His bundle (and thus the proximal portion of the His bundle erroneously incorporated in the lower common pathway) would be quite low. However, we cannot exclude the theoretical possibility that the "most proximal

His-bundle potential" could be generated from the distal portion of the AV node, resulting in an artificially longer HAt and shorter HAe and, therefore, possible erroneous incorporation of the distal portion of the AV node in the His bundle. Conduction velocity over the retrograde fast pathway and lower common pathway might be faster during parahisian entrainment than tachycardia because of the larger current from the rapidly conducting His bundle than that from anterograde conduction over the slow pathway.[32] Similarly, conduction velocity over the retrograde fast pathway might be slower during tachycardia than parahisian entrainment because of conduction delay associated with the change in direction of the wavefront at the junction of the two pathways during tachycardia.[33] The retrograde atrial activation sequence was reported to be different in as many as 50% of patients with AVNRT during tachycardia and ventricular pacing.[34] Theoretically, entrainment of AVNRT ensures use of the same circuit and therefore the same retrograde pathway as the tachycardia itself. In the present study, we used "parahisian entrainment pacing," so it is unlikely that the retrograde conduction path was changed during entrainment.

As mentioned, the results of lower common pathway evaluation using this methodology would be greatly influenced by whether or not certain prerequisites were met, and the differences in the incidence of the lower common pathway in various studies possibly could be derived from these factors. However, the highly consistent results from electrophysiologic and pharmacologic evaluations in the present study strongly suggest that the prerequisites mentioned were fulfilled and that the concealed atriohisian tracts participated in the reentrant circuit as a retrograde limb in one third of typical AVNRT patients.

Anatomic perspectives on the atriohisian tract

Although a large amount of electrophysiologic data suggesting the participation of the atriohisian tract in typical AVNRT have been reported in the literature, anatomic evidence supporting the presence of an atriohisian tract are sparse. In a histologic study of 687 autopsy hearts, Brechenmacher[22] reported that a true atriohisian connection was found in only 2 (0.3%) hearts. Ho et al[24] found no atriohisian tracts in a histologic study of 10 explanted human hearts with a documented dual pathway physiology. Nevertheless, the negative data from these histologic studies do not necessarily exclude the possibility of participation of a concealed atriohisian tract in typical AVNRT, because the subjects of those histologic studies were not selected patients with electrophysiologic evaluations. Furthermore, the results from our study suggest the participation of an atriohisian tract in only one third of patients; therefore, the incidence of a true atriohisian tract among general autopsy hearts or individuals with a dual AV nodal pathway physiology is expected to be quite low. In experimental studies, Patterson and Scherlag[18] proved the presence of the atriohisian tracts in 13 (13%) of 102 rabbit hearts and concluded that these atriohisian tracts provide anatomic and physiologic bases for rapid retrograde VA conduction and possible retrograde fast pathways for sustained AVNRT. Their reports[18,19] support our concept and add validity to the observations of the present study.

Clinical implications

ATP is frequently used to differentiate retrograde conduction over the accessory pathway from that over the AV node during electrophysiologic study.[35] In the present study, one third of the retrograde fast pathways were resistant to ATP and were demonstrated to be concealed atriohisian tracts. However, conventional slow pathway ablation was equally effective for AVNRTs with and without participation of a concealed atriohisian tract. Therefore, it is important to remember that even if participation of a concealed atriohisian tract was demonstrated, the anterograde slow pathway rather than the atriohisian tract should be targeted during ablation of typical AVNRT.

Study limitations

This study had several theoretical and technical limitations. One theoretical limitation is that some of the prerequisites for the lower common pathway evaluation[32] might not have been fulfilled. The dosage of ATP used in the present study (0.5 ± 0.2 mg/kg) might have been insufficient to conclude that the retrograde fast pathway in the ATP-R group was the atriohisian tract. Other studies used 0.2 mg/kg adenosine[7] and 0.1–0.3 mg/kg ATP[9] to evaluate the sensitivity of the retrograde fast pathway to each drug. Considering that adenosine is twice as potent as ATP,[10] the dosage of ATP used in the present study was larger than that used in previous studies. We did not demonstrate that the concealed atriohisian fiber was included in the critical component of the reentrant circuit of typical AVNRT; therefore, the theoretical possibility that the concealed atriohisian tract is a bystander that becomes manifest during ventricular entrainment cannot be definitively excluded. Technical limitations of the study include inaccurate measurements of the HAe due to poor visualization of the end of the His-bundle potential during entrainment pacing, although we used the "parahisian entrainment"[3] technique to separate local ventricular from His-bundle potentials and clearly visualized the end of the His-bundle potential. Although each electrophysiologic measurement was reproducible with "intraobserver" measurement error <5 ms, we did not evaluate "interobserver" measurement error by having more than one person measure the same intracardiac recordings. This might limit the objectivity of each electrophysiologic measurement. Because 24 (24%) of the 98 enrolled patients were excluded from the study, the incidence of a concealed atriohisian tract (36.5%) might be inaccurate. During the diagnostic procedure, a supraventricular tachycardia using a slow pathway as the anterograde limb and atriohisian tract as the retrograde limb was theoretically expected to be reset by a ventricular extrastimulus delivered when the proximal His bundle was refractory but the part of the His bundle distal to the lower turnaround was not refractory.[20] How-

ever, the tachycardia was never reset by a ventricular extrastimulus delivered when at least the proximal portion of the His bundle was refractory; this suggests that the proximal part of the His bundle, even if involved in the reentrant circuit, would be quite short in length and the lower turnaround site would be located within the His bundle very close to the junction between the slow pathway and His bundle. This study demonstrated the participation of a concealed atriohisian tract in one third of typical AVNRT cases using electrophysiologic and pharmacologic maneuvers. In a strict sense, however, the anatomic issues cannot be settled unequivocally by electrophysiologic and pharmacologic probes. Therefore, we consider that the definitive presence of an atriohisian tract can never be demonstrated without direct anatomic evidence.

Conclusion

In one third of typical AVNRT cases, the retrograde fast pathway was resistant to ATP and the H-A interval was shorter during entrainment from the RV than during the tachycardia, suggesting that the lower turnaround site was located within the His bundle and the concealed atriohisian tract constituted the retrograde limb of the reentrant circuit.

References

1. Jackman WM, Beckman KJ, McClelland JH, Xunzhang W, Friday KJ, Roman CA, Moulton KP, Twidale N, Hazlitt HA, Prior MI, Oren J, Overholt ED, Lazzara R. Treatment of supraventricular tachycardia due to atrioventricular nodal reentry by radiofrequency catheter ablation of slow pathway conduction. N Engl J Med 1992;327:313–318.
2. Miller JM, Rosenthal ME, Vassallo JA, Josephson ME. Atrioventricular nodal reentrant tachycardia: studies on upper and lower "common pathways." Circulation 1987;75:930–940.
3. Anselme F, Poty H, Cribier A, Josephson ME, Saoudi N. Entrainment of typical AV nodal reentrant tachycardia using para-Hisian pacing: evidence for a lower common pathway within the AV node. J Cardiovasc Electrophysiol 1999;10:655–661.
4. Li YG, Bender B, Bogun F, Gronefeld G, Hohnloser SH. Location of the lower turnaround point in typical AV nodal reentrant tachycardia: a quantitative model. J Cardiovasc Electrophysiol 2000;11:34–40.
5. Heidbuchel H, Ector H, Van de Werf F. Prospective evaluation of the length of the lower common pathway in the differential diagnosis of various forms of AV nodal reentrant tachycardia. Pacing Clin Electrophysiol 1998;21:209–216.
6. Heidbuchel H, Jackman WM. Characterization of subforms of AV nodal reentrant tachycardia. Europace 2004;6:316–229.
7. Fishberger SB, Mehta D, Rossi AF, Langan MN, Marx SO, Gomes JA. Variable effects of adenosine on retrograde conduction in patients with atrioventricular nodal reentry tachycardia. Pacing Clin Electrophysiol 1998;21:1254–1257.
8. Mewis C, Kuhlkamp V, Mermi J, Bosch RF, Seipel L. High variability of retrograde fast pathway sensitivity to adenosine. Clin Cardiol 2000;23:576–578.
9. Miyata A, Kobayashi Y, Jinbo Y, Chiyoda K, Nakagawa H, Tanno K, Kurano K, Kikushima S, Baba T, Katagiri T. Effects of adenosine triphosphate on ventriculoatrial conduction—usefulness and problems in assessment of catheter ablation of accessory pathways. Jpn Circ J 1997;61:323–330.
10. Rankin AC, Oldroyd KG, Chong E, Dow JW, Rae AP, Cobbe SM. Adenosine or adenosine triphosphate for supraventricular tachycardias? Comparative double-blind randomized study in patients with spontaneous or inducible arrhythmias. Am Heart J 1990;119:316–323.
11. Gomes JA, Dhatt MS, Damato AN, Akhtar M, Holder CA. Incidence, determinants and significance of fixed retrograde conduction in the region of the atrioventricular node. Evidence for retrograde atrioventricular nodal bypass tracts. Am J Cardiol 1979;44:1089–1098.
12. Spurrell RA, Krikler DM, Sowton E. Concealed bypasses of the atrioventricular node in patients with paroxysmal supraventricular tachycardia revealed by intracardiac electrical stimulation and verapamil. Am J Cardiol 1974;33:590–595.
13. Kerr CR, Benson DW, Gallagher JJ. Role of specialized conducting fibers in the genesis of "AV nodal" re-entry tachycardia. Pacing Clin Electrophysiol 1983;6:171–184.
14. Narula OS. Paroxysmal supraventricular tachycardia due to reciprocation via concealed accessory pathways. In: Narula OS, editor. Cardiac Arrhythmias. Electrophysiology, Diagnosis and Management. Baltimore: Williams & Wilkins, 1979:318–346.
15. Narula OS. Retrograde pre-excitation. Comparison of antegrade and retrograde conduction intervals in man. Circulation 1974;50:1129–1143.
16. Akhtar M, Damato AN, Batsford WP, Ruskin JN, Ogunkelu JB. A comparative analysis of antegrade and retrograde conduction patterns in man. Circulation 1975;52:766–778.
17. Schuilenburg RM. Patterns of V-A conduction in the human heart in the presence of normal and abnormal A-V conduction In: Wellens HJJ, Lie KI, Janse MJ, editors. The Conduction System of the Heart. Philadelphia: Lea & Febiger, 1976:485–778.
18. Patterson E, Scherlag BJ. Fast pathway-His bundle connections in the rabbit heart. J Interv Card Electrophysiol 2004;10:121–129.
19. Patterson E, Scherlag BJ. Anatomic and functional fast atrioventricular conduction pathway. J Cardiovasc Electrophysiol 2002;13:945–949.
20. Stein KM, Engelstein ED, Lippman N, Lerman BB. Physiologic role of atrio-Hisian and nodo-Hisian bypass tracts in supraventricular tachycardia. Am Heart J 1994;128:759–768.
21. Okumura K, Yamabe H, Yasue H. Radiofrequency catheter ablation of concealed atrio-His bypass tract involved in paroxysmal supraventricular tachycardia. Pacing Clin Electrophysiol 1994;17:1686–1690.
22. Brechenmacher C. Atrio-His bundle tracts. Br Heart J 1975;37:853–855.
23. Brechenmacher C, Laham J, Iris L, Gerbaux A, Lenegre J. Histological study of abnormal conduction pathways in the Wolff-Parkinson-White syndrome and Lown-Ganong-Levine syndrome. Arch Mal Coeur Vaiss 1974;67:507–519.
24. Ho SY, McComb JM, Scott CD, Anderson RH. Morphology of the cardiac conduction system in patients with electrophysiologically proven dual atrioventricular nodal pathways. J Cardiovasc Electrophysiol 1993;4:504–512.
25. Josephson ME. Supraventricular tachycardias. In: Clinical Cardiac Electrophysiology. Techniques and Interpretations. Third edition. Philadelphia: Lippincott Williams & Wilkins, 2002:168–271.
26. Hirao K, Otomo K, Wang X, Beckman KJ, McClelland JH, Widman L, Gonzalez MD, Arruda M, Nakagawa H, Lazzara R, Jackman WM. Para-Hisian pacing. A new method for differentiating retrograde conduction over an accessory AV pathway from conduction over the AV node. Circulation 1996;94:1027–1035.
27. Knight BP, Zivin A, Souza J, Flemming M, Pelosi F, Goyal R, Man C, Strickberger SA, Morady F. A technique for the rapid diagnosis of atrial tachycardia in the electrophysiology laboratory. J Am Coll Cardiol 1999;33:775–781.
28. Yagi T, Yang Y, Keung EC, Collins KK, Scheinman MM. Significance of bundle branch block during atrioventricular nodal reentrant tachycardia. Am J Cardiol 2003;91:1184–1189.
29. Lee DT, Tai CT, Lin YJ, Lai WT, Chen SA. Variation of HA intervals in atrioventricular nodal reentrant tachycardia with atrioventricular block: what is the mechanism? J Cardiovasc Electrophysiol 2004;15:1103–1104.
30. Lin YJ, Tai CT, Chen SA. Unusual phenomenon of spontaneous termination of atrioventricular nodal reentrant tachycardia with 2:1 atrioventricular block. J Cardiovasc Electrophysiol 2003;14:437–438.
31. Castillo C, Samet P. Retrograde conduction in complete heart block. Br Heart J 1967;29:553–558.
32. Otomo K, Wang Z, Lazzara R, Jackman WM. Atrioventricular nodal reentrant tachycardia: electrophysiological characteristics of four forms and implications for the reentrant circuit. In: Zipes DP, Jalife J, editors: Cardiac Electrophysiology. From Cell to Bedside. Third edition. Philadelphia:WB Saunders, 2000:504–521.
33. Spach MS, Josephson ME. Initiating reentry: the role of nonuniform anisotropy in small circuits. J Cardiovasc Electrophysiol 1994;5:182–209.
34. Anselme F, Hook B, Monahan K, Frederiks J, Callans D, Zardini M, Epstein LM, Zebede J, Josephson ME. Heterogeneity of retrograde fast-pathway conduction pattern in patients with atrioventricular nodal reentry tachycardia: observations by simultaneous multisite catheter mapping of Koch's triangle. Circulation 1996;93:960–968.
35. DiMarco JP, Sellers TD, Berne RM, West GA, Belardinelli L. Adenosine: electrophysiologic effects and therapeutic use for terminating paroxysmal supraventricular tachycardia. Circulation 1983;68:1254–1263.

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Implications of 2:1 atrioventricular block during typical atrioventricular nodal reentrant tachycardia

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Abstract
Objective The effects of 2:1 AV block (AVB) on AV nodal reentrant tachycardia (AVNRT) remain to be elucidated. This study was performed to localize the site of 2:1 AVB and elucidate the effects of 2:1 AVB on typical AVNRT.
Methods The His bundle (HB) electrograms during typical AVNRT with 2:1 AV block were reviewed in 24 patients. It was hypothesized that if 2:1 AVB at the HB or below changed tachycardia cycle length (TCL), the lower turnaround point of the reentrant circuit (RC) might be located within the HB and parts of the HB might be involved in the RC.
Results A HB potential was absent in blocked beats during 2:1 AVB in four patients (supra-Hisian block), and the maximal amplitude of the HB potential in blocked beats was the same as that in conducted beats in four patients (infra-Hisian block), and was significantly smaller than that in conducted beats (0.1±0.1 versus 0.5±0.2 mV, $P<0.05$) in 16 patients (intra-Hisian block). Eight patients (33%) with intra-Hisian block had a nearly identical prolongation of the H–A and A–A intervals in blocked beats (12±3 and 13±2 ms, respectively) with unchanged A–H intervals, while the remaining 16 patients (67%) exhibited invariable A–A and/or H–A intervals.
Conclusion The site of 2:1 AVB during typical AVNRT was estimated to be at the HB or below in 83% of the cases. Two-to-one intra-Hisian block transiently prolonged TCL, possibly indicating involvement of the proximal HB in the RC in one-third of typical the AVNRT cases with 2:1 AVB.

Keywords Atrioventricular nodal reentrant tachycardia · Atrioventricular block · His bundle · Lower turnaround point

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1 Introduction

Typical (slow–fast form) atrioventricular (AV) nodal reentrant tachycardia (AVNRT) occasionally exhibits 2:1 AV block without a tachycardia interruption, and which has been traditionally interpreted to suggest the presence of a lower common pathway between the reentrant circuit and His bundle [1, 2]. More recently, 2:1 AV block during typical AVNRT was reportedly due to a functional conduction block within or below the His bundle in the majority of the patients [3, 4]. Several studies presented the possibility that the lower turnaround point of the reentrant circuit in typical AVNRT was located at the proximal His bundle and the proximal part of the His bundle may be involved in the reentrant circuit [5–12]. Although 2:1 AV block during typical AVNRT has been conventionally believed to have no effect on the tachycardia itself [13], it may have some influence on the tachycardia timing intervals, assuming that the sites of the lower turnaround point as well as the sites of the 2:1 AV block are located close to one another within the proximal His bundle (Fig. 1).

The purposes of this study were to (1) localize the site of the 2:1 AV block during typical AVNRT, (2) assess the effects of the 2:1 AV block during typical AVNRT on the tachycardia timing intervals, and (3) localize the lower

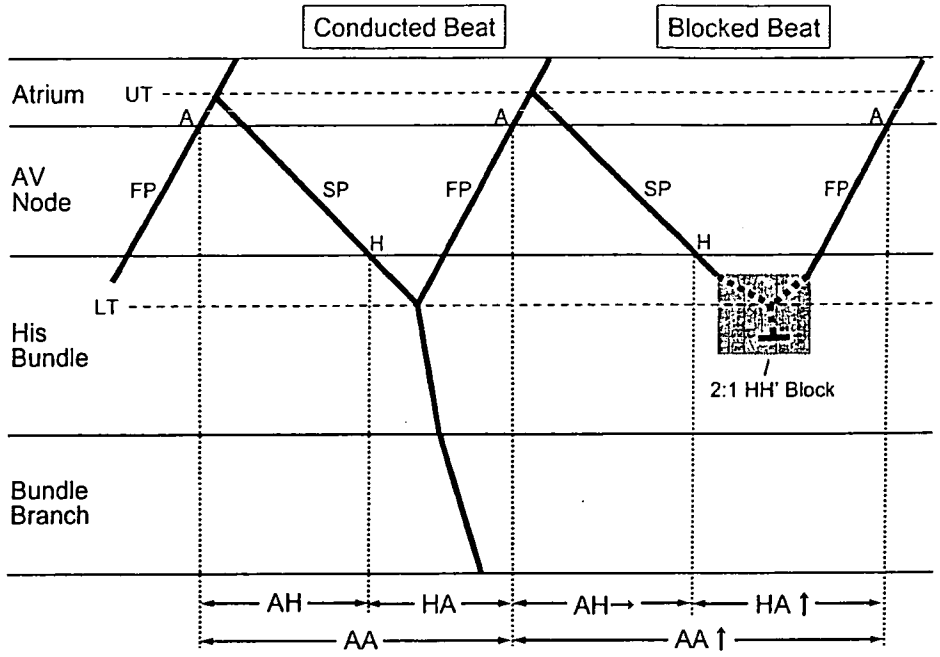


Fig. 1 The hypothetical reentrant circuit depicted by the laddergram showing the activation sequence during a typical AVNRT with 2:1 HH' block and the hypothetical mechanism by which the 2:1 HH' block influences the tachycardia timing intervals. The *shaded area* indicates the area with a functional conduction delay and block during 2:1 AV block. See the text for details. *A* represents the earliest atrial electrogram; *FP* retrograde fast pathway; *H* the earliest His bundle potential; *LTP* lower turnaround point; *SP* anterograde slow pathway; and *UTP* upper turnaround point

turnaround point of the reentrant circuit to assess if parts of the His bundle were involved in the reentrant circuit of the typical AVNRT.

2 Methods

2.1 Patients

This study included 24 consecutive patients who had at least one episode of typical AVNRT with sustained 2:1 AV block that lasted for more than 30 seconds during the electrophysiological study. These 24 patients accounted for 8% out of the 302 patients who had inducible typical AVNRT during the electrophysiological study in our institution. There were 10 men and 14 women with a mean age of 47±15 years. The mean sinus cycle length (CL), atrio-His (AH) interval and His-ventricular (HV) interval during sinus rhythm were 909±102, 78±18 and 40±5 ms, respectively. Two patients (8%) had right bundle branch block during sinus rhythm.

2.2 Electrophysiological study

The study protocol was reviewed and approved by the Institutional Committee on Human Research at the National Cardiovascular Center and each patient gave written informed consent prior to the procedure. All antiarrhythmic drugs had been discontinued for at least five half-lives before the procedures. With the patients under local anesthesia, venous access was obtained from the femoral and antecubital veins to introduce 4 electrode catheters. Three multipolar catheters were introduced from the femoral veins and positioned in the high right atrium, His bundle region and right ventricular apex. A His bundle catheter (decapolar catheter with a 1 mm-electrode width and 2-mm-inter-electrode spacing) was positioned across the tricuspid annulus so as to record the most proximal His bundle potential. An octapolar catheter was introduced from the right antecubital vein and positioned within the coronary sinus. Baseline electrophysiological evaluations and tachycardia inductions were performed during incremental pacing and extrastimulation (basic CL: 500–700 ms) from the right ventricular apex, high right atrium and coronary sinus using a programmable cardiac stimulator (EP-3 Computerized Stimulator, EP Med Systems, Inc., West Berlin, NJ, USA) with a pulse width of 2 ms and stimulus output of twice the diastolic pacing threshold. If AVNRT was not induced at baseline, isoproterenol (0.5–2.0 mg/min) was administered intravenously to facilitate the tachycardia induction. The intracardiac bipolar electrocardiograms were filtered through a bandpass of 30–500 Hz, displayed on a real-time monitor at a paper speed of 100 mm/s and stored with a 2-kHz sampling frequency on magneto-optical disks (Bard LabSystem Duo, Bard Electrophysiology, Lowell, MA, USA; or CardioLab, Prucka Engineering, Inc., Houston, TX, USA).

The exclusion of the tachycardia mechanisms other than AVNRT and diagnosis of AVNRT were performed based upon the classical criteria [13]. The absence of an AV accessory pathway was confirmed by the following criteria: ventricular pre-excitation was absent during sinus rhythm and atrial

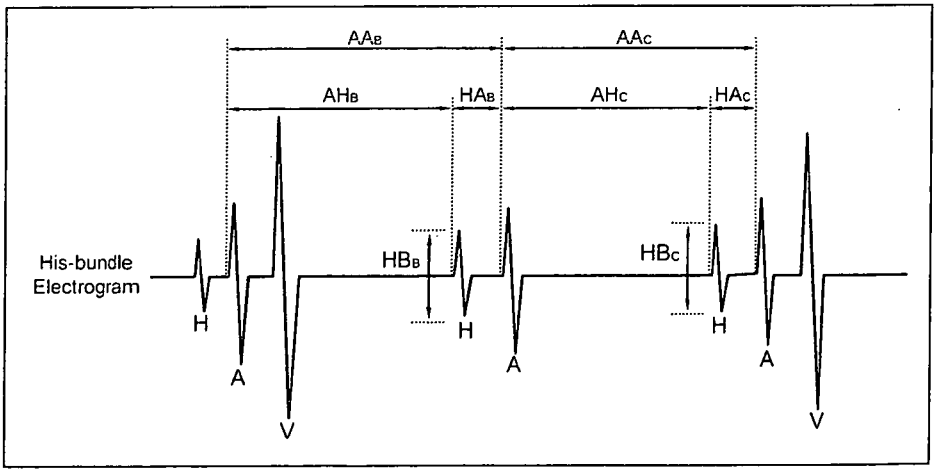
pacing; the tachycardia was not reset by ventricular extrastimuli delivered during the most proximal His bundle's refractoriness; and para-Hisian pacing [14] during sinus rhythm exhibited a retrograde AV nodal conduction pattern. Atrial tachycardia and atrial flutter were excluded when a "V–A–V sequence" (not a "V–A–A–V sequence") was observed upon cessation of ventricular pacing associated with a 1:1 ventriculo-atrial conduction during the tachycardia [15]; the tachycardia was induced by ventricular pacing with a "V–A–V sequence"; and the tachycardia was reproducibly terminated with ventricular extrastimuli not reaching the atrium. The diagnosis of AVNRT was made if AV reciprocating tachycardia using AV accessory pathways and atrial tachycardia were excluded by the criteria mentioned above. The slow–fast form of AVNRT was diagnosed when the anterograde conduction occurred over the slow pathway with an AH interval during the tachycardia of 200 ms or longer; and the retrograde conduction proceeded over the fast pathway with the H–A interval during RV pacing at the tachycardia CL of less than 70 ms [16].

2.3 Definition and classification of the 2:1 AV block patterns during AVNRT

Sustained 2:1 AV block during typical AVNRT was defined as 2:1 AV block that persisted for 30 s or longer. The patterns of the 2:1 AV block were classified into one of the following; (1) AH block (supra-Hisian block), defined by the absence of any discernible His bundle potentials in the blocked beats, (2) HH' block (intra-Hisian block), defined by a lower amplitude (amplitude reduction of 50% or more) of the His bundle potentials in the blocked beats than those in the conducted beats, and (3) HV block (infra-Hisian block), defined by the same amplitudes of the His bundle potentials in the blocked and conducted beats.

2.4 Measurements of the electrophysiological parameters during AVNRT with 1:1 and 2:1 AV conduction

During the episodes of the typical AVNRT with sustained 2:1 AV block, the His bundle catheter was manipulated to maximize the amplitude of the His bundle potential in the conducted and blocked beats. From the recordings of the intracardiac electrocardiograms during the episodes of typical AVNRT with stable 2:1 AV block, the following parameters were retrospectively measured both in the conducted and blocked beats (Fig. 2): the atrial–atrial (AA) interval [AAC and AAB (in milliseconds), respectively]; His–atrial (HA) interval [HAC and HAB (in milliseconds), respectively]; AH interval [AHC and AHB (in milliseconds), respectively]; and amplitude of the His bundle potential as measured in the His bundle electrograms [HBC and HBB (in millivolts), respectively]. The increments of the AA interval [ΔAA (=AAB−AAC; in milliseconds)], HA interval [ΔHA (=HAB−HAC; in milliseconds)] and AH interval [ΔAH (=AHB−AHC; in milliseconds)] in the consecutive conducted and blocked beats were calculated. The percent reduction in the mean amplitude of the His bundle potential in the blocked beats as compared to that in the conducted beats [HBR (=100−



ΔAA (msec)=AAB−AAC
ΔAH (msec)=AHB−AHC
ΔHA (msec)=HAB−HAC
HBR (%)=100−HBB/HBC×100

Fig. 2 Schematic representation of the His bundle electrogram during typical AVNRT with 2:1 AV block, depicting the timing intervals measured in the present study. See the text for details

100×HBB/HBC: in percentage)] was calculated. The HAB, AHB, HBB, ΔHA, ΔAH and HBR were measured only in the patients with HH' and HV block. The AA, AH and HA intervals were also measured during episodes of typical AVNRT with 1:1 AV conduction just after conversion from 2:1 to 1:1 AV conduction. To exclude the influence of the basal instability of the tachycardia on the timing intervals, the electrocardiographic recordings within 30 s of the initiation and termination of the tachycardia were excluded from the analyses. Each parameter was measured for 20 consecutive beats with a paper speed of 100–200 mm/s and was presented as an average value. The 2:1 AV block during AVNRT was considered to have influenced the tachycardia if the ΔAA and/or ΔHA were 5 ms or longer.

2.5 Hypotheses

In this study, the site of the 2:1 AV block during the AVNRT was presumably determined according to the different AV block patterns during the episodes of 2:1 AV block [3, 4]. In the patients with 2:1 AH block during the AVNRT, the site of the block was assumed to be the lower common pathway within the AV node or junction between the AV node and His bundle. Among those with 2:1 HH' block, the site of the block was assumed to be the proximal part of the His bundle, because the block within the proximal His bundle would result in a reduction in the amount of the His bundle tissue depolarized and an amplitude reduction of the His bundle potential in the blocked beats [3, 4]. Among those with 2:1 HV block, the site of the block was assumed to be the distal His bundle or below.

In our hypothesis, 2:1 AV block at a site distant from the lower turnaround point of the reentrant circuit would be expected to have no effect on the AVNRT timing intervals. Assuming that 2:1 AV block occurred just below the lower turnaround point as a consequence of a transient conduction disturbance around the lower turnaround point, it would be expected to change the timing intervals of the AVNRT (Fig. 1). Therefore, it was hypothesized that if 2:1 AV block at the His bundle or below prolonged the AA and/or HA intervals, the lower turnaround point would be located within the His bundle or below, and parts of the His bundle would be involved in the reentrant circuit of the typical AVNRT (Fig. 1).

2.6 Statistical analysis

All the continuous variables were expressed as the mean± standard deviation. The Wilcoxon *t* test and Mann–Whitney *U* test were used to compare the paired and unpaired variables, respectively. A *P* value of less than 0.05 was considered statistically significant.

3 Results

Among 24 patients with sustained 2:1 AV block during typical AVNRT, 4 (17%), 16 (66%) and 4 patients (17%) had AH, HH' and HV block, respectively (Figs. 3, 4 and 5). The mean AA interval was significantly shorter during the 2:1 than 1:1 AV conduction (300±23 versus 308±23 ms; $P<0.01$). The 2:1 AV block occurred just after the initiation of AVNRT in 14 (58%), spontaneously with the shortening of the AA interval under the infusion of isoproterenol in 6 (25%), or after spontaneous or induced ventricular premature depolarizations in 4 patients (17%). The episodes of

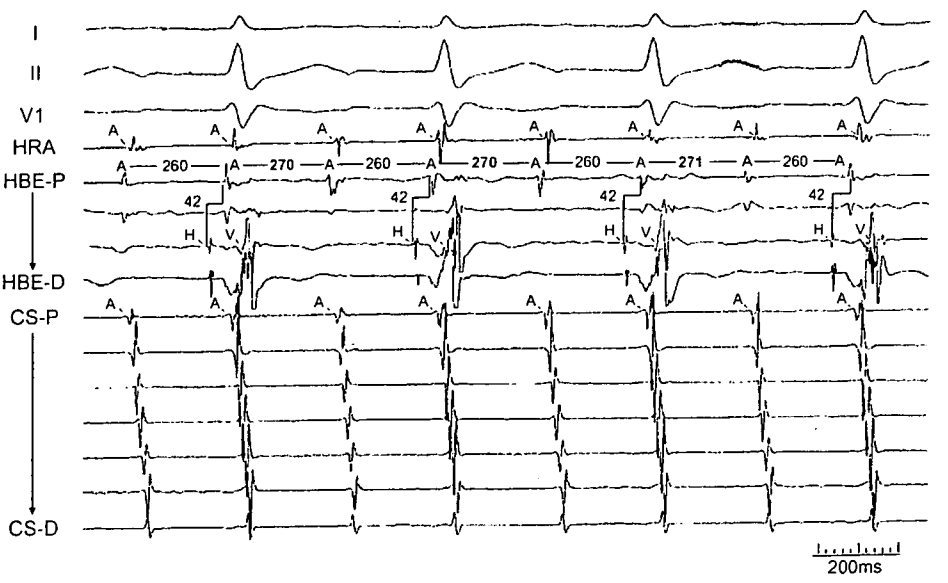


Fig. 3 Body-surface and intracardiac electrocardiograms during 2:1 AH block. Small but distinct prolongations were observed in the AAB. All figures are in millisecond. See the text for details. *CS-D* and *CS-P* represent the distal and proximal bipole pairs of the coronary sinus catheter, respectively; *HBE-D* and *HBE-P*, distal and proximal bipole pairs of the His bundle catheter, respectively; and HRA, high right atrium

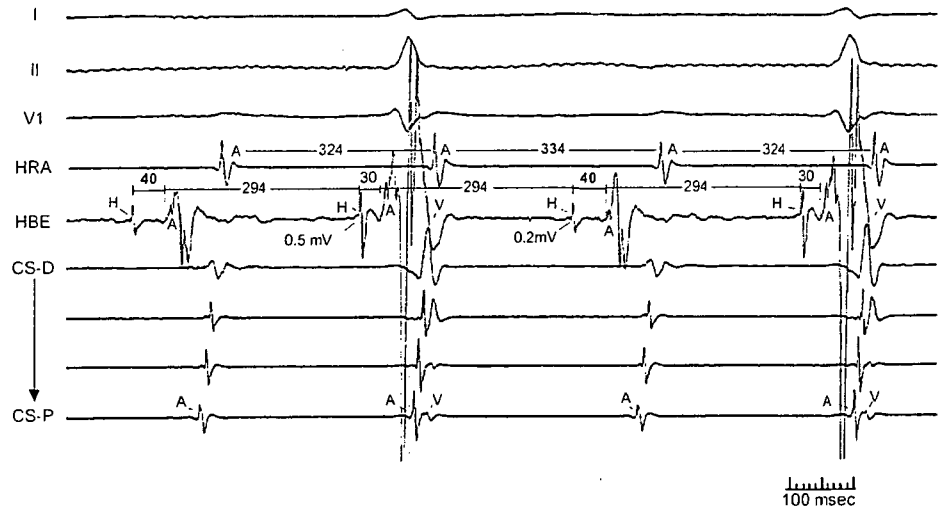


Fig. 4 Body-surface and intracardiac electrocardiograms during 2:1 HH' block. Nearly identical prolongations were observed in the AAB and HAB with an invariable AHB. All figures are in millisecond unless otherwise indicated. See the text for details. The abbreviations are as in the previous figures

the AVNRT with sustained 2:1 AV block occurred once in 7 (29%), twice in 7 (29%), three times in 9 (38%) and four times in 1 patient (4%). The conversion from 2:1 to 1:1 AV conduction was observed in all 24 patients (100%), and occurred in association with a spontaneous prolongation in the AA and AH intervals in 24 patients (100%) and/or after the introduction of a single ventricular extrastimulus in 4 patients (17%).

3.1 Influence of the 2:1 AV block on the AVNRT with the different AV block patterns

The influence of the 2:1 AV block on the typical AVNRT in the different AV block patterns is summarized in Table 1. Among the four patients with AH block, three patients (75%) exhibited a prolongation of the AAB as compared to the AAC during the AVNRT with 2:1 AV block (AAC: 298±33 ms, AAB: 309±34 ms; $P>0.05$, ΔAA: 11±1 ms; Fig. 3), which disappeared as soon as the 1:1 AV conduction resumed (AA, AH, and HA intervals during the tachycardia with 1:1 AV conduction: 303±52, 255±18, and 48±7 ms, respectively). In one other patient (25%) with AH block, the AAB and AAC were similar during the AVNRT with 2:1 AV block (AAC: 310 ms, AAB: 312 ms, ΔAA: 2 ms). Among the 16 patients with HH' block, 8 patients (50%) exhibited nearly identical prolongations in the AAB and HAB as compared to the AAC and HAC, respectively (AAC: 298±25 ms, AAB: 310±24 ms; $P<0.05$,

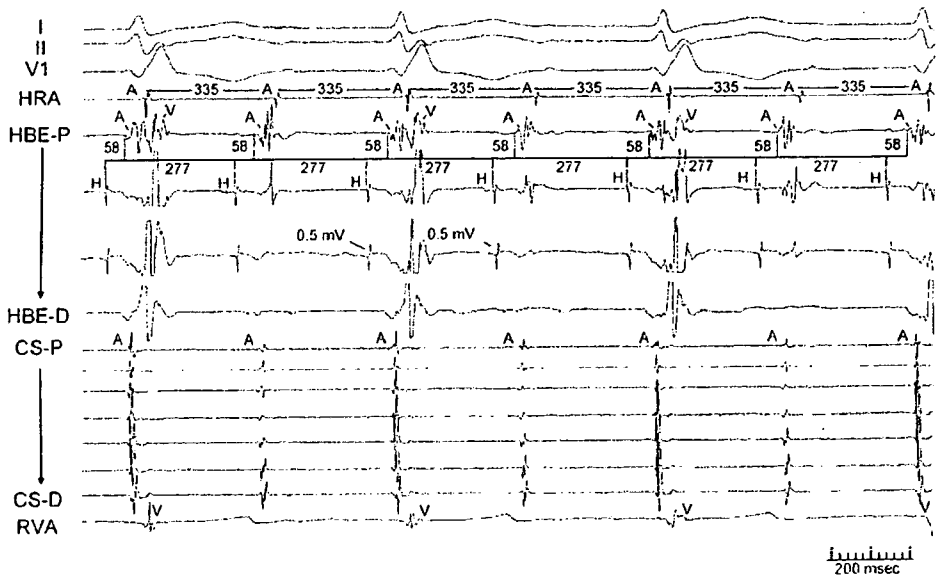


Fig. 5 Body-surface and intracardiac electrocardiograms during 2:1 HV block. No prolongation was observed in the AAB and HAB. All figures are in millisecond unless otherwise indicated. See the text for details. *RVA* represents the right ventricular apex. The other abbreviations are as in the previous figures

Table 1 Influence of 2:1 AV block on the slow-fast AVNRT in different AV block patterns

Patterns of 2:1 AV block	AH block (n=4)		HH' block (n=16)		HV block (n=4)	
ΔAA, ΔHA	<5 ms (n=1)	≥5 ms (n=3)	<5 ms (n=8)	≥5 ms (n=8)	<5 ms (n=4)	≥5 ms (n=0)
ΔAA (ms)	2	11±1	0±2*	13±2*	0±2	-
ΔAH (ms)	-	-	1±1	0±1	1±1	-
ΔHA (ms)	-	-	−1±2*	12±3*	−1±1	-

*P<0.01 by Mann–Whitney U test.

ΔAA: 13±2 ms, HAC: 49±13 ms, HAB: 62±14 ms; P< 0.05, ΔHA: 12±3 ms) with an invariable AHB (AHC: 249± 27 ms, AHB: 249±28 ms; P>0.05, ΔAH: 0±1 ms) during the AVNRT with 2:1 AV block (Fig. 4), which disappeared as soon as the 1:1 AV conduction resumed (Fig. 6). In the other 8 patients (50%) with HH' block, the AAB, AHB and HAB during 2:1 AV block were similar to the AAC, HAC and AHC, respectively (AAC: 300±20 ms, AAB: 300± 19 ms; P>0.05, ΔAA: 0±2 ms, AHC: 244±20 ms, AHB: 245±19 ms; P>0.05, ΔAH: 1±1 ms, HAC: 56±13 ms, HAB: 55±12 ms; P>0.05, ΔHA: −1±2 ms). Among the 16 patients with HH' block, the HBB was significantly smaller than HBC in both patient groups with and without prolongations in AAB and HAB (HBC and HBB in the 8 patients with prolongation in AAB and HAB: 0.5±0.2 versus 0.1±0.1 mV, respectively; P<0.05, HBC and HBB in the 8 patients without prolongation in AAB and HAB: HBC: 0.5±0.2 versus 0.1±0.1 mV, respectively; P<0.05). Among the 16 patients with HH' block, the HBR was not different between the patient groups with and without prolongations

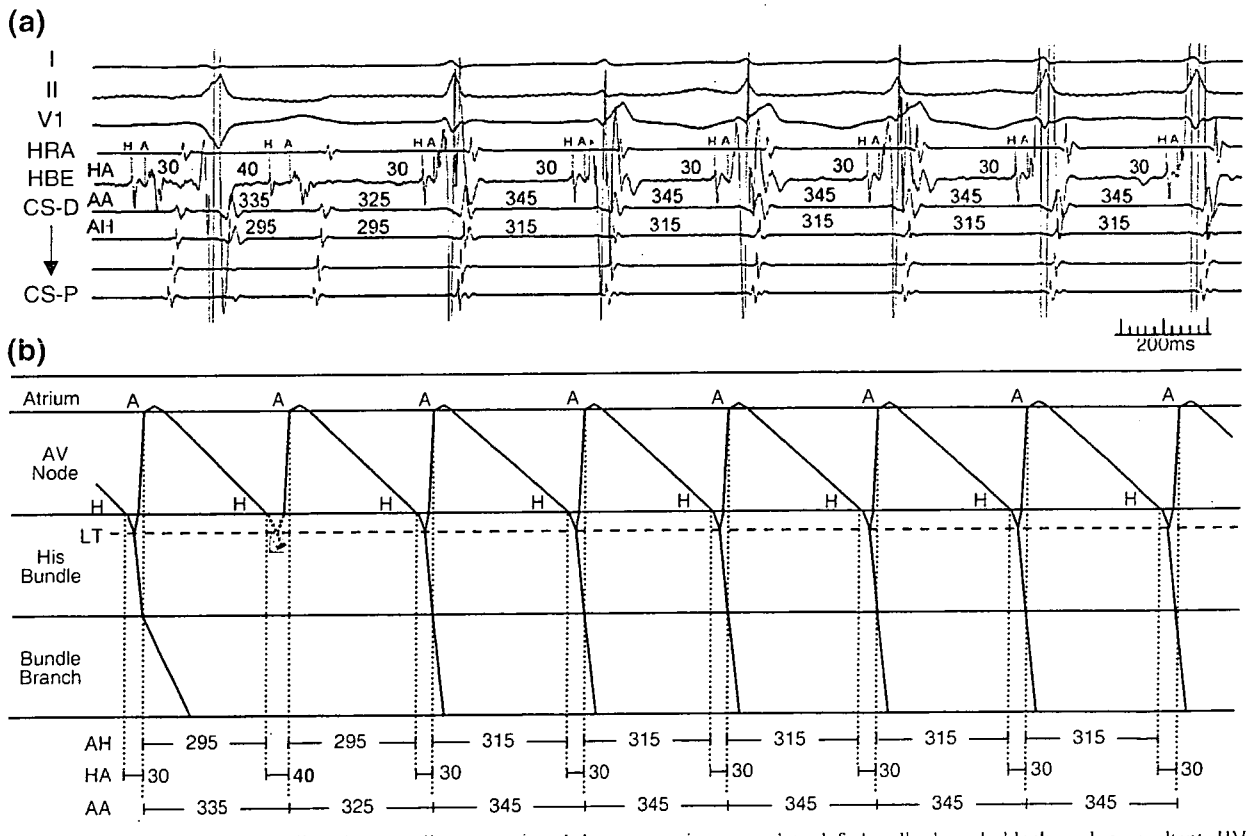


Fig. 6 Body-surface and intracardiac electrocardiograms (a) and the laddergram depicting the activation sequence during the conversion from 2:1 to 1:1 AV conduction in the same patient as in Fig. 4 (b). As soon as the 1:1 AV conduction resumed, the prolongations in HAB and AAB disappeared. The first QRS complex is associated with a transient complete left bundle branch block and a resultant HV interval prolongation. The *shaded area* indicates the area with a functional conduction delay and block during 2:1 AV block. All figures are in millisecond. See the text for details. The abbreviations are as in the previous figures

in AAB and HAB (81±7 versus 82±6%, respectively; $P>0.05$). None of the four patients with HV block exhibited prolongation in the AAB, AHB and HAB as compared to the AAC, AHC and HAC, respectively, during the AVNRT with 2:1 AV block (AAC: 290±27 ms, AAB: 290±28 ms; $P>0.05$, ΔAA: 0±2 ms, AHC: 245±51 ms, AHB: 246±51 ms; $P>0.05$, ΔAH: 1±1 ms, HAC: 45±24 ms, HAB: 44±23 ms; $P>0.05$, ΔHA: −1±1 ms; Fig. 5). Among the four patients with HH' block, there were no difference in the HBC and HBB (HBC: 0.5±0.3 mV, HBB: 0.5±0.2 mV; $P>0.05$, HBR: 3±6%).

Therefore, the 2:1 AV block during the typical AVNRT prolonged the HAB and/or AAB in 11/24 patients (46%). The nearly identical prolongations in the HAB (ΔHA: 12±3 ms) and AAB (ΔAA: 13±2 ms) in the eight patients (33%) with HH' block suggested the possibility that the lower turnaround point was located within the His bundle and 2:1 AV block occurred within the His bundle below the lower turnaround point.

3.2 Conversion from 2:1 to 1:1 AV conduction during typical atrioventricular nodal reentrant tachycardia

A spontaneous conversion from 2:1 to 1:1 AV conduction was observed in all 24 patients, and was associated with a slight prolongation in the AA interval in all episodes (mean AA intervals during 2:1 versus 1:1 AV conduction: 300±23 versus 308±23 ms, respectively; $P<0.01$), mainly due to the prolongation of the AH interval during the 1:1 AV conduction (mean AH intervals during 2:1 versus 1:1 AV conduction: 248±28 versus 257±23 milliseconds, respectively; $P<0.05$; Fig. 6). The AA, AH and HA intervals did not exhibit a beat-to-beat variation during the AVNRT with a stable 1:1 AV conduction in any of the 24 patients. The HA interval during the 1:1 AV conduction was similar to the HAC during the 2:1 AV block in all 24 patients (the HA interval during 1:1 AV conduction versus the HAC: 51±13 versus 50±14 ms, respectively; $P>0.05$), but was significantly shorter than the HAB in 8 patients with a prolongation in the AAB and HAB during the 2:1 HH' block (the HA interval during 1:1 AV conduction versus the HAB: 51±18 versus 62±14 ms, respectively; $P<0.05$). These findings supported the hypothesis that the 2:1 AV block during typical AVNRT was a consequence of a rate-dependent block around the lower turnaround point, and the prolongation in the HAB and AAB was derived from the conduction delay around the lower turnaround point associated with a 2:1 block just below the lower turnaround point.

3.3 Presumed sites of the 2:1 AV block and the lower turnaround

From the observations in this study, the site of the 2:1 AV block during the typical AVNRT was presumably localized to the distal part of the AV node or AV node–His bundle junction in 4 patients with AH block (17%), proximal part of the His bundle in 16 patients with HH' block (66%; Fig. 7), and distal His bundle or below it in 4 patients with HV block (17%). The lower turnaround point of the reentrant circuit was localized to the distal part of the AV node or AV node–His bundle junction in 4 patients with AH block (17%), and proximal part of the His bundle in

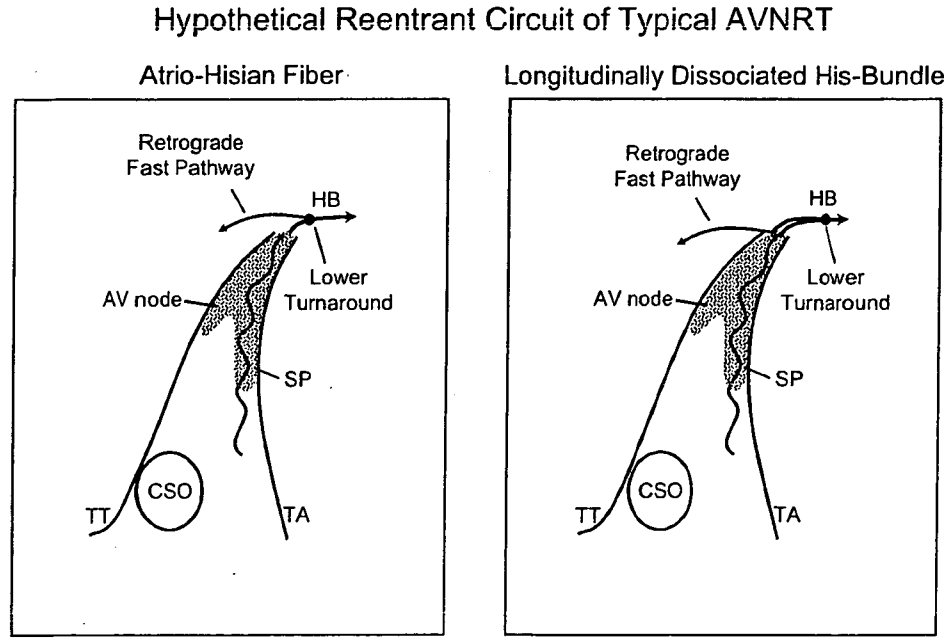


Fig. 7 Schematic representations of the hypothetical reentrant circuits of the typical AVNRT with the intra-Hisian location of the lower turnaround point. *Left*, reentrant circuit incorporating an atrio-Hisian fiber as the retrograde fast pathway. *Right*, reentrant circuit incorporating a longitudinally dissociated His bundle. See the text for details. *CSO* represents the ostium of the coronary sinus; *HB* His bundle; *SP* slow pathway; *TA* tricuspid annulus; and *TT* tendon of Todaro

8 patients with HH' block (33%). In 8 other patients with HH' block and 4 patients with HV block (50%), although the precise localization of the lower turnaround point was not feasible to determine from only the observations in this study, the lower turnaround point of the reentrant circuit was presumably localized to the AV node, AV node–His bundle junction, or proximal His bundle.

4 Discussion

4.1 Major findings

The present study showed that the site of the 2:1 AV block during the typical AVNRT was located in the His bundle or below in 83%, and the lower turnaround point of the reentrant circuit was located within the His bundle in at least 33% of the typical AVNRT cases exhibiting the 2:1 AV block during the tachycardia. Therefore, the proximal part of the His bundle might be involved in the reentrant circuit in at least one-third of the typical AVNRT cases exhibiting the 2:1 AV block.

4.2 Site of the 2:1 AV Block during typical atrioventricular nodal reentrant tachycardia

Previous reports [1–4, 17–20] have indicated that 2:1 AV block during AVNRT occurred either within the AV node, between the AV node and His bundle, within the His bundle or below. In the previous reports [1–4, 17–20] and this report, the localization of the exact site of the 2:1 AV block depended mainly on the evaluation of the His bundle potential in the blocked beats. However, Man et al. [3] reported that even without the His bundle potential in the blocked beats, the 2:1 AV block during typical AVNRT was due to functional infra-nodal block, because no conversion from 2:1 to 1:1 AV conduction was observed in response to the atropine administration. They concluded that most of the 2:1 AV block during typical AVNRT was due to functional infra-nodal block. In the present study, although not evaluated pharmacologically, the site of the 2:1 AV block was presumably localized to the His bundle or below it in 83% of the patients determined by evaluating the His bundle potential in the blocked beats, which was consistent with the results from the previous studies [3, 4].

4.3 Site of the lower turnaround point in typical atrioventricular nodal reentrant tachycardia

The site of the lower turnaround point of the reentrant circuit in typical AVNRT has been controversial [5–12, 21–25]. The present study showed that in at least 33% of typical AVNRT cases with 2:1 AV block, the lower turnaround point was located within the His bundle and the proximal part of the His bundle was involved in the reentrant circuit. Both the earlier [8–12] and recent studies [5–7, 21–23] also pointed out the possibility that the lower turnaround point of typical AVNRT was located within the His bundle and therefore the proximal part of the His bundle was involved in the reentrant circuit. The observations supporting the intra-Hisian location of the lower turnaround point included (1) the HA interval during ventricular pacing at the tachycardia rate was shorter than that during tachycardia [5–7]; (2) the presence of a retrograde fast pathway with a non-decremental property and resistance to adenosine, adenosine triphosphate or verapamil, suggested an atrio-Hisian fiber [5, 8–12, 26–29]; (3) the variation in the HA interval during typical AVNRT was simultaneous with the occurrence of HV block or bundle branch block [21, 22]; and (4) the tachycardia terminated with simultaneous HA and HV blocks [23]. Therefore, it is likely that in at least some patients, the lower turnaround point may be located within the His bundle, and the proximal part of the His bundle may be involved in the reentrant circuit of the typical AVNRT.

In the present study, the lower turnaround point was localized to the distal part of the AV node or AV node–His bundle junction in four patients with AH block (17%) and proximal part of the His bundle in eight patients with HH' block (33%), while in eight other patients with HH' block and four patients with HV block (50%), the precise localization of the lower turnaround point was not feasible to determine from only the observations in this study. In the latter 12 patients, the lower turnaround point of the reentrant circuit could be in the AV node, AV node–His bundle junction, or proximal His bundle. Those findings suggested that the lower turnaround point may be heterogeneously distributed around the AV node and proximal His bundle region in slow–fast AVNRT cases. In the 4 patients with HV block, 2:1 AV block did not have any influence on the tachycardia timing intervals; this finding could be interpreted to suggest that the lower turnaround point would not be located far distally at the distal His bundle or below in slow–fast AVNRT cases.

4.4 Effects of the 2:1 AV block during typical atrioventricular nodal reentrant tachycardia

As far as we know, only one study [20] has been reported in the literature evaluating the effects of 2:1 AV block on typical AVNRT. Lee et al. [20] reported that the AAB was longer than the AAC in 21 (81%) of 26 patients with 2:1 AV block during AVNRT. In contrast to our results, they found that the prolongation in the AAB was a consequence of the prolongation in the AHB with an invariable HAB, and they speculated that this phenomenon was caused by the

atrial stretch as a result of the ventricular contraction, or the phasic changes in the vagal tone caused by the blood pressure alternans during 2:1 AV conduction. Although no plausible explanation for these inconsistent results between the studies was available, the discrepancies might come from the relatively small sample sizes in both studies, different manners of measuring the timing intervals, or the relatively small changes in the AAB, AHB and HAB.

In the present study, the prolongations in the HAB and AAB observed in 11 patients (46%) indicated that 2:1 AV block occurred just below the lower turnaround point of the reentrant circuit and the transient conduction disturbance around the lower turnaround point gave rise to both 2:1 AV block below the lower turnaround point and a conduction delay at and/or just above the lower turnaround point. On the other hand, among 13 patients (54%) without any influence of the 2:1 AV block, the site of the 2:1 AV block was estimated to be located far distally from the lower turnaround point. Therefore, whether or not the 2:1 AV block during typical AVNRT influenced the AVNRT would probably be determined by the positional relationship between the lower turnaround point and the site of the 2:1 AV block.

4.5 Hypothetical models for the reentrant circuit with an Intra-Hisian location of the lower turnaround point

There could be at least two hypothetical explanations for the intra-Hisian location of the lower turnaround point (Fig. 7). The first one could be that the retrograde fast pathway consisted of a concealed atrio-Hisian fiber [30, 31] that originated from the proximal His bundle (Fig. 7, left) [5, 9–13, 32, 33]. The second one could be that there was a functional and longitudinal dissociation of the His bundle into two parts; one for the anterograde and the other for retrograde conduction during the tachycardia (Fig. 7, right) [22]. From the observations obtained from the present study, both hypotheses would be possible; however, the absence of double His bundle potentials during the tachycardia [34] would prefer the former explanation. The participation of a concealed atrio-Hisian fiber as a retrograde fast pathway has been reported in the literature [5, 9–13, 32, 33], and is compatible with the observations in this study.

4.6 Study limitations

This study had several limitations. The number of the patients included in the present study might be too small to convincingly prove our hypothesis. The determination of the exact site of the 2:1 AV block only by the evaluation of the His bundle potential in the blocked beats might be difficult. It might not be possible to record a very small His bundle potential from a conventional electrode catheter during 2:1 intra-Hisian block. Hence, even in those with no discernible His bundle potentials in the blocked beats during the 2:1 AV block, the intra Hisian block could not be definitively ruled out. Variations in the amplitudes of the recorded His bundle potentials during the 2:1 AV block might possibly be due to the catheter instability during the AVNRT with 2:1 AV block. The theoretical possibility that the His bundle potentials with a very low amplitude were generated from the distal AV node cannot be definitively ruled out. In the present study, a pharmacological assessment using drugs such as atropine was not performed to test if the 2:1 AV conduction converted to 1:1 AV conduction. The changes in the AAB and HAB during the 2:1 AV block were so small that only a margin of measurement error might have led to different results. The possibility that the prolongations in the AAB and HAB in only the blocked beats during the 2:1 AV block were derived from the beat-to-beat alternations in the conduction time over the retrograde fast pathway cannot be completely excluded. However, the invariable AH interval during the 2:1 AV block (AHC=AHB) with distinct prolongations in the AAB and HAB would argue against this possibility. Furthermore, the prolongation in the AAB and HAB during the 2:1 AV block completely disappeared as soon as the 1:1 AV conduction resumed after a subtle prolongation in the AA interval (Fig. 6), which suggested that the prolongations in the AAB and HAB were strongly related to the occurrence of the 2:1 AV block. The observation that the HA interval during the 1:1 AV conduction was similar to the HAC during the 2:1 AV block would also indicate that the prolongation in the HAB was strongly related to the 2:1 AV block. Nevertheless, the influence of the atrial stretch as a result of the ventricular contraction [35] and phasic changes in the vagal tone caused by the blood pressure alternans during the 2:1 AV conduction [36] on the changes in the timing intervals during the typical AVNRT with 2:1 AV block cannot be definitively excluded from the possible mechanisms.

5 Conclusion

The site of the 2:1 AV block during the tachycardia was located at the His bundle or below in 83% of the typical AVNRT cases with 2:1 AV block. The 2:1 AV block during the tachycardia prolonged the HA and/or AA intervals in the blocked beats in 11 patients (46%) of the typical AVNRT cases with 2:1 AV block. Similar prolongations in the HA and AA intervals in the blocked beats in eight patients (33%) with intra-Hisian block suggested that the lower turnaround point was located within the His bundle and the proximal part of the His bundle was involved in the reentrant circuit in at least one-third of the typical AVNRT cases with 2:1 AV block.

References

1. Schmitt, C., Miller, J. M., & Josephson, M. E. (1988). Atrioventricular nodal supraventricular tachycardia with 2:1 block above the bundle of His. *Pacing Clinical Electrophysiology, 11*, 1018–1023.
2. Wellens, H. J., Wesdorp, J. C., Duren, D. R., & Lie, K. I. (1976). Second degree block during reciprocal atrioventricular nodal tachycardia. *Circulation, 53*, 595–599.
3. Man, K. C., Brinkman, K., Bogun, F., Knight, B., Bahu, M., Weiss, R., et al. (1996). 2:1 atrioventricular block during atrioventricular node reentrant tachycardia. *Journal of the American College of Cardiology, 28*, 1770–1774.
4. Lee, S. H., Tai, C. T., Chiang, C. E., Yu, W. C., Cheng, J. J., Ding, Y. A., et al. (2003). Spontaneous transition of 2:1 atrioventricular block to 1:1 atrioventricular conduction during atrioventricular nodal reentrant tachycardia: evidence supporting the intra-Hisian or infra-Hisian area as the site of block. *Journal of Cardiovascular Electrophysiology, 14*, 1337–1341.
5. Otomo, K., Suyama, K., Okamura, H., Noda, T., Satomi, K., Shimizu, W., et al. (2007). Participation of a concealed atriohisian tract in the reentrant circuit of the slow–fast type atrioventricular nodal reentrant tachycardia. *Heart Rhythm, 4*, 703–710.
6. Li, Y. G., Bender, B., Bogun, F., Gronefeld, G., & Hohnloser, S. H. (2000). Location of the lower turnaround point in typical AV nodal reentrant tachycardia: a quantitative model. *Journal of Cardiovascular Electrophysiology, 11*, 34–40.
7. Heidbuchel, H., Ector, H., & Van de Werf, F. (1998). Prospective evaluation of the length of the lower common pathway in the differential diagnosis of various forms of AV nodal reentrant tachycardia. *Pacing Clinical Electrophysiology, 21*, 209–216.
8. Gomes, J. A., Dhatt, M. S., Damato, A. N., Akhtar, M., & Holder, C. A. (1979). Incidence, determinants and significance of fixed retrograde conduction in the region of the atrioventricular node. Evidence for retrograde atrioventricular nodal bypass tracts. *American Journal of Cardiology, 44*, 1089–1098.
9. Spurrell, R. A., Krikler, D. M., & Sowton, E. (1974). Concealed bypasses of the atrioventricular mode in patients with paroxysmal supraventricular tachycardia revealed by intracardiac electrical stimulation and verapamil. *American Journal of Cardiology, 33*, 590–595.
10. Kerr, C. R., Benson, D. W., & Gallagher, J. J. (1983). Role of specialized conducting fibers in the genesis of "AV nodal" reentry tachycardia. *Pacing Clinical Electrophysiology, 6*, 171–184.
11. Narula, O. S., ed. (1979). Paroxysmal supraventricular tachycardia due to reciprocation via concealed accessory pathways. Cardiac Arrhythmias. Electrophysiology. Diagnosis and Management. Baltimore: Williams & Wilkins. 318–546.
12. Narula, O. S. (1974). Retrograde pre-excitation. Comparison of antegrade and retrograde conduction intervals in man. *Circulation, 50*, 1129–1143.
13. Josephson, M. E., ed. (2002). Supraventricular tachycardias. Clinical Cardiac Electrophysiology. Techniques and Interpretations. 3rd ed. Philadelphia: Lippincott Williams & Wilkins. 168–271.
14. Hirao, K., Otomo, K., Wang, X., Beckman, K. J., McClelland, J. H., Widman, L., et al. (1996). A new method for differentiating retrograde conduction over an accessory AV pathway from conduction over the AV node. *Circulation, 94*, 1027–1035.
15. Knight, B. P., Zivin, A., Souza, J., Flemming, M., Pelosi, F., Goyal, R., et al. (1999). A technique for the rapid diagnosis of atrial tachycardia in the electrophysiology laboratory. *Journal of the American College of Cardiology, 33*, 775–781.
16. Heidbuchel, H., & Jackman, W. M. (2004). Characterization of subforms of AV nodal reentrant tachycardia. *Europace, 6*, 316–329.
17. Willems, S., Shenasa, M., Borggrefe, M., Hindricks, G., Chen, X., Rotman, B., et al. (1993). Atrioventricular nodal reentry tachycardia: electrophysiologic comparisons in patients with and without 2:1 infra-His block. *Clinical Cardiology, 16*, 883–888.
18. Miles, W. M., Hubbard, J. E., Zipes, D. P., & Klein, L. S. (1994). Elimination of AV nodal reentrant tachycardia with 2:1 VA block by posteroseptal ablation. *Journal of Cardiovascular Electrophysiology, 5*, 510–516.
19. Kantoch, M. J., & Kimber, S. K. (1996). Narrow QRS tachycardia with atrioventricular block. *Pacing Clinical Electrophysiology, 19*, 1386–1387.
20. Lee, S. H., Chen, S. A., Tai, C. T., Chiang, C. E., Wen, Z. C., Ueng, K. C., et al. (1997). Electrophysiologic characteristics and radiofrequency catheter ablation in atrioventricular node reentrant tachycardia with second-degree atrioventricular block. *Journal of Cardiovascular Electrophysiology, 8*, 502–511.
21. Lee, D. T., Tai, C. T., Lin, Y. J., Lai, W. T., & Chen, S. A. (2004). Variation of HA intervals in atrioventricular nodal reentrant tachycardia with atrioventricular block: What is the machanism? *Journal of Cardiovascular Electrophysiology, 15*, 1103–1104.
22. Yagi, T., Yang, Y., Keung, E. C., Collins, K. K., & Scheinman, M. M. (2003). Significance of bundle branch block during atrioventricular nodal reentrant tachycardia. *American Journal of Cardiology, 91*, 1184–1189.
23. Lin, Y. J., Tai, C. T., & Chen, S. A. (2003). Unusual phenomenon of spontaneous termination of atrioventricular nodal reentrant tachycardia with 2:1 atrioventricular block. *Journal of Cardiovascular Electrophysiology, 14*, 437–438.
24. Miller, J. M., Rosenthal, M. E., Vassallo, J. A., & Josephson, M. E. (1987). Atrioventricular nodal reentrant tachycardia: studies on upper and lower 'common pathways'. *Circulation, 75*, 930–940.
25. Josephson, M. E., & Miller, J. M. (1993). Atrioventricular nodal reentry: evidence supporting an intranodal location. *Pacin Clin Electrophysiol, 16*, 599–614.
26. Fishberger, S. B., Mehta, D., Rossi, A. F., Langan, M. N., Marx, S. O., & Gomes, J. A. (1998). Variable effects of adenosine on retrograde conduction in patients with atrioventricular nodal reentry tachycardia. *Pacing Clinical Electrophysiology, 2*, 1254–1257.
27. Mewis, C., Kuhlkamp, V., Mermi, J., Bosch, R. F., & Seipel, L. (2000). High variability of retrograde fast pathway sensitivity to adenosine. *Clinical Cardiology, 23*, 576–578.
28. Souza, J. J., Zivin, A., Flemming, M., Pelosi, F., Oral, H., Knight, B. P., et al. (1998). Differential effect of adenosine on anterograde and retrograde fast pathway conduction in patients with atrioventricular nodal reentrant tachycardia. *Journal of Cardiovascular Electrophysiology, 9*, 820–824.
29. Miyata, A., Kobayashi, Y., Jinbo, Y., Chiyoda, K., Nakagawa, H., Tanno, K., et al. (1997). Effects of adenosine triphosphate on ventriculoatrial conduction-usefulness and problems in assessment of catheter ablation of accessory pathways. *Japanese Circulation Journal, 61*, 323–330.
30. Brechenmacher, C. (1975). Atrio-His bundle tracts. *British Heart Journal, 37*, 853–855.
31. Brechenmacher, C., Laham, J., Iris, L., Gerbaux, A., & Lenegre, J. (1974). Histological study of abnormal conduction pathways in the Wolff-Parkinson-White syndrome and Lown-Ganong-Levine syndrome. *Archives des maladies du coeur et des vaisseaux, 67*, 507–519.
32. Patterson, E., & Scherlag, B. J. (2004). Fast pathway–His bundle connections in the rabbit heart. *Journal of Interventional Cardiac Electrophysiology, 10*, 121–129.

33. Patterson, E., & Scherlag, B. (2002). Anatomic and functional fast atrioventricular conduction pathway. *Journal of Cardiovascular Electrophysiology, 13*, 945–949.
34. Morady, F. (1996). Ventriculoatrial block during a narrow-QRS tachycardia: what is the mechanism? -IV. *Journal of Cardiovascular Electrophysiology, 7*, 174–177.
35. Solti, F., Vecsey, T., Kekesi, V., & Juhasz-Nagy, A. (1989). The effect of atrial dilatation on the genesis of atrial arrhythmias. *Cardiovascular Research, 23*, 882–886.
36. Stambler, B. S., & Ellenbogen, K. A. (1996). Elucidating the mechanisms of atrial flutter cycle length variability using power spectral analysis techniques. *Circulation, 94*, 2515–2525.

Comparison of Long-Term Follow-Up of Electrocardiographic Features in Brugada Syndrome Between the SCN5A-Positive Probands and the SCN5A-Negative Probands

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To investigate changes of electrocardiographic parameters with aging and their relation to the presence of SCN5A mutation in probands with Brugada syndrome (BS), we measured several electrocardiographic parameters prospectively during long-term follow-up (10 ± 5 years) in 8 BS probands with SCN5A mutation (SCN5A-positive group, all men; age 46 ± 10 years) and 36 BS probands without SCN5A mutation (SCN5A-negative group, all men; age 46 ± 13 years). Throughout the follow-up period, depolarization parameters, such as P-wave (lead II), QRS (leads II, V_2, V_5), S-wave durations (leads II, V_5), and PQ interval (leads II) were all significantly longer and S-wave amplitude (II, V_5) was significantly deeper in the SCN5A-positive group than in the SCN5A-negative group. The SCN5A-positive group showed a significantly longer corrected QT interval (lead V_2) and higher ST amplitude (lead V_2) than those in the SCN5A-negative group. The depolarization parameters increased with aging during the follow-up period in both groups; however, the PQ interval (lead II) and QRS duration (lead V_2) were prolonged more prominently and the QRS axis deviated more to the left with aging in the SCN5A-positive group than in the SCN5A-negative group. In conclusion, conduction slowing was more marked and more progressively accentuated in Brugada probands with SCN5A mutation than in those without SCN5A mutation. (Am J Cardiol 2007; 100:649–655)

Brugada syndrome (BS) is characterized by a ST-segment elevation in the right precordial leads V_1 to V_3 and is associated with sudden cardiac death (SCD) secondary to a rapid polymorphic ventricular tachycardia (VT) or ventricular fibrillation (VF).[1–9] It has been suggested that a transient outward current-mediated action potential notch and a loss of action potential dome in the epicardium of the right ventricular outflow tract (RVOT) give rise to a transmural voltage gradient, resulting in ST-segment elevation in the right precordial lead in BS.[8] Conversely, the SCN5A gene encoding the cardiac sodium channel has been reported to be linked to BS,[10] and mild conduction abnormalities and QRS prolongation have been described.[5,11] Smits et al[12] have compared these electrocardiographic parameters between SCN5A mutation carriers and those who do not carry the mutation. Probst et al[13] meticulously studied aging-associated electrocardiographic parameters in SCN5A-related BS.[13] However, progressive changes of the depolarization and repolarization parameters on the electrocardiogram (ECG) with aging during long-term follow-up in relation to the SCN5A mutation have not been fully evaluated. In the present study, we prospectively measured several electrocardiographic parameters during long-term follow-up periods and compared them between patients with BS with and without SCN5A mutation.

Methods

The study population consisted of 44 probands with BS admitted to the National Cardiovascular Center in Suita, Japan, due to history of aborted SCD, syncope, or evaluation of electrocardiographic abnormality, who could be prospectively followed up for >5 years (average 10 ± 5 years) at regular outpatient clinics in our hospital. All probands were men, and their age on admission (i.e., at early period) ranged from 20 to 72 years (mean 46 ± 12 years). BS was diagnosed when a type 1 coved-type ST-segment elevation (≥0.2 mV at J point) was observed in >1 of the right precordial leads (V_1 to V_3) in the presence or absence of a sodium channel blocker in conjunction with 1 of the following: (1) documented VF or polymorphic VT, (2) a family history of SCD at <45 years of age, type 1 ECG in family members, (3) inducibility of VF or polymorphic VT with programmed electrical stimulation, and (4) history of aborted cardiac arrest with or without documentation of VF,

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Table 1
SCN5A mutations, common variants and promotor haplotype

Coding*	No. of Patients	Type	Coding	No. of Patients	Type
	SCN5A Positive Group (n = 8)			SCN5A Negative Group (n = 36)	
Mutation					
A735V	1	Missense			
P1719fsX1786	1	Frameshift			
L276Q	1	Missense			
V1764fsX1786	1	Frameshift			
L136P	1	Missense			
R367H	2	Missense			
T1709M	1	Missense			
Common variant					
H558R	1	Missense	H558R	4	Missense
Promotor haplotype					
AA	5		AA	12	
AB	2		AB	4	
BB	0		BB	1	

* The numbers and letters refer to the amino acid coding of the mutant channel protein.
AA = haplotype A (common alleles) homozygotes; AB = haplotype A/haplotype B (minor alleles) heterozygotes; BB = haplotype B homozygotes. See detail in Bezzina et al.[14]

syncopal episodes of unknown origin, or nocturnal agonal respiration.[4]

We divided the 44 Brugada probands into 2 groups according to the presence or absence of an SCN5A coding region mutation: SCN5A-positive group (n = 8) and SCN5A-negative group (n = 36).

The standard 12-lead ECGs were recorded at least every 6 months prospectively at regular outpatient clinics with a paper speed of 25 mm/s and an amplitude of 10 mm/mV. The ECGs were magnified to 150%, and several electrocardiographic parameters were measured manually by an investigator (MY) blinded to clinical and genetic information. As depolarization parameters, P-wave duration (lead II), PQ interval (lead II), QRS duration (leads II, V_2, and V_5), S-wave duration and amplitude (leads II, V_5), and QRS axis were measured. Conversely, corrected QT interval (QTc, leads II, V_2, and V_5), corrected JT interval (JTc, leads II, V_2, and V_5), and ST amplitude at the J point and 40 ms after theJ point (STJ and STJ40, lead V_2) were measured as repolarization parameters. The absolute values of these parameters and the change of each parameter between early and late periods were compared between the 8 probands in the SCN5A-positive group and the 36 in the SCN5A-negative group.

In all patients, we screened SCN5A mutation in all 28 exons of SCN5A gene by a direct sequencing method using an ABI 3700 system (Applied Biosystems, Foster City, California). An SCN5A mutation was defined when the mutation was not identified in any of the 100 control subjects. We also screened the SCN5A promoter haplotype, which we have recently identified in an Asian population,[14] in 7 recent SCN5A-positive probands and 17 SCN5A-negative probands.

Numeric values were expressed as means ± SD. Comparisons of each electrocardiographic parameter between the SCN5A-positive group and the SCN5A-negative group and between the early and the late periods were made using 2-way repeated-measures analysis of variance (ANOVA) followed by the Scheffe multiple-comparison test. Comparisons of changes in each parameter between the SCN5A-positive group and the SCN5A-negative group were made using 1-way ANOVA followed by Scheffe test. Comparisons of the clinical, electrophysiologic, and follow-up data between the SCN5A-positive group and the SCN5A-negative group were made using chi-square test or 1-way ANOVA followed by Scheffe test. A p value <0.05 was considered significant.

Results

The SCN5A mutations, which were identified at a coding region in the SCN5A-positive group, are shown in Table 1. Five missense mutations and 2 frameshift mutations were identified. A missense mutation, R367H, was identified in 2 unrelated Brugada probands. The common variant and SCN5A promoter haplotype[14] in both groups are also shown in Table 1. There were no significant differences in the frequency of the common variant and the promoter haplotype between the 2 groups.

The comparison of the clinical and electrophysiologic characteristics between the 8 SCN5A-positive probands and the 36 SCN5A-negative probands are shown in Table 2. There were no significant differences in the age on admission, when the clinical diagnosis of BS was made, between the 2 groups. No significant differences were observed in the incidence of spontaneous type 1 ECG, documented VF until the early period, family history of SCD, implantation of implantable cardioverter defibrillator, complete right bundle branch block (RBBB) at the early period and the latest follow-up period (i.e., late period), and late potentials. The HV interval during the electrophysiologic study was significantly longer in the SCN5A-positive group than in the SCN5A-negative group. There were no significant differ-

Table 2
Clinical and electrophysiologic characteristics and follow-up

Characteristic	SCN5A-Positive Group (n = 8)	SCN5A-Negative Group (n = 36)	p Value
Clinical characteristics			
Age on admission (yrs)	46 ± 10	46 ± 13	0.938
Spontaneous type 1 ECG	6 (75%)	25 (69%)	0.755
Documented VF until early period	2 (25%)	17 (47%)	0.251
Family history of SCD	3 (38%)	4 (11%)	0.065
ICD implantation	8 (100%)	26 (72%)	0.090
Complete RBBB at early period	1 (13%)	2 (5%)	0.481
Complete RBBB at late period	1 (13%)	6 (17%)	0.771
Late potentials	7/7 (100%)	24/33 (73%)	0.117
Electrophysiologic characteristics			
Induction of VF	5/8 (63%)	25/33 (76%)	0.658
Mode (triple/double/single)	1/3/1	12/11/2	–
HV interval (ms)	65±5 (n=7)	41±8 (n=27)	<0.001
Follow-up			
Follow-up period (yrs)	10 ± 5	10 ± 4	0.993
Arrhythmic events during follow-up periods	4/8 (50%)	12/36 (33%)	0.375
Previous VF	2/2 (100%)	8/17 (47%)	0.156
No previous VF	2/6 (33%)	4/19 (21%)	0.539

EPS = electrophysiological study; HV = His-ventricular interval; ICD = implantable cardioverter-defibrillator.

ences in the frequency and mode of VF induction between the 2 groups.

Figure 1 illustrates the standard 12-lead ECGs at early and late periods during the follow-up period in representative patients with BS in the SCN5A-positive group (Figure 1) and the SCN5A-negative group. Table 3 shows composite data of the electrocardiographic parameters at the early and late periods in the 8 SCN5A-positive probands and 36 SCN5A-negative probands during the follow-up period.

As depolarization parameters, the P-wave duration (lead II), PQ interval (lead II), and QRS duration (lead II) significantly increased with aging from early to late periods in both groups and were all significantly longer in the SCN5A-positive group than in the SCN5A-negative group at both early and late periods. The QRS duration (lead V_2) in the SCN5A-positive group and the S-wave duration (leads II and V_5) in the SCN5A-negative group significantly increased with aging. The QRS duration (leads V_2 and V_5) and the S-wave duration (leads II and V_5) were significantly longer, and the S-wave amplitude (leads II and V_5) was significantly deeper in the SCN5A-positive group at early and late periods. The QRS axis was not different between the 2 groups at the early period; however, it was significantly smaller (i.e., deviated to the left) at the late period in the SCN5A-positive group.

As a repolarization parameter, the corrected QT interval (lead V_2) was significantly prolonged from the early period to the late period in the SCN5A-positive group, and was significantly longer in the SCN5A-positive group than in the SCN5A-negative group at the early and late periods. However, the QTc intervals (leads II and V_5) did not change from the early period to the late period in both groups and were not different between groups at the early and late periods. Conversely, no JTc intervals (leads II, V_2, and V_5) changed from the early period to the late period in both groups, and the JTc interval (lead V_2) at the late period was significantly longer in the SCN5A-positive group. The STJ amplitude (lead V_2) and STJ40 amplitude (lead V_2) did not change throughout the follow-up period in both groups, but were significantly greater in the SCN5A-positive group than in the SCN5A-negative group at the early and late periods. Even if we eliminated probands with BS with complete RBBB (1 SCN5A-positive proband and 2 SCN5A-negative probands at the early period, 1 SCN5A-positive proband and 6 SCN5A-negative probands at the late period), the main results and statistical differences were not significant.

Table 4 depicts comparison of the change of the electrocardiographic parameters from early to late periods between the SCN5A-positive group and the SCN5A-negative group.

The changes in PQ interval (lead II) and QRS duration (lead V_2) were significantly longer in the SCN5A-positive group than in the SCN5A-negative group. The change in QRS axis was greater (i.e., deviated more to the left) in the SCN5A-positive group than in the SCN5A-negative group.

There were no significant differences in the duration of follow-up period and the incidence of arrhythmic events during the follow-up period between the 2 groups (Table 2). Because a history of documented VF (until the early period) was proven to be the strongest predictor for subsequent arrhythmic events, arrhythmic events were compared between the 2 groups separately in probands with previous VF and those without previous VF, but no significant differences were observed (Table 2).

Discussion

The present study includes what is, to our knowledge, the longest follow-up of changes of electrocardiographic parameters in SCN5A-positive probands and SCN5A-negative probands with BS.

Mild conduction abnormalities, such as widening of the P wave, prolongation of QRS duration and PQ and HV intervals, and higher incidence of RBBB, have been described in patients with BS, especially those with

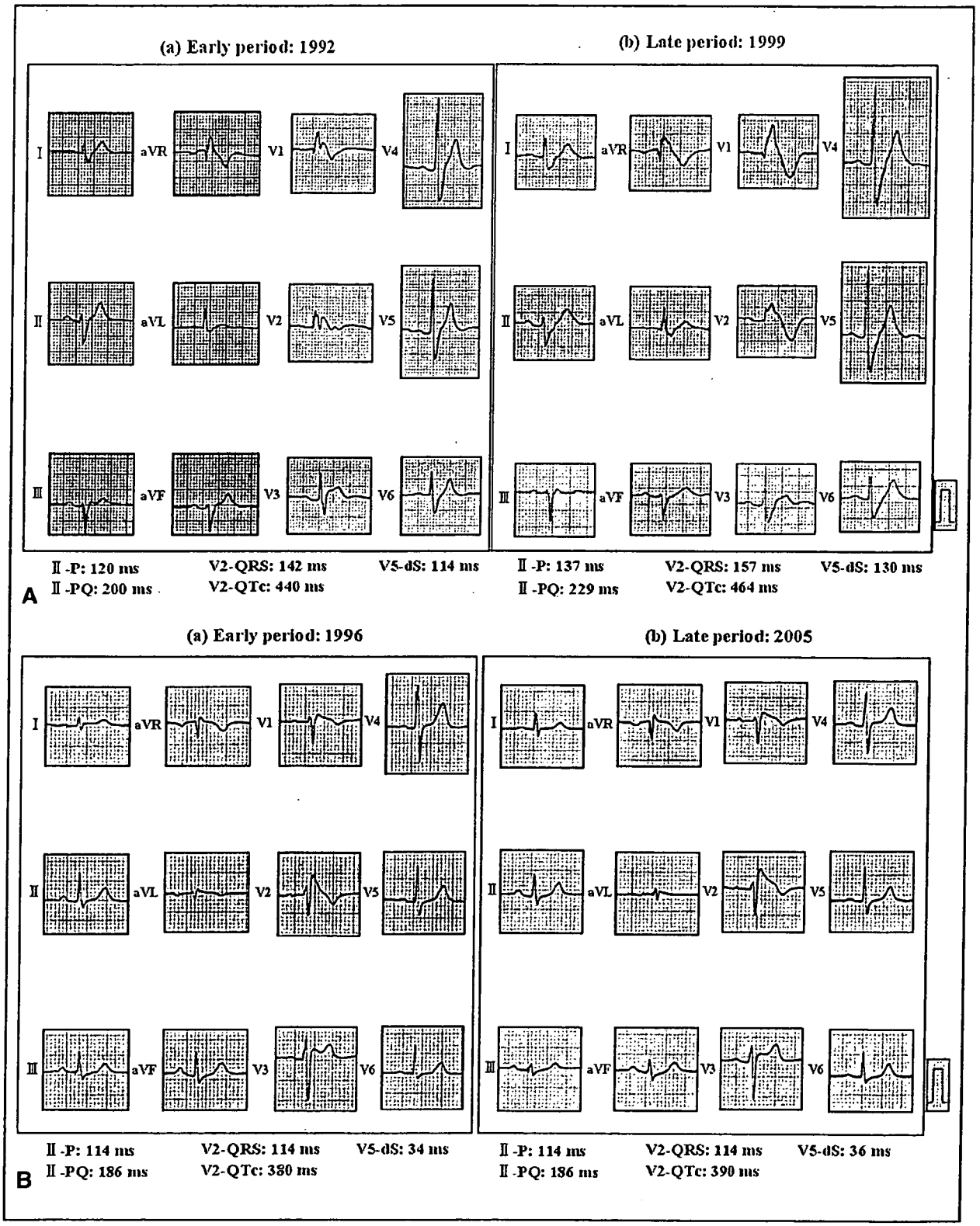

Figure 1. Standard 12-lead ECG at early and late periods during follow-up in representative cases of BS. *A*, in an *SCN5A*-positive proband (follow-up period, 7 years), the P-wave (lead II), QRS (lead V_2), and S-wave (lead V_5) durations and PQ interval (lead II) were prolonged even at the early period (47 years of age, *a*). The S-wave amplitude (lead V_5) was also deep, and the QRS axis deviated to the left. The QTc interval (lead V_2) was borderline prolonged. At the late period (*b*), all these parameters further increased. *B*, in an SCN5A-negative proband (follow-up period, 9 years), the P-wave (lead II), QRS (lead V_2), and S-wave (lead V_5) durations, PQ interval (lead II), and QTc interval (lead V_2) were less prolonged compared with those in an SCN5A-positive proband at the early period (51 years of age, *a*). At the late period (*b*), these parameters did not change significantly. V_5-dS = S-wave duration in lead V_5.

Table 3
Electrocardiographic parameters during follow-up period

ECG Parameter (leads)	Early Period			Late Period		
	SCN5A-Positive Group (n = 8)	SCN5A-Negative Group (n = 36)	p Value	SCN5A-Positive Group (n = 8)	SCN5A-Negative Group (n = 36)	p Value
Heart rate (beats/min)	66 ± 11	64 ± 10	0.924	60 ± 6	67 ± 12	0.194
P-wave duration (II) (ms)	137 ± 21	110 ± 12	<0.001	155 ± 19†	119 ± 16†	<0.001
PQ interval (II) (ms)	227 ± 31	179 ± 18	<0.001	257 ± 22*	190 ± 22†	<0.001
QRS duration (II) (ms)	125 ± 22	102 ± 18	<0.001	142 ± 41‡	111 ± 19‡	<0.001
QRS duration (V_2) (ms)	135 ± 15	110 ± 13	<0.001	157 ± 28*	115 ± 16	<0.001
QRS duration (V_5) (ms)	130 ± 28	101 ± 15	<0.001	147 ± 42	108 ± 17	<0.001
S-wave duration (II) (ms)	65 ± 38	35 ± 24	<0.001	77 ± 54	43 ± 26‡	<0.001
S-wave duration (V_5) (ms)	69 ± 40	37 ± 19	<0.001	78 ± 50	49 ± 17*	<0.001
S-wave amplitude (II) (mV)	0.37 ± 0.23	0.23 ± 0.24	0.005	0.43 ± 0.24	0.21 ± 0.17	<0.001
S-wave amplitude (V_5) (mV)	0.83 ± 0.47	0.34 ± 0.25	<0.001	0.88 ± 0.48	0.47 ± 0.27†	<0.001
QRS axis (°)	44 ± 81	49 ± 43	0.954	10 ± 76‡	43 ± 41	0.001
QTc interval (II) (ms)	409 ± 37	396 ± 28	0.535	432 ± 40	410 ± 34	0.164
QTc interval (V_2) (ms)	427 ± 51	392 ± 37	0.038	471 ± 38‡	405 ± 38	<0.001
QTc interval (V_5) (ms)	401 ± 43	389 ± 29	0.593	408 ± 39	398 ± 36	0.746
JTc interval (II) (ms)	279 ± 32	290 ± 30	0.554	292 ± 44	293 ± 34	0.100
JTc interval (V_2) (ms)	285 ± 39	279 ± 35	0.960	316 ± 42	283 ± 38	0.044
JTc interval (V_5) (ms)	265 ± 26	286 ± 30	0.108	262 ± 42	283 ± 32	0.105
STJ amplitude (V_2) (mV)	0.42 ± 0.19	0.29 ± 0.13	0.014	0.37 ± 0.23	0.24 ± 0.17	0.011
STJ40 amplitude (V_2) (mV)	0.38 ± 0.14	0.23 ± 0.12	<0.001	0.34 ± 0.17	0.21 ± 0.15	0.006

Data are presented as means ± SD.
* p <0.001 versus early period.
† p <0.01 versus early period.
‡ p <0.05 versus early period.
ECG = electrocardiographic; JTc = corrected JT; QTc = corrected QT; STJ amplitude = ST amplitude at J point; STJ 40 amplitude = ST amplitude 40 ms after J point.

Table 4
Comparison of the change of electrocardiographic parameters during follow-up

Change in ECG Parameter (leads)	SCN5A-Positive Group (n = 8)	SCN5A-Negative Group (n = 36)	p Value
Heart rate (beats/min)	−7 ± 10	3 ± 13	0.046
P-wave duration (II) (ms)	19 ± 12	9 ± 13	0.077
PQ interval (II) (ms)	30 ± 22	11 ± 14	0.004
QRS duration (II) (ms)	17 ± 22	8 ± 15	0.163
QRS duration (V_2) (ms)	22 ± 20	6 ± 11	0.003
QRS duration (V_5) (ms)	17 ± 29	8 ± 14	0.161
S-wave duration (II) (ms)	12 ± 17	8 ± 13	0.423
S-wave duration (V_5) (ms)	9 ± 15	12 ± 14	0.604
S-wave amplitude (II) (mV)	0.06 ± 0.10	−0.02 ± 0.14	0.152
S-wave amplitude (V_5) (mV)	0.05 ± 0.27	0.13 ± 0.18	0.331
QRS axis (°)	−34 ± 55	−6 ± 16	0.010
QTc interval (II) (ms)	22 ± 32	15 ± 34	0.562
QTc interval (V_2) (ms)	44 ± 49	13 ± 40	0.064
QTc interval (V_5) (ms)	6 ± 37	9 ± 30	0.845
JTc interval (II) (ms)	13 ± 27	3 ± 28	0.339
JTc interval (V_2) (ms)	31 ± 48	5 ± 38	0.094
JTc interval (V_5) (ms)	−3 ± 29	−3 ± 29	0.990
STJ amplitude (V_2) (mV)	−0.05 ± 0.18	−0.05 ± 0.12	0.949
STJ40 amplitude (V_2) (mV)	−0.04 ± 0.16	−0.02 ± 0.11	0.642

Abbreviations as in Table 3.

SCN5A mutation.[5,11] Smits et al[12] observed significantly longer PQ and HV intervals at baseline and a larger increase in PQ and QRS intervals after administration of sodium channel blockers in patients with BS with SCN5A mutations than in those without SCN5A mutations. Age-dependent variability in the conduction parameters was evidenced in SCN5A-positive patients with BS.[13,15] Moreover, this concept has been mechanistically investigated in vivo in heterozygous SCN5A mice, which showed progressive impairment with aging of atrial and