Correlation between Transient Hypotension and Exclusively Exercise-induced Symptoms of Two-to-One Atrioventricular Block

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Abstract:
A 62-year-old woman with activity-dependent two-to-one atrioventricular block (2:1AVB) and a normal left ventricular ejection fraction was referred to our department for the evaluation of exclusively exercise-induced marked symptoms. The treadmill test helped establish a clear correlation between 2:1AVB and symptoms. The test results demonstrated that exercise-induced marked symptoms were attributed to abrupt transient hypotension combined with relative bradycardia, probably due to increased diastolic mitral and tricuspid regurgitation because of 2:1AVB during moderate-to-heavy exercise. After pacemaker implantation for 2:1AVB, the symptoms and transient hypotension disappeared, and her exercise capacity improved.

Key words: two-to-one atrioventricular block, exclusively exercise-induced symptom, transient hypotension, normal left ventricular ejection fraction, diastolic mitral and tricuspid regurgitation, treadmill test

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Introduction

Exercise-induced second-degree atrioventricular (AV) blocks are rare. However, they can cause profound exercise intolerance (1, 2). Two-to-one atrioventricular block (2:1AVB) shows the lowest AV conduction rates among second-degree AV blocks, except for advanced AV block. This suggests that exercise-induced 2:1AVB, even with a normal left ventricular (LV) function, is rare and can cause profound exercise intolerance.

A 62-year-old woman with activity- and rate-dependent 2:1AVB and a normal LV function was referred to our hospital for the evaluation of exclusively exercise-induced marked symptoms. According to the current Japanese guidelines, if second AV block, including 2:1AVB, is accompanied by clearly correlated symptoms, pacemaker implantation (PMI) is recommended as a Class I indication; under the current American guidelines, however, it is considered reasonable as at least a Class IIa indication (3, 4).

However, 2:1AVB is sometimes activity-dependent or exercise-induced, and its symptoms are also exercise-induced but do not always occur in the setting of 2:1AVB. Therefore, it is difficult to establish a clear correlation between 2:1AVB and symptoms based on daily clinical practice using a 12-lead electrocardiogram (ECG) or Holter monitoring. Furthermore, there are very few reports concerning the detailed mechanism underlying exclusively exercise-induced symptoms of 2:1AVB with a normal LV function.

These issues raise the concern that exercise-induced serious symptoms may not be able to be resolved, even with PMI therapy, in 2:1AVB patients with changeable and transient symptoms. It is important to clearly correlate exercise-induced 2:1AVB with the changeable symptoms and consider the detailed mechanism underlying the transient symptoms that develop prior to PMI.

We herein report a case of activity-dependent 2:1AVB with exclusively exercise-induced marked symptoms due to

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Case Report

A 62-year-old woman was referred to our hospital for the evaluation of shortness of breath on effort and 2:1AVB. There was neither a significant personal nor family history. She had been treated with long-term 2.5 mg amlodipine for hypertension. One month prior to the referral, she developed shortness of breath and easy fatigability upon ascending stairs. Thereafter, she developed various marked symptoms. These symptoms included shortness of breath and tension in both shoulders throughout a brisk daily walk, dizziness and dimmed vision while walking around 1-kilometer distance, and fatigue after her daily walk. Her previous ECGs at annual health examinations had shown complete right bundle branch block (CRBBB) since nine years ago. A resting 12-lead ECG at a neighboring hospital showed a normal axis, CRBBB, first-degree AV block, and 2:1AVB at a sinus rate of about 100 beats/minute (Fig. 1A). She had no symptoms during 2:1AVB on the resting ECG.

A physical examination revealed no abnormal findings at the first visit to our hospital. Laboratory data that included C-reactive protein and high-sensitive cardiac troponin I were within normal ranges, except for the serum levels of total cholesterol [229 mg/dL; (128-219 mg/dL)] and brain natriuretic peptide [71.18 pg/mL; (<18.4 pg/mL)]. Although a chest X-ray film showed mild cardiomegaly with a cardiothoracic ratio of 53.0%, echocardiography during sinus rhythm revealed a left ventricular ejection fraction (LVEF) of 69% with no LV dilatation or any other abnormal echocardiographic findings that included wall thinning or thickness, focal area of akinesia, and aneurysm, suggesting cardiac sarcoidosis or other myocardial diseases.

Holter monitoring in daily activities demonstrated 90,913 of total heart beats during 22 hours and 2 minutes of recording, first-degree AV block, and two kinds of second-degree AV blocks: Wenckebach second-degree AV block and 2:1AVB (Fig. 1B-a, b). After starting 24-hour Holter monitoring, the sinus rate was at around 100 bpm and 2:1AVB continued in the daytime. The episodes of 2:1AVB that occurred during the daytime were rate- and activity-dependent. When the sinus rate increased to over 100 bpm during daily activities, the sinus rhythm changed transitionally to Wenckebach second-degree AV block and then to 2:1AVB. Conversely, when the sinus rate dropped below 100 bpm, 2:1AVB returned to Wenckebach second-degree AV block and then to sinus rhythm again. However, after 8:00 PM on the day Holter monitoring began, neither of the second-degree AV blocks developed again, even though the sinus rate transiently increased to about 110 bpm in the nighttime and up to 120 bpm in the next morning. She manifested no symptoms during the 2:1AVB through Holter monitoring as well.

We then conducted a modified Bruce protocol treadmill test to investigate her symptoms for a more advanced AV block or ischemic heart disease and examine the correlation between the symptoms and the ECG findings. When the sinus rate reached 107 bpm at 2 minutes and 30 seconds of exercise, Wenckebach second-degree AV block occurred (Fig. 2A-a). When the sinus rate went on to
Figure 2. Recording in leads V2 and V5 during the modified Bruce protocol treadmill test. ECGs A-a and b and ECGs B-a and b are continuous in each lead. Wenckebach second-degree AV block appeared during exercise and transitonally changed to 2:1AVB rate-dependently. First-degree AV block and CRBBB continued throughout the treadmill test. ECG: electrocardiogram, AV: atroventricular, 2:1AVB: two-to-one atrioventricular block, CRBBB: complete right bundle branch block

Figure 3. Time course of the BP and HR during the modified Bruce protocol treadmill test. As soon as Wenckebach second-degree AV block transitionally changed to 2:1AVB, abrupt hypotension and relative bradycardia appeared and continued to the endpoint. The exercise was terminated at the endpoint of 7 minutes and 42 seconds of exercise due to the reproduced symptoms of dizziness and shortness of breath

BP: blood pressure, HR: heart rate, min: minute, bpm: beats per minute, AV: atrioventricular, 2:1AVB: two-to-one atrioventricular block

Exceed 120 bpm at 4 minutes of exercise, it subsequently led to 2:1AVB (Fig. 2A-b), which continued until the endpoint of 7 minutes and 42 seconds of exercise due to the reproduced symptoms of dizziness and shortness of breath (Fig. 2B-a).

From the moment that the Wenckebach second-degree AV block occurred during exercise, the ventricular rate began to decrease (Fig. 3). When the sinus rate exceeded 120 bpm and 2:1AVB developed, the ventricular rate rapidly decreased to nearly 60 to 70 bpm and remained around the same rate until the endpoint. While the 2:1AVB was occurring, the systolic blood pressure (BP) also decreased to nearly 90 mmHg and remained around the same level. During the exercise-induced bradycardia and transient hypotension due to 2:1AVB, more marked symptoms than usually expected from 2:1AVB alone were reproduced simulta-
Ischemic heart disease might be considered in the differential diagnosis or as a comorbid disease in patients with exercise-induced AV block (4). Our patient, however, did not have a history of coronary heart disease, and her treadmill test did not reveal any axis deviation (5), significant ST-T change (5, 6), or typical anginal symptoms except for shortness of breath and dizziness (Fig. 4). Furthermore, multidetector-row computed tomography showed an Agatston score of 0 in all coronary arteries, and coronary computed tomography angiography revealed no significant stenosis in the three major coronary arteries.

The 2:1AVB during moderate-to-heavy exercise obviously correlated with marked symptoms and transient hypotension simultaneously. We thus implanted a DDD-mode pacemaker in this patient according to the PMI indication in the guidelines as well as from a hemodynamic viewpoint. The programed pacemaker parameters were as follows: pacing mode, DDD without rate-response mode; lower rate limit, 55 bpm; maximum tracking rate, 130 bpm; both paced and sensed atrioventricular interval ranges, 120-350 ms; postventricular atrial refractory period range, 240-270 ms, and 2:1AVB response rate, ≥167 bpm.

A re-examination of the modified Bruce protocol treadmill test after PMI confirmed that no bradycardia, hypotension, or marked symptoms were reproduced during exercise because of the elimination of 2:1AVB. In addition, her exercise capacity improved to 10 minutes and 30 seconds of exercise until termination due to leg fatigue (Fig. 5). Her marked symptoms resolved and have not recurred to date after PMI.

### Discussion

Isolated exercise-induced 2:1AVB without any other underlying diseases, including more advanced AV block, myocardial ischemia, and ventricular dysfunction, is a rare entity among uncommon exercise-induced second-degree AV blocks and can cause profound exercise intolerance (1, 2). Nevertheless, there are few detailed reports concerning the underlying mechanism: it remains unclear how the exclusively exercise-induced symptoms of 2:1AVB with a normal ventricular function develop. Our patient, who had activity- and rate-dependent 2:1AVB and a normal LVEF, had exclusively exercise-induced marked symptoms.

If 2:1AVB is clearly accompanied by symptoms, PMI is recommended as a Class I indication in the current Japanese guidelines (3), whereas it is considered at least reasonable as a Class IIa indication in the current American guidelines (4). However, 2:1AVB itself is not usually accompanied by a long pause, nor does it always provoke symptoms at rest or in daily activities. In our case, at first, we were unable to establish a clear correlation between the symptoms and 2:1AVB because no accompanying symptoms were noted during the 2:1AVB on either 12-lead ECG at rest or Holter monitoring in daily activities. Therefore, there was some concern that her marked symptoms might not be resolved after PMI therapy for just 2:1AVB.

We then conducted a treadmill test on our patient to examine the response of the bradyarrhythmia to exercise, confirm the correlation between the symptom and the 2:1AVB or resulting bradyarrhythmia, and diagnose the presence of more advanced AV block or myocardial ischemia. In the treadmill test, there was neither more advanced AV block nor myocardial ischemia. However, 2:1AVB and transient hypotension developed simultaneously, and real-time marked symptoms were reproduced. This clear correlation between 2:1AVB and symptoms was a Class I indication for PMI in the current Japanese guidelines and at least a Class IIa indication in the current American guidelines (3, 4).

However, we were unable to identify the level of AV block, despite performing a treadmill test (Class IIa test in the American guidelines) (4). While this patient manifested exercise-induced 2:1AVB, which, along with CRBBB, might suggest infranodal block (4), the AV conduction changed transitionally from Wenckebach second-degree AV block to 2:1AVB during the treadmill test, which implied infranodal AV block (7). These were ambiguous results.

As the next step, an electrophysiological study (Class IIb test in the American guidelines) was considered able to accurately identify the anatomic site of AV block (4). If the infranodal block could be identified on an electrophysiological study, PMI would then have been recommended as a Class I indication in the current American guidelines (4). However, an electrophysiological study might not have been able to
reproduce activity-dependent symptoms in the supine position on an examining table. To make a confident decision concerning PMI therapy for the elimination of the exercise-induced marked symptoms in our patient, we needed to establish a clear correlation between the symptoms and 2:1 AVB (Class I PMI indication in the Japanese guidelines) (3) on a treadmill test (Class IIa test in the American guidelines) rather than identifying the site of AV block (Class I PMI indication in the American guidelines) on a treadmill test (Class IIa test in the American guidelines) or even an electrophysiological study (Class IIb test in the American guidelines) (4).

There have been few detailed reports on how symptoms of 2:1 AVB in cases with a normal ventricular function develop exclusively upon exercise, and there are even fewer reports suggesting that exclusively exercise-induced symptoms are related to transient hypotension. One case report of 2:1 AVB with a normal LV function and the same symptoms as in our patient noted that resting echocardiography revealed moderate diastolic mitral and tricuspid regurgitation immediately following blocked P waves of 2:1 AVB (8). These manifestations improved after PMI therapy for 2:1 AVB.

In our patient with a normal LVEF, the symptoms developed during 2:1 AVB exclusively on moderate-to-heavy exercise, such as the treadmill test, whereas no symptoms developed during 2:1 AVB on a 12-lead ECG at rest or on Holter monitoring during mild daily activities. This might be because moderate-to-heavy exercise reduced the compliance of cardiac ventricles (9), thereby increasing diastolic mitral and tricuspid regurgitation immediately after blocked P waves of 2:1 AVB (8), and thus this condition, along with the relative bradycardia, failed to maintain the BP (Fig. 3), resulting in hemodynamic collapse despite a normal LVEF.

A previous study found that, in an athlete with asymptomatic complete AV block, the stroke index increased, and the mean arterial BP was maintained at almost the same level despite bradycardia throughout a progressive cycle ergometer test, unlike in our case (10). This was likely achieved through an enlarged end-diastolic volume, as per the Frank-Starling mechanism (11). However, another recent article referred to hypotension as a sign of hemodynamic instability of second-degree AV block that should be urgently treated with atropine, sympathomimetic agents, or temporary cardiac pacing (7). Nevertheless, to our knowledge, there are no reports on the detailed mechanism underlying the exclusively exercise-induced symptoms of 2:1 AVB patients with a normal ventricular function. In our patient with a normal LVEF, it was thought that the compensatory maintenance of arterial BP was absent, but that the abrupt transient hypotension occurred exclusively during the treadmill test or moderate-to-heavy exercise in daily activities, resulting in her marked symptoms (Fig. 3).

These factors noted above were suggestive of the hemodynamic advantages of DDD-mode PMI therapy (8, 9). After PMI for 2:1 AVB, transient hypotension disappeared, her exercise-induced marked symptoms resolved and the exercise capacity also improved in the re-examination of the treadmill test (Fig. 5).

In addition, in the present case, 2:1 AVB developed at a sinus rate of about 100 bpm on a 12-lead ECG at rest and Holter monitoring in mild daily activities, whereas 2:1 AVB...
developed at a sinus rate of only over 120 bpm on moderate-to-heavy exercise, such as the treadmill test. Furthermore, symptoms of 2:1AVB developed exclusively on moderate-to-heavy exercise, whereas no symptoms developed even during 2:1AVB in mild daily activities. Namely, symptoms accompanied by 2:1AVB occurred depending on the extent of exercise rather than the development of 2:1AVB alone.

Although echocardiography at our hospital revealed neither underlying disease nor LV systolic dysfunction, moderate-to-heavy exercise was able to reduce the cardiac ventricle compliance (9), probably due to the Frank-Starling mechanism (10). Therefore, at any age, the development of symptoms as well as transient hypotension correlated with 2:1AVB on moderate-to-heavy exercise might depend directly on the balance between exercise strength and the extent of cardiac ventricular diastolic dysfunction, both of which are individually and independently affected by aging.

Several limitations associated with the present study warrant mention. First, we did not perform cardiac magnetic resonance imaging or positron emission tomography/computed tomography, as there were no abnormal echocardiographic findings. Therefore, we were unable to discuss the pathological or anatomical evaluations in greater detail. Second, we did not conduct an electrophysiological study, as the correlated symptoms with 2:1AVB were evident, which otherwise could be a limitation from an anatomical viewpoint.

Conclusions

A 62-year-old woman with activity-dependent 2:1AVB and normal LVEF was referred to our department for the evaluation of exclusively exercise-induced marked symptoms. In this case, the treadmill test helped reproduce the marked symptoms and 2:1AVB simultaneously, thereby establishing a clear correlation between the two.

The exercise-induced marked symptoms of 2:1AVB may have been caused by the abrupt transient hypotension along with relative bradycardia exclusively on moderate-to-heavy exercise, probably due to increased diastolic mitral and tricuspid regurgitation. DDD-mode PMI was thought to have improved the 2:1AVB and the abrupt hypotension simultaneously and restored the hemodynamic collapse, particularly during moderate-to-heavy exercise, resulting in the elimination of the exclusively exercise-induced marked symptoms of our presenile 2:1AVB patient.

The authors state that they have no Conflict of Interest (COI).

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