Neurally Mediated Syncope and Arrhythmias

— A Study of Syncopal Patients Using The Head-up Tilt Test —

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Understanding the causes of syncope in patients with arrhythmia is important in determining the therapeutic interventions. Neurally mediated syncope (NMS) was evaluated in 55 patients with various arrhythmias. The head-up tilt test with or without isoproterenol infusion induced NMS in 41 (74%) patients. When these patients were categorized into 3 types, depending on the development of syncope, vasodilatation was significant in a majority of patients. In 46% of patients with tachyarrhythmias, NMS was accompanied by an increase in extrasystole. It was concluded that the evaluation of vasodilatation is important for the preventive strategy of NMS in patients with arrhythmias and that NMS may induce arrhythmias. (*Jpn Circ J* 1999; 63: 339–342)

Key Words: Arrhythmias; Head-up tilt test; Neurally mediated syncope

Although it is occasionally difficult to clarify the cause of syncope in patients with arrhythmias,¹ evaluation of the syncope is important in determining an appropriate therapy [eg, pharmacological and/or nonpharmacological intervention (pacemaker, cardioverter-defibrillator implantation)]. Syncopal hypotension and/or bradycardia in neural circulatory control are thought to account for the neurally mediated syncope (NMS)² that often accompanies various arrhythmias. Kenny et al³ reported that 36 patients still experienced fainting out of 147 syncopal patients with a pacemaker. It is suggested that the NMS is sometimes misjudged as Adams-Stokes syncope and artificial pacemaker therapy may be indicated.

The head-up tilt test (HUT) is well known for stimulating NMS.³ We investigated whether there were differences between patients with and without arrhythmias in the development of NMS and characterized NMS in syncopal patients with arrhythmia. We also used the HUT to assess the possibility that the arrhythmia may contribute to the generation of NMS.

Methods

Patients

We studied a total of 143 patients with syncope (60 men, 83 women; mean age, 42.5±18.8 years). Although all patients had received a thorough physical examination and 12-lead electrocardiogram, chest radiograph, echocardiogram, brain computed tomography, and ambulatory electrocardiographic monitoring, the cause of the syncope was still unknown. None of the patients had any indication of organic heart disease or used medication except for 6

patients with a pacemaker. Fifty-five (38%) patients (20 men, 35 women; mean age, 44.2±18.8 years) showed frequent or persistent arrhythmias during ambulatory electrocardiogram (arrhythmias group). The remaining 88 (62%) patients (40 men, 48 women; mean age, 41.4±18.8 years) had no arrhythmias or less than 720/day premature contractions (no-arrhythmias group). We divided the arrhythmias-group further into tachyarrhythmias subgroups [persistent atrial fibrillation (n=4), atrial premature contractions (APC) >720/day (n=7), and ventricular premature contractions (VPC) >720/day (n=26)] and bradyarrhythmias subgroups [sinus bradycardia and/or sino-atrial block (n=12); atrioventricular block (n=6)]. Six bradyarrhythmias patients in the arrhythmias-group already had an artificial pacemaker implanted because of frequent syncopal attacks (2 patients had complete atrioventricular block, 3 patients had sinus bradycardia and/or sino-atrial block, and 1 patient had atrial fibrillation with slow ventricular response).

Protocol of HUT

In this study, each patient was placed in 80° upright posture on an electrically controlled tilt table with a foot board for weight-bearing. The tilting was performed for 15 min or until development of presyncope or syncope.⁴ Blood pressure and electrocardiogram monitoring were performed continuously. If no presyncope or syncope appeared, the patient was lowered to the supine position and then continuous intravenous isoproterenol infusion^{5,6} was started at 0.01 µg kg⁻¹ min⁻¹. If syncope did not develop during HUT with the 0.01 µg kg⁻¹ min⁻¹ isoproterenol provocation, the dosage was increased up to 0.03 µg kg⁻¹ min⁻¹. There was an interval of 10–15 min between each HUT. In the patients with pacemaker, the pacemaker was started during HUT.

The hemodynamics at syncope were classified into 3 types according to Sutton's criteria:⁷ (1) cardioinhibitory type characterized by a heart rate (HR) of less than 40 beats/min persisting for more than 10 s after the appearance

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Fig 1. Response of patients with and without arrhythmia to upright tilt. (A) In the arrhythmias group, 41 subjects (74%) developed neurally mediated syncope (NMS); 4 subjects (9%) developed the cardioinhibitory type, and 13 (32%) and 24 (59%) subjects developed the vasodepressor and mixed type of NMS, respectively (lower panel). (B) In the no-arrhythmias group, 4 subjects (6%) developed the cardioinhibitory type of NMS, and 29 (48%) and 28 (46%) subjects developed the vasodepressor and mixed type NMS, respectively (lower panel).

Fig 2. Characteristics of neurally mediated syncope (NMS) in the arrhythmias group. (A) In the tachyarrhythmias-subgroup, 28 (76%) patients developed syncope: cardioinhibitory type (n=2), 7%; vasodepressor type (n=7), 25%; mixed type (n=19), 68%. (B) In the bradyarrhythmias-subgroup, 13 (73%) patients developed syncope: cardioinhibitory type (n=2), 15%; vasodepressor type (n=6), 46%; mixed type (n=5), 39%.

Fig 3. An increase in extrasystole immediately before syncope. In 46% of tachyarrhythmia patients, neurally mediated syncope was accompanied by an increase in extrasystoles immediate before the development of syncope.

of a transient rise in HR or hypotension accompanying cardiac arrest of more than 3 s duration; (2) vasodepressor type characterized by a fall in HR of not more than 10%;

and (3) mixed type characterized by a HR of less than 40 beats/min that did not persist for more than 10 s.

Statistics

The measured values were expressed as mean $\pm$ SD. The data obtained were analyzed by the chi-squared test for paired observations, as appropriate. A p-value less than 0.05 was considered significant.

Results

Comparison of No-Arrhythmias Group With Arrhythmias Group

In the no-arrhythmias group, 61 of 88 (69%) patients developed syncope during HUT. In the arrhythmias group, 41 of 55 (74%) patients developed syncope during HUT. The incidence of syncope was similar between the 2 groups. As shown in Fig 1, with respect to the type of syncopal response in the arrhythmias group (and the no-arrhythmias group), 9% (6%) of patients demonstrated the

cardioinhibitory type, 32% (48%) had the vasodepressor type, and 59% (46%) showed the mixed type. The incidence of the types of syncopal response was also not different between both groups. The cardioinhibitory type was not frequent (<10%) in both groups.

NMS in the Arrhythmias Group

In the tachyarrhythmias-subgroup, 28 (76%) patients developed syncope: cardioinhibitory type (n=2), 7%; vasodepressor type (n=7), 25%; and mixed type (n=19), 68% (Fig 2A). In the bradyarrhythmias-subgroup, 13 (73%) patients developed syncope: cardioinhibitory type (n=2), 15%; vasodepressor type (n=6), 46%; mixed type (n=5), 39% (Fig 2B). Although the incidence of the type of syncopal response was not different between both the subgroups, it should be noted that the incidence of the cardioinhibitory type response was not frequent in either subgroup (tachyarrhythmias-subgroup, 7%; bradyarrhythmias-subgroup, 15%). As shown in Fig 3, in the tachyarrhythmias-subgroup, 12 of 37 (46%) patients demonstrated the manifest increase of premature contractions immediately before the development of syncope. Although 5 patients had no APC or VPC during the pre-upright posture (supine position), these patients had 10 ± 5 (/min) premature contractions immediately before the development of syncope.

Three patients (50%) with a pacemaker developed the vasodepressor type of syncope during HUT. The remaining 3 patients exhibited the mixed type of syncope. In only 3 of 6 patients was cardiac pacing observed.

Discussion

In our study, the vasodepressor and mixed type of syncopal response were frequent. On the other hand, the incidence of the cardioinhibitory type response was not frequent. According to Sutton's criteria,⁷ 3 types (cardioinhibitory, vasodepressor, and mixed) of NMS are described. There is argument about his criteria because it was derived from the pattern of hemodynamic changes during the development of NMS, which does not reflect sufficiently the mechanism of the development of NMS. Although marked bradycardia or cardiac arrest is important for the diagnosis of the cardioinhibitory type, there are some reports that cardiac pacing was ineffective in preventing NMS, and several investigators have argued that drug therapy alone can prevent the NMS with cardiac arrest of more than 5-s duration.⁸⁻¹⁰ In our study, patients with a pacemaker exhibited the vasodepressor and mixed type of NMS despite the prevention of bradycardia. What is significant in this argument is that the fall in blood pressure caused by vasodilatation is more important than the bradycardia itself.^{11,12} In many cases, it has been suggested that vasodilatation may have contributed to the development of NMS.

Comparison of the No-Arrhythmias Group With the Arrhythmias Group

Although we investigated whether there were differences in the incidence of NMS between patients with or without arrhythmias, we could not demonstrate any. It is suggested that arrhythmia patients do not have a substrate for NMS.

NMS May Induce Arrhythmia

The mechanisms of NMS are also unknown, but it is

postulated to originate from various sites in the cardiovascular system. The assumed mechanism is as follows: pooling of blood in the lower limbs, which arises in the orthostatic position, decreases the venous return and the decreased cardiac output induces a fall in arterial blood pressure. The combination of reduced left ventricular filling and raised sympathetic tone results in vigorous ventricular contraction, which can paradoxically stimulate ventricular mechanoreceptors. Then, the Bezold-Jarish reflex may occur.¹³ In fact, serum catecholamine levels are elevated just before syncope.¹⁴ Recently, the concept of postural orthostatic tachycardia syndrome, which is characterized by orthostatic tachycardia and presyncope, has been advocated,¹⁵ characterized by an excessive compensatory response of HR in the upright posture because of a deficiency in peripheral vascular contraction. This enhanced sympathetic tone may induce some kind of arrhythmia, such as triggered activity. During bradycardia, even in the supine position, latent sympathetic nerve activity may accelerate so excessively that NMS may be induced further in the orthostatic position. For example, 46% of the patients with a positive response to HUT in the tachyarrhythmias-subgroup demonstrated an increase in premature contractions immediately before the development of syncope. It follows that such enhanced sympathetic nerve activity may induce some arrhythmias, such as the mechanism of triggered activity.

Study Limitation

We did not evaluate the serum catecholamine level during HUT. In fact, the relationship between sympathetic nerve activity and NMS in the tachyarrhythmias-subgroup could not be identified in the present study. Based on some other studies, we speculate that increased sympathetic nerve tone induces not only NMS but also arrhythmias. Therefore, further study will be needed to estimate sympathetic nerve activity using the serum catecholamine level and the changes in HR.

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