Diagnosis and Treatment of Syncope

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Accurate diagnosis of syncope is essential because it ranges from cardiac syncope with a very poor prognosis to neurally-mediated syncope (NMS) with a relatively favorable prognosis. Diagnosis of syncope, however, is difficult in many patients even by HUT, so a new loading method for HUT or implanted Holter ECG monitoring will be required in the future. The prognosis of NMS itself may be favorable, but it may cause the aggravation of complications.

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Key words: Neurally-mediated syncope, Head-up tilt test, Arrhythmia

I. Approach to Syncope of Unknown Etiology

Syncope is transient loss of consciousness. The first thing to be done after the patient regains consciousness is to find the cause. Making a correct diagnosis is important because the severity of the condition depends on the cause. Accurate diagnosis and treatment is particularly necessary for cardiac syncope because it is life-threatening. However, the cause remains unknown in many patients and some of them have a multifactorial etiology. Syncope recurs in many patients and is often accompanied by trauma, so some patients need treatment regardless of the etiology. Symptoms may be aggravated if the wrong diagnosis is made, so various problems arise during the management of syncope.

1. Frequency of syncope

Syncope is defined as sudden loss of consciousness and inability to maintain an upright posture caused by decreased cerebral blood flow. Patients with syncope account for 3 to 3.5% of all those presenting to emergency services and it occurs in 1 to 6% of inpatients. The Framingham study followed the occurrence of syncope over 26 years in 5,209 subjects, and the prevalence was 3.0% in men and 3.5% in women.1 A total of 822 syncope events were assessed in the subsequent study that followed up 7,814 subjects for an average of 17 years, and the frequency of initial syncope was reported to be 6.2 per 1,000 subjects/year.2 Syncope is thus a symptom that occurs very frequently. With respect to the age distribution of syncope, a sudden increase occurs in patients over 70 years old.3

2. Classification of syncope

Among the many methods published for the classification of syncope, the classification according to the guidelines for diagnosis and treatment of syncope released by the European Society of Cardiology is shown here (ESC Guidelines 2004).3 Causes of syncope are classified into the following 5 categories: neurally-mediated (reflex), orthostatic hypotension, cardiac arrhythmias as primary cause, structural cardiac or cardiopulmonary disease, and...
cerebrovascular causes. The main limitation of this classification is that more than one factor is often involved in the pathology of syncope in many patients, and abnormal neurological reflexes such as delayed or inadequate compensatory vasoconstriction have a role in syncope induced by bradycardia or tachycardia. The prognosis is poor for syncope due to arrhythmias and structural cardiac or cardiopulmonary disease, which are often considered together as cardiac or cardiogenic syncope.

3. Prognosis of syncope

Neurally-mediated syncope, such as vasovagal syncope, has a favorable prognosis, while at the other extreme lies cardiac syncope with a poor prognosis. It should also be considered that the causes differ greatly between patients presenting to an emergency unit, outpatients, and inpatients. The common problem is that the cause remains unknown in 13 to 47% of patients (Figure 1). According to the report by Kapoor et al., among 433 inpatients with syncope, reflex syncope and orthostatic hypotension accounted for 27%, which was comparable with the proportion of 26% for cardiac syncope, while the cause was unknown in as high as 41%. The prognosis of cardiogenic syncope is significantly worse compared with that of non-cardiac syncope and the 5-year mortality rate reaches 50%. The mortality for syncope of unknown etiology, on the other hand, is approximately 30% within 5 years and there is no significant difference with the mortality for non-cardiac syncope of approximately 23%. It was recently shown by the Framingham study that the prognosis of cardiac syncope is poor whereas the prognosis of patients with vasovagal syncope is as good as that of persons without syncope, while the prognosis of syncope with an unknown etiology ranks between the other two. Such results suggest the importance of determining the cause of syncope for prediction of the prognosis.2)

4. Diagnosis of syncope

1) Probable cause based on medical history, symptoms, and routine tests (Figure 2)

When a syncope patient presents for treatment, the patient is examined, a medical history is obtained, and routine tests are performed, such as ECG, chest X-ray, and hematology. When a cause other than cerebrovascular syncope is suspected, the presence or absence of any evidence of cardiac disease on routine tests becomes a significant point for making a differential diagnosis. Whether the history of syncope is long or short is another important point for differentiation. Cardiac syncope should be suspected in patients with a course of 4 years or less versus neurally-mediated syncope (NMS) in patients with a longer course.9)

The posture and symptoms at the onset of syncope are also important for predicting the diagnosis.

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Figure 1 Cause of syncope.5–7)

The common problem is that the cause remains unknown in 13 to 47% of patients. VVS: vasovagal syncope; Reflex: Other reflex syncope; Orthostatic: Orthostatic hypotension; Cardiac: Cardiac syncope; Metabolic: Syncope due to metabolic disturbance; Neurogenic: Syncope due to neurological disease; Psychogenic: Syncope due to psychological disease; Unknown: Syncope of unknown origi.
(1) Posture at the onset of syncope
NMS only develops in the standing or sitting position. Many people experience NMS while standing in a commuter train during the morning rush hour. NMS may also develop during dental treatment, even in the sitting position. Cardiac syncope can occur regardless of the posture.

(2) Causes of syncope
The situations that generally induce NMS include uncomfortable scenes, sounds, odors, pain, standing up for a long time, sudden standing after lying prone or sitting for a long time, hypoxemia, fever, hunger, dehydration, heavy intake of alcohol, and blood loss. Situational syncope develops at the time of micturition, defecation, swallowing, coughing, or after exercise. Cardiac syncope induced by ventricular tachycardia or ventricular fibrillation may develop due to a change in autonomic tone such as when awakening or during/after exercise. Idioventricular fibrillation may also develop during sleep, but it often causes sudden death rather than syncope. Syncope due to vasospastic angina is followed by chest pain and occurs at a time of high stress, while smoking, after exercise, or on getting up in the morning.

(3) Time of onset
Syncope frequently occurs at a certain time of day depending on its cause. As described above, idioventricular fibrillation due to vasospastic angina or Brugada syndrome occurs spontaneously during the nighttime or early morning. Torsade des pointes in patients with congenital long QT syndrome develops on awakening, during the daytime, or while exercising. NMS may occur at any time, but syncope associated with micturition or defecation is likely to happen at night. Vasovagal syncope tends to occur in the morning.

(4) Prodromal symptoms and symptoms at the time of syncope
A sensation of hotness, thirst, or feeling of suffocation are the initial prodromal symptoms of NMS, while gastric discomfort, belching, abdominal pain, a desire to defecate, sighing, yawning, blurred vision, palpitations, or dizziness may develop at the same time or immediately afterward. The patient then becomes pale with dilated pupils and sweating, after which he/she loses consciousness. When the prodromal symptoms last for 10 seconds or more, NMS can be strongly suspected. Rigidity of the limbs, tremor, and convulsions may also occur at the time of syncope. The patient complains of nausea, tremor, and headache even after recovery and often has a desire to urinate. Cardiac syncope may be accompanied by prodromal symptoms such as palpitations or chest pain, but these do not last for very long and syncope occurs rapidly. Among the types of NMS, few prodromal symptoms are associated with cardioinhibitory syncope or situational syncope. Elderly patients may have few prodromal symptoms.
2) Investigation of syncope (Figure 3)

Whether syncope has a cerebrovascular or cardiovascular cause is judged from the symptoms observed and the results of routine tests. Cerebral computer tomography (CT) scanning and magnetic resonance imaging are often performed as an initial test because it is widely available in Japan, but the incidence of cardiovascular syncope is high so Holter ECG monitoring, the head-up tilt test (HUT), carotid sinus massage (CSM), and echocardiography should actually be performed first to identify cardiovascular causes, except when a cerebrovascular etiology is strongly suspected. If the patient has arrhythmia, exercise testing, ventricular signal-averaged electrocardiogram, and T-wave alternans are performed, and cardiac electrophysiological study of the heart may also be required. When ischemic heart disease is suspected, exercise scintigraphy and cardiac angiography should be performed. If cerebrovascular syncope is suspected, on the other hand, brain CT scanning, cervical Doppler ultrasound, and electroencephalography should be performed. Neuropsychiatric evaluation should be done if all of the above tests are negative. The most important test for elucidating the cause of syncope is head-up tilt test.

(1) Head-up tilt test (HUT)

This test is useful for diagnosis of neurally mediated syncope (NMS), which accounts for approximately 30% of all syncope. When we employed the method of making the patient stand for 30 minutes at a slope angle of 80°, prodromal symptoms or syncope were induced in 68 subjects (27%) among 249 consecutive patients with syncope of unknown etiology. The positive rate was a high 53% in young patients under 25 years old, whereas it was only 13% in patients over 50 years old. Among drug provocations employed to reduce the false-negative rate, isoproterenol is the most commonly used. Among 153 of 249 patients who were negative in the control tilt test, 78 patients (51%) became positive with isoproterenol. When the results of the control tilt test and isoproterenol loading test were combined, 148 out of 249 patients (59%) were diagnosed as NMS, but the cause was unknown in 41%. The proportion of patients with an unknown etiology was higher among the elderly. It seems that the HUT has a high detection rate for vasovagal syncope that is common in young patients, whereas its detection rate is low for reflex syncope such as micturition syncope that is common in the elderly. Also, there are often multiple factors causing syncope in the elderly, such as administration of antihypertensive therapy, vasodilators, etc., or cerebral arterial stenosis. It is also possible that cardiac syncope with a poor prognosis may be masked in the elderly.

CT: computed tomography; MRI: magnetic resonance imaging; Carotid Doppler: carotid Doppler ultrasonography; CSM: carotid sinus massage.
elderly. The cause should therefore be identified as clearly as possible, and loading tests with nitrates or ATP have also been employed in recent years (Figures 4, 5). In order to assess the effectiveness of the treatment using HUT, a high reproducibility is needed. The acute reproducibility is higher than the chronic reproducibility.\textsuperscript{11–16} Although the use of HUT for assessing the effectiveness of different treatments has important limitations,\textsuperscript{17,18} the assessment of drug treatment using HUT in the acute phase may be useful for predicting follow-up results.\textsuperscript{19}

(2) Implantable loop recorder

It was recently reported that the implantable loop recorder (ILR) is useful for the diagnosis of syncope and that its diagnostic rate is significantly higher compared with ordinary methods.

The ILR is as small as a finger and has no lead, and observation is possible for 14 months. At the onset of an event, the ECG can be recorded for up to 40 minutes before the event when the patient pushes the activating switch. Several types of recording are possible depending on the pattern of syncope and automated recording is also possible.

Among several of the ILR, the results of the Randomized Assessment of Syncope Trial (RAST) are shown below.\textsuperscript{20} The subjects were 60 syncope patients with an unknown etiology who showed no abnormalities on HUT, Holter ECG for at least 24 hours, and echocardiography. An external loop recorder (wearable for about 1 week), HUT, and electrophysiological testing were used for 30 subjects in the conventional test (CV) group, whereas 30 other subjects were randomly allocated to the ILR group and were observed for 12 months. The groups were crossed over when a diagnosis could not be made. The ILR diagnostic rate was significantly higher (52%) compared with that of ordinary methods (20%). The diagnostic rate achieved with ILR was even higher (62%) after crossover when a diagnosis could not be made by ordinary methods. When the results obtained before and after crossover were combined, ILR diagnosis was possible in 55% of the patients, which was significantly higher than 19% for the standard methods. Arrhythmia was the most frequent diagnosis made by ILR, with 14 patients having bradycardia and 3 patients having tachycardia.

5. Problems with syncope

1) Recurrence

The percentage of patients with recurrent syncope is very high (37 to 47%) and some patients frequently attend the emergency unit.\textsuperscript{4,5,8}

2) Trauma

One of the problems associated with syncope is a high incidence of trauma, since the rate of occurrence at the time of syncope ranges between 16 to 35%.\textsuperscript{5,8} The trauma rate among NMS patients was 13% according to our statistics. When we tried to determine the type of patient most likely to suffer from trauma, we found that NMS induced by HUT was of the cardioinhibitory type and trauma was observed in 78% of patients with cardiac arrest lasting for $>4$ seconds. This was significantly higher compared with the rate of 20% for patients with cardiac arrest lasting $<4$ seconds. Attention should be paid to cardioinhibitory syncope because it develops without prodromal symptoms, and HUT should be performed for prediction of trauma.

3) Driving and syncope patients

a. Cardiac syncope

The high recurrence rate of syncope places various limitations on daily life,\textsuperscript{21,22} and interference with driving is observed in 60% of patients. Patients with potentially fatal ventricular arrhythmias continued to drive in a comparative study of antiarrhythmic drug therapy and implantable cardioverter defibrillator (ICD) (Antiarrhythmic Versus Implantable Defibrillator: AVID).\textsuperscript{23} In the AVID study, the effect of antiarrhythmic drugs and the implantable defibrilla-
tor was compared in patients resuscitated from life-threatening ventricular arrhythmia. An anonymous questionnaire was mailed to each patient participating in the study to obtain information about driving habits and experiences. It was found that 88% of the patients resumed driving within 12 months and 2% of them had experienced syncope during driving. During driving, electrical shocks were delivered by ICD in 8% of the 295 patients with a defibrillator. Fifty patients reported at least 1 accident and a total of 55 accidents were reported during the follow-up period after resuming driving (3.4% per patient-year). It was concluded that development of symptoms related to arrhythmia occurred frequently during driving, but accidents were uncommon, with the frequency being lower than 7.1%, which was the annual accidents rate of the general driving population in the USA. This frequency, however, would be higher here than in the USA when considering the traffic situation in Japan.

b. Syncope during driving in NMS patients

Li et al.\textsuperscript{24)} reported on syncope during driving in 245 successive patients undergoing HUT. Of the 23 patients (9%) who had syncope during driving, 19 were HUT positive and 4 were negative. Nine patients had accidents and 1 of them caused the death of another driver. Seven of the patients who had accidents were HUT positive. Although 4 patients were HUT negative, they still had syncope during driving and 2 of them caused accidents. This means that a negative HUT dose not necessarily guarantee safety during driving. Bhatia\textsuperscript{25)} reported that 2 of 155 patients with HUT-induced NMS suffered from syncope during driving and 1 of them was injured. In our study, 2 out of 175 patients with HUT-induced NMS had syncope during driving and 1 of them was injured. The above results show that car accidents are not uncommon in NMS patients and driving should be prohibited for patients who are HUT-positive and have the cardioinhibitory type of syncope. NMS may improve in some patients over time, so the possibility of driving again should be investigated periodically.

II. Treatment of Syncope

1. Treatment of cardiac syncope

Most patients regain consciousness shortly after an attack of syncope, but cardiac syncope should be treated according to the underlying disease. Many NMS patients also have arrhythmias, as described below, and HUT should be performed in suspected cases.

2. Treatment of NMS

Prevention is the major therapeutic measure for NMS and few patients require emergency treatment. Which patients require treatment for NMS and whether HUT is useful for confirming the efficacy of therapy remains a big issue. Grimm et al.\textsuperscript{26)} investigated this problem in 80 untreated patients with suspected NMS who experienced at least 1 episode of syncope, had no cardiac disease, and had no other obvious cause of syncope. Thirty-nine of these patients formed a group with only one syncope attack (group A) and 41 formed a group with 2 or more attacks (group B). NMS developed in 4 patients (10%) from group A and 10 patients (24%) from group B (p = 0.1). A significant difference was observed in the recurrence of syncope over 23 ± 8 months since the rate was 10% in group A and 54% in group B (p < 0.5), but no difference in recurrence was observed regardless of a positive or negative baseline tilt test (43% vs. 30%). In other words, recurrence was not observed in 90% of the untreated patients with 1 syncope attack regardless of their HUT results, but patients with 2 or more attacks should be treated. Given that there was no difference of the HUT-positive rate between patients with recurrence and non-recurrence, it was concluded that HUT was not effective for predicting the recurrence of syncope in untreated patients. Among the patients in our study, recurrence was not observed in 20 out
of 21 patients (94%) for whom propranolol was effective and 12 out of 13 patients (92%) for whom disopyramide was effective according to the HUT. Syncope recurred in all of 15 patients in whom an effective drug could not be found by HUT. It is therefore considered that treatment with a drug shown to be effective by HUT is useful for prevention of recurrence. The value of HUT is thus controversial for prediction of recurrence in untreated patients and for judgment of treatment efficacy.

There is no consensus with respect to the period for which treatment should be continued, but we discontinue drug therapy after dose reduction when 1 year has passed without symptoms because remission is observed over the long-term and recurrence often occurs within 1 year after the initial attack. However, discontinuation of treatment should be carefully decided in patients who frequently develop syncope or who suffer from trauma, and the drug doses should be adjusted by repeating HUT. Many drugs have been used in the treatment of NMS (beta-blockers, disopyramide, scopolamine, clonidine, theophylline, fludrocortisone, ephedrine, etilefrine, midodrine, clonidine, serotonin reuptake inhibitors, etc.). In general, while the results have been satisfactory in uncontrolled trials or short-term controlled trials, several long-term placebo-controlled prospective trials have been unable to show a benefit of the active drug over placebo, with one exception. This revealed that subjects may not be homogeneous because NMS results from multifactorial causes such as effectors and the central nervous system. So, the effective therapy will not be homogeneous, but it depends on the individual patient. Recently, in the patients with recurrent NMS, the prescription of progressively prolonged periods of enforced upright posture (so-called ‘tilt-training’) may reduce syncope recurrence.

3. Arrhythmia and syncope

Adams-Stokes syndrome and NMS can be differentiated by reference to the posture and symptoms at the onset of syncope. However, even if an arrhythmia that is likely to induce syncope is detected by Holter ECG or EPS, syncope should not be instantly diagnosed as Adams-Stokes syndrome because vasovagal reflexes may contribute to syncope in some arrhythmia patients. For instance, Brignole et al. reported that bradyarrhythmic syncope induced by carotid sinus massage and HUT in 60% and 54%, respectively, of the patients were diagnosed as sick sinus syndrome (SSS). It was also reported that 80% of them showed a cardioinhibitory response or mixed response, and 11% of them showed a vascular inhibitory response, indicating that autonomic reflexes were involved in syncope among SSS patients. Among these patients, syncope is likely to recur in those who still show a vascular inhibitory response or mixed response after implantation of a pacemaker. We have also experienced bradyarrhythmic patients with recurrence of syncope after implantation of a pacemaker, and reported a subject in whom syncope was induced by HUT. Some of these patients already had suspected NMS at the time of pacemaker implantation, or NMS developed after implantation. In any case, implantation of a pacemaker is the final treatment method for syncope due to bradycardia and HUT should be performed in patients for whom this indication is even slightly applicable. Involvement of neural reflexes has also been reported with regard to the relationship between bradyarrhythmia and syncope. When HUT

![Figure 6] NMS in the patients with arrhythmias. We performed HUT in 55 patients who developed syncope of unknown etiology with some type of arrhythmia. NMS was detected in 41 patients (74%) by control HUT or isoproterenol loading.
was performed during sinus rhythm and tachycardia to investigate the involvement of vasovagal reflexes in syncope associated with supraventricular tachycardia (SVT), syncope developed with HUT during tachycardia in 7 out of 22 patients. The blood pressure decreased significantly in patients who developed syncope, but a significant difference of the heart rate was not observed compared with the patients who did not develop syncope. Because 6 out of 7 patients developed syncope with HUT during sinus rhythm, it was concluded that vasomotor factors rather than a rapid heart rate per se were involved in syncope during tachycardia. We also performed HUT in 55 patients who developed syncope of unknown etiology with prodromal symptoms and some type of arrhythmia. NMS was detected in 41 patients (74%) by control HUT or isoproterenol loading (Figure 6). In addition, NMS was induced in 76% of patients with tachyarrhythmias including extrasystole, and aggravation of arrhythmia was observed immediately before syncope in half of them (Figures 7A and 7B). Furthermore, NMS was induced in 73% of patients with bradyarrhythmia, and half of them had the cardioinhibitory type or mixed type in whom bradycardia was further aggravated (Figure 8).

Arrhythmia and NMS often develop at the same time and are closely related, so the cause of syncope should be carefully determined to select the best treatment.

4. Is the prognosis of NMS really good?

Kikushima et al. reported that epinephrine is excessively secreted just before NMS (Figure 9). Furthermore, when heart rate variability is measured upon induction of NMS, the high-frequency (HF) component (which indicates vagal tone) decreases after standing up while the LF/HF ratio (indicating sympathetic tone) rises and HF increases immediately before the onset of syncope (Figure 10). This “autonomic turmoil” aggravates the underlying disease and may sometimes induce a serious outcome, so it should be carefully identified.
Diseases influenced by vagal tone
(1) Vasospastic angina\textsuperscript{46,47}  
We have treated a patient in whom vasospastic angina was induced at the onset of NMS.\textsuperscript{47}
(2) Brugada syndrome  
The association of NMS and this syndrome has been reported.
(3) Atrial fibrillation  
Atrial fibrillation is sometimes induced at the onset of NMS.

Diseases influenced by sympathetic tone
(1) Long QT syndrome\textsuperscript{48–50}  
We have treated a patient with NMS and long QT syndrome in whom the QT interval was extremely variable.
(2) Ventricular arrhythmia  
According to the report of Shinohara\textsuperscript{43} mentioned above, aggravation of arrhythmia was observed immediately before syncope in half of their tachyarrhythmia patients who had NMS.

5. Syncope in hypertensive patients  
Soteriades, E. S.\textsuperscript{2} reported that syncope was induced by drug therapy in 10\% of their patients. Among the drugs causing syncope, antihypertensive agent and coronary vasodilators (nitrates) induce orthostatic hypotension and NMS, whereas \(\beta\)-agonists and cilostazol only induce NMS. Drugs that cause prolongation of the QT interval induce syncope due to torsade de pointes. For performing antihypertensive therapy which avoids induction of NMS, neither activation of sympathetic tone nor

\begin{figure}[h]
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\caption{NMS in the patients with bradyarrhythmias.\textsuperscript{43} NMS was induced in 73\% of patients with bradyarrhythmia, and half of them had the cardioinhibitory type or mixed type in whom bradycardia was further aggravated.}
\end{figure}

\begin{figure}[h]
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\includegraphics[width=\textwidth]{image2.png}
\caption{Epinephrine is excessively secreted just before NMS.\textsuperscript{11} Propranolol could not inhibit excessive epinephrine in the patients who developed syncope during HUT without isoproterenol provocation (isoproterenol-independent group: upper panel) though it was suppressed to a low level of epinephrine in the patients who developed syncope with isoproterenol provocation (isoproterenol-dependent group).}
\end{figure}
maintenance of normal baroreceptor sensitivity are required. Thus, β-blockers are used for treatment of NMS and are also useful for treatment of hypertension complicated by NMS. It was recently reported that angiotension II receptor antagonists also maintain normal baroreceptor sensitivity.

References

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