INVITED REVIEW / DAVETLİ DERLEME

What role might cardioneuroablation strategy have in syncope guidelines?

Senkop kılavuzunda kardiyonöroablasyon stratejisinin yeri ne olabilirdi?

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Summary– Vasovagal syncope (VVS) is the most common type of syncope. Although it is not related to an increase in mortality, recurrent syncope episodes may be disabling and reduce the quality of life. There are no optimal treatment strategies currently available, especially for the cardioinhibitory type of VVS. Cardioneuroablation (CNA) is a relatively novel technique that aims to eliminate vagal efferent output during VVS. The objective of this review was to explore the potential role of CNA strategy in syncope guidelines.

Özet– Vazovagal senkop (VVS), senkopun en sık rastlanan tipidir. Mortalite riskinde artış olmamasına rağmen tekrarlayan senkop atakları ciddi sakatlanmalara ve yaşam kalitesinde azalmaya neden olabilir. Günümüzde etkin ve önerilen bir tedavi stratejisi bulunmamaktadır. Bu durum özellikle kardiyoinhibitör tip VVS olguları için geçerlidir. Kardiyonöroablasyon VVS esnasında vagal efferent çıktıların ortadan kaldırılmasını amaçlayan göreceli olarak yeni bir tekniktir. Biz bu derleme yazısında senkop kılavuzunda kardiyonöroablasyon stratejisinin yeri ne olabilirdi? sorusunun olası cevabını bulmayı amaçladık.

Guidelines are intended to present all the relevant evidence on a wide range of conditions in order to help physicians weigh the benefits and risks of particular diagnostic or therapeutic procedures.[1] The main purpose is to provide the best possible advice to practicing physicians, clarify current areas of consensus and disagreement, improve standards in clinical practice, and to help in everyday clinical decision-making. Traditionally, guidelines are written as a consensus among experts based on current medical knowledge,[2] which is especially true for expert consensus statements. However, there are some methodological limitations. In particular, when analyzing medical literature in an unmethodical way, biased conclusions may result.[2] Moreover, the effect may be unnecessary delays in the recommendation of effective interventions and delays in the withdrawal of ineffective or harmful treatments.[3]

Syncope is a transient loss of consciousness due to transient global cerebral hypoperfusion characterized by rapid onset, short duration, and/or spontaneous and complete recovery, and is classified into 3 groups: reflex syncope, syncope due to orthostatic hypotension, and cardiac syncope.[4] Vasovagal syncope (VVS) is the most common type of reflex syncope. The underlying pathophysiology of VVS results from intermittently impaired cardiovascular reflexes causing sympathetic withdrawal-mediated hypotension and parasympathetic hyperactivity-based bradycardia, triggered by prolonged standing or exposure to emotional stress, pain, or medical procedures.

Abbreviations:

BJR	*Bezold-Jarisch reflex*
CI	*Confidence interval*
CNA	*Cardioneuroablation*
ECG	*Electrocardiogram*
ESC	*European Society of Cardiology*
GP	*Ganglionated plexus*
ILR	*Implantable loop recorder*
ISSUE	*International Study on Syncope of Uncertain Etiology*
NICE	*National Institute for Health and Clinical Excellence*
PICO	*Population, intervention, comparator, and outcome*
SUP 2	*Syncope Unit Project 2*
TT	*Tilt testing*
VASIS	*Vasovagal Syncope International Study*
VVS	*Vasovagal syncope*

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[5] Despite its benign course, recurrent VVS may be disabling.

The cornerstone of management of these patients is non-pharmacological treatment, including education, lifestyle modification, and physical counter-pressure maneuvers.[5] Cardiac pacing may be necessary for patients with severe forms, such as very frequent syncope affecting quality of life; recurrent syncope without prodromal symptoms, which exposes the patient to a risk of trauma; and syncope occurring during a high-risk activity. However, the efficacy of cardiac pacing is questionable if hypotension coexists. Due to the lack of sufficient evidence from studies, at this time, cardiac pacing cannot be recommended to patients aged <40 years.[5]

As a new treatment strategy, some observational studies and case reports have described the use of radiofrequency catheter ablation of ganglionated plexi (GPs) located close to the sinus, and atrioventricular nodes have been reported to eliminate vagal efferent output during VVS.[6–9] Those who first applied the technique called it cardioneuroablation (CNA).[6] Due to the small size of the studies and the lack of control groups, the CNA treatment strategy was not included in the 2018 European Society of Cardiology (ESC) or 2017 American Heart Association, American College of Cardiology, and Heart Rhythm Society syncope guidelines.[5,10]

The present review examines the potential role of CNA strategy in syncope guidelines.

The Development Process for Clinical Guidelines and Expert Consensus Documents

Initially, the key clinical issues that must be included should be identified. Next, an overview of what the clinical guidelines will include and exclude should be provided. At that point, the clinical issues listed in the scope need to be translated into review questions. All of these questions must be clear, focused, and narrowly defined within the boundaries of the main topic. Then, a search strategy for the relevant database should be developed for each review question. To correctly identify the evidence to be included, ensuring the sensitivity and specificity of search terms is the most important step. The following part of the article is a description of the method of formulating and developing review questions to evaluate the potential role of CNA in patients with VVS.

Development and Formulating a Review Question

A good review question should be focused on a specific patient problem, such as treatment of recurrent VVS. Each treatment strategy listed in the scope is likely to require at least 1 review question and possibly more, depending on the populations and outcomes of interest. The National Institute for Health and Clinical Excellence (NICE) defined features of a well-formulated review question on the effectiveness of an intervention using the population, intervention, comparator and outcome (PICO) framework.[11]

Choice of the Target Population

The population of interest should be chosen carefully. VVS is a neurally mediated condition and is characterized by an abrupt failure of the autonomic nervous system to maintain adequate blood pressure and or heart rate for cerebral perfusion.[3] The Bezold-Jarisch reflex (BJR) is still the most accepted explanation for the pathogenesis of vasovagal syncope.[12] The BJR involves the activation of mechanoreceptors in the left ventricle in response to a trigger, such as a decrease in venous return due to volume depletion or prolonged standing, causing an increase in cardiac contractility from sympathetic activation which stimulates C fibers. The reflex leads to vagal activation and withdrawal of sympathetic outflow, which causes a drop in cerebral perfusion and syncope. There are 3 well-defined responses to the BJR: a cardioinhibitory response due to vagal activation manifested by persistent bradycardia or prolonged pauses and the absence of significant hypotension, a vasodepressor response due to sympathetic withdrawal manifested by significant hypotension in the absence of bradycardia, and a mixed response manifested by co-existing bradycardia and hypotension.[13] Thus, when selecting a target population, other causes of syncope, such as orthostatic hypotension and cardiac syncope, must be excluded.

The most recent ESC guidelines advocate non-pharmacological treatment, including education, lifestyle modification, and reassurance regarding the benign nature of the condition as the cornerstone of management of VVS patients.[4] Additional treatment was only suggested for patients with severe forms, defined as very frequent syncope that alters the quality of life; recurrent syncope without, or with a very short prodrome, that exposes the patient to a risk of trauma;

and when syncope occurs during a high-risk activity. Another essential discrimination point for the choice of therapy is age. Therefore, a decision pathway consisting of clinical form, the severity of syncope, and age should be used to define the target population as suggested by the current guidelines.[4]

Discussion of the Proven or Well-Accepted Methods

Questions regarding interventions, treatments and approaches used for VVS are the next step. The following treatment strategies have been discussed and suggested by the guidelines: (1) physical counterpressure maneuvers, (2) tilt training, (3) pharmacological therapy, and (4) cardiac pacing.[4]

What is the Effectiveness of Physical Counterpressure Maneuvers in Adults With VVS?

It has been demonstrated that isometric handgrip exercises or other physical counterpressure maneuvers might induce a significant blood pressure increase in normal and even hypertensive subjects. Therefore, the primary theoretical background of these strategies is to counter the decrease in venous return from volume depletion or prolonged standing in the first part of the BJR. It may cause an endogenous catecholamine release and prevent the withdrawal of sympathetic outflow in the final part of the reflex mechanism.[14] The effectiveness of physical counterpressure maneuvers was assessed in 3 clinical studies and a prospective, multicenter, randomized trial.[15–18] Though there were promising results and better recurrence-free survival rates, only 2 of these studies included a placebo-controlled group.[15,18] In the first placebo-controlled study, Brignole et al.[15] evaluated the effect of handgrip and arm-tensing in 19 patients affected by tilt-induced VVS. The acute tilt testing (TT) results of active and placebo-controlled groups were compared. In the follow-up, the arm-tensing maneuver was used by all patients. During a mean follow-up of 9±3 months, 11 patients experienced impending syncope. Two patients had a syncopal relapse, but were unable to perform the maneuver at the time. In 1 case, syncope developed despite treatment. As another crucial point, the diagnosis was mixed type VVS in the vast majority of cases. The cardioinhibitory type was the primary diagnosis in only 26% of the cases. The second study was a multicenter, prospective, randomized clinical trial.[18] A diagnostic tilt-table test was used for about 93% of patients and a cardioinhibitory type response was observed in only 26% of the cases. The data related to physical counterpressure maneuvers seem to indicate that it is effective in both mixed and vasodepressive type of VVS, but care should be taken when adapting the same results to cardioinhibitory VVS patients.

What is the Effectiveness of Tilt Training in Patients with VVS in Adults?

Daily repeated TT may affect more than one mechanism in the same patient.[19] Clinical studies have revealed that TT therapy may restore orthostatic tolerance to a level that prevents syncope in some patients.[19–21] Verheyden et al.[22] investigated underlying mechanisms through which TT improved symptoms in patients with a clinical diagnosis of VVS and demonstrated that daily repeated tilt testing or training restored orthostatic tolerance by increasing the degree of vasomotor reserve available for vasoconstriction. Jang et al.[20] studied the prognosis after TT in 119 patients with recurrent VVS to determine the predictors of recurrence. Of 119 patients, 81 patients (68%) were determined to have vasodepressive VVS, 9 patients (7.7%) had cardioinhibitory VVS, and 29 patients (24.3%) had mixed VVS. Syncope recurred in 26.1% of the patients.

Evaluation of the TT patients according to recurrence of VVS revealed a significant difference in age (years) and time-to-tilt syncope (minutes). The recurrence group was younger than the nonrecurrence group and had a longer the time-to-tilt syncope (minutes) compared with the non-recurrence group.

Due to conflicting study results and the low patient compliance with continued training for an extended period, a TT strategy should only be offered to highly motivated young patients with recurrent vasovagal symptoms triggered by orthostatic stress. In addition, the vast majority of positive results with physical counterpressure maneuvers have been seen in mixed and vasodepressive VVS cases. It may not be reasonable to anticipate similar results in cardioinhibitory VVS patients.

What is the Effectiveness of Pharmacological Therapy in Adult Patients with VVS?

Many drugs tested in patients who have recurrent syncope despite education and lifestyle modifications

have demonstrated disappointing results, with some exceptions, such as fludrocortisone and alpha-agonists.[23,24]

The rationale for the use of fludrocortisone is to enhance sodium and fluid retention and to block the first part of the BJR. In a recently published placebo-controlled study, the benefit of fludrocortisone in preventing VVS was assessed.[23] The patients included in the study were ≥14 years of age and had >2 lifetime syncopal spells. The median age was 30 years. A total of 214 patients were randomized. Thirty patients discontinued the medication and 14 patients were lost to follow-up. There was no significant difference in the 12-month syncope event rate between the fludrocortisone and placebo arms of the study. Although fludrocortisone is frequently used in patients with orthostatic hypotension, it is less well studied in recurrent VVS without orthostatic hypotension. There was no subgroup analysis of different types of VVS, such as cardioinhibitory, vasodepressor, and mixed VVS.

Beta blockers have previously been suggested as a means to prevent the increase in cardiac contractility from sympathetic activation in the first of reflex arc. The Prevention of Syncope Trial assessed the effectiveness of metoprolol in treating VVS. While the overall results of the trial were disappointing, subgroup analyses demonstrated that it might be useful in suppressing VVS in patients older than 42 years of age.[25,26]

The rationale for using alpha-agonists is to increase peripheral vascular tone by stimulating alpha-adrenergic receptors. Midodrine is the most widely studied. A randomized crossover trial of Midodrine and a placebo (STAND-trial) did not show a significant improvement in symptoms with midodrine use; however, a meta-analysis excluding the STAND-trial found midodrine to be effective.[27,28]

Kaya et al.[29] investigated the effect of amitriptyline, a tricyclic antidepressant drug, to determine the anticholinergic effects in preventing syncopal episodes in 74 patients with VVS. At the end of the sixth month of the follow-up period, 67 patients (91%) were symptom-free. Only 2 patients (0.3%) did not tolerate amitriptyline due to side effects.

Nonetheless, as a result of contrasting results from multiple trials, medications should only be suggested in patients with the orthostatic form of VVS.

What is the Effectiveness of Cardiac Pacing in Adult Patients with VVS?

Among the suggested treatment strategies, only cardiac pacing appears to be effective if asystole is a dominant feature of VVS. In order to identify patients who may benefit from pacing, the relationship between symptoms and bradycardia should be investigated through a clinical evaluation and serial electrocardiograms (ECGs).

In the first study conducted by the International Study on Syncope of Uncertain Etiology (ISSUE) investigators, an implantable loop recorder (ILR) was inserted in 111 patients with syncope, absence of significant structural heart disease, and a normal ECG; TT was negative in 82 (isolated syncope) and positive in 29 (tilt-positive).[30] In the tilt-positive group, an asystolic response was detected in only 21% of the cases. The primary endpoint of this study was the analysis of the electrocardiographic tracing obtained during the first syncopal episode that was correctly recorded by the device. All of the patients were seen at the outpatient clinic every 3 months until the primary endpoint was reached or the study ended. The authors emphasized the following points as study's important results: (1) the patients with isolated unexplained syncope and those with a positive response to TT had similar clinical characteristics and outcomes; (2) in the patients of both groups who had a documented recurrence, the most frequent finding was bradycardia at the time of the episode; (3) in the tilt-positive patients, asystolic syncope was also recorded, despite a vasodepressor or mixed response to TT. A correlation between the type of response observed during TT and the documented events was made in only 8 patients. Furthermore, an asystolic episode was not detected in any patients demonstrating a vasodepressor response in TT.

In the second study performed by same group, the patients were at least 30 years of age and had suffered 3 or more episodes that were suspected to be neurally mediated syncope which were considered by the attending physician to be a severe clinical presentation (because of a large number of episodes that affected the patient's quality of life or presented a high risk for physical injury due to unpredictable occurrence) requiring the initiation of treatment in the previous 2 years.[31] After ILR implantation, Phase I comprised quarterly follow-up visits until the first ECG documented syncope or for a maximum of 24 months. The

ILR documentation of this episode determined the subsequent therapy and commenced Phase II follow-up. The recommended therapies were dual-chamber cardiac pacing in asystolic and bradycardic patients. Typical vasovagal/situational presentation was detected in only 41% of cases. TT was performed in 88% and demonstrated a positive response in 48% of cases. Syncope recurred in 4/47 (9%) patients who received a pacemaker (burden 0.05±0.15 episodes per patient/year) with an actuarial 3, 6, 12, and 24 months recurrence rate of 0, 2, 5, and 12%. This rate was significantly lower than that observed in patients with asystole or bradycardia who did not receive a pacemaker (recurrence in 4/13 [31%], 90% relative risk reduction [95% confidence interval [CI]: 57–98%); p=0.002). As part of a multivariable Cox regression analysis, pacemaker therapy was the strongest independent predictor of the absence of syncope relapse during Phase II.

The last study of the ISSUE group was a double-blind, randomized, placebo-controlled study.[32] Patients included in this study were ≥40 years of age and had experienced, in the previous 2 years, ≥3 syncopal episodes of likely neurally mediated syncope etiology. The pacemaker implantation criteria were documentation of syncope with ≥3 seconds of asystole or ≥6 seconds of asystole without syncope. The patients who met the criteria for pacemaker implantation were randomly assigned to dual-chamber pacing with rate drop response or to sensing only. The 2-year estimated syncope recurrence rate was 57% with pacemaker OFF and 25% with pacemaker ON. The risk of recurrence was reduced by 57% (95% CI: 4–81%).

In a recently published the Syncope Unit Project 2 (SUP 2) study, the patients included in the study were aged ≥40 years, affected by severe, unpredictable, recurrent, reflex syncope.[33] Syncope was defined as severe when it impaired the patient's quality of life due to high frequency and the occurrence was unpredictable, thus exposing the patients to a risk of trauma. Syncope was defined as recurrent when the patient had at least 2 episodes during the previous year or 3 episodes during the previous 2 years. During enrollment, patients initially underwent carotid sinus massage; if a diagnosis of cardioinhibitory carotid sinus syndrome was made, a dual-chamber pacemaker was proposed, and follow-up was implemented immediately. If the carotid sinus massage result was negative or the response was vasodepressor, the patient underwent TT. If a diagnosis of the cardioinhibitory form according to the new Vasovagal Syncope International Study (VASIS) classification was made, a dual-chamber pacemaker was proposed, and follow-up began immediately.[34] If TT was negative or the response was vasodepressor, the patient underwent ILR implantation and was followed up until a diagnosis was made or the study ended. The diagnosis of the cardioinhibitory form was similar to that used in the ISSUE-3 study.[31] Of 281 patients who met the inclusion criteria, 137 (49%) received a pacemaker. Syncope recurred in 18%. At 3 years, the actuarial syncope recurrence rate was significantly lower than in the 142 patients who did not receive a pacemaker and were observed with an ILR (43% [95% CI: 29–57%]; p=0.01). Surprisingly, the probability of recurrence of syncope was lower among patients who had a negative response during TT than in those who had a positive response (asystolic or not asystolic) or those who had not undergone TT. In patients demonstrating a negative response in TT but an asystolic response with ILR, the recurrence rate after cardiac pacing was very low: around 5% at 3 years.

In a subgroup analysis of the ISSUE-3 study, the role of TT in predicting recurrences was investigated.[35] Using the new VASIS classification, TT was considered positive if syncope occurred in the presence of hypotension with or without bradycardia. TT was considered negative if syncope did not occur. An asystolic response (type IIB of the VASIS classification) predicted a similar asystolic form during ILR monitoring, with a positive predictive value of 86%. The corresponding values were 48% in patients with non-asystolic TT (p=0.001 versus asystolic TT) and 58% in patients with negative TT (p=0.001 versus asystolic TT). Fifty-two patients (26 TT+ and 26 TT-) with asystole as documented by ILR received a pacemaker. Apart from the TT response, the 2 groups had similar clinical characteristics. Syncope recurred in 8 (31%) TT+ patients and in 1 (4%) TT- patient. In multivariable analysis, TT+ and the total number of events were the only independent predictors of syncope recurrence. Furthermore, the recurrence rate in TT+ patients was similar to that seen in 45 untreated controls. There was no significant difference according to the type of positive response, such as vasodepressor or cardioinhibitory. Although the minimal age for inclusion in ISSUE-3 and SUP 2 studies was 40 years, the actual mean age of the paced patients was much higher 63±14 and 73±11 years, respectively.

Based on all of these data, dual-chamber cardiac pacing is suggested to reduce the recurrence of syncope when the correlation between symptoms and ECG is established in patients ≥40 years of age with Class IIa indication.

Do We Need an Alternative Intervention?

As discussed, there is still no well-defined, effective strategy for all recurrent VVS cases. The studies investigating the effectiveness of physical counterpressure maneuvers and TT have yielded conflicting results and low compliance rates. The second important point is that the clear majority of positive results have been related to mixed and vasodepressive-type VVS cases. Thus, there are no precise data to adapt the same results to cardioinhibitory VVS patients. Lastly, compliance seems to be the most challenging barrier to manage. A similar reality is evident for pharmacological therapy. Even if the unsuccessful studies are excluded, there are only 2 widely studied medications. Although the results seem promising for orthostatic hypotension cases, the data are not sufficient to say that the effectiveness of these medications in classic VVS cases will apply to the cardioinhibitory type of VVS.

Considering the limited data regarding patients with cardioinhibitory type VVS, prevention of bradycardia or asystole episodes through cardiac pacing stands out as an attractive strategy. The current guidelines suggest that cardiac pacing should be considered in patients with frequent recurrent reflex syncope aged >40 years and when the correlation between symptoms and ECG is established. In patients with the clinical features of those in the ISSUE studies, cardiac pacing is suggested with Class IIa and level of evidence B. In patients with a tilt-induced asystolic response who are >40 years with recurrent frequent unpredictable syncope, the level of recommendation is weaker (Class IIb, level of evidence B). The first reason for such a definition is that patients under the age of 40 were not included in the studies, including the studies demonstrating positive results, like ISSUE-3 and SUP 2.[32,34] Other relatively well-designed trials, such as the Vasovagal Pacemaker Study (VPS) II and the Vasovagal Syncope and Pacing trial (SYNPACE), showed no benefit as a result of pacing in those with the pacemaker ON compared with those who had the pacemaker OFF.[36,37]

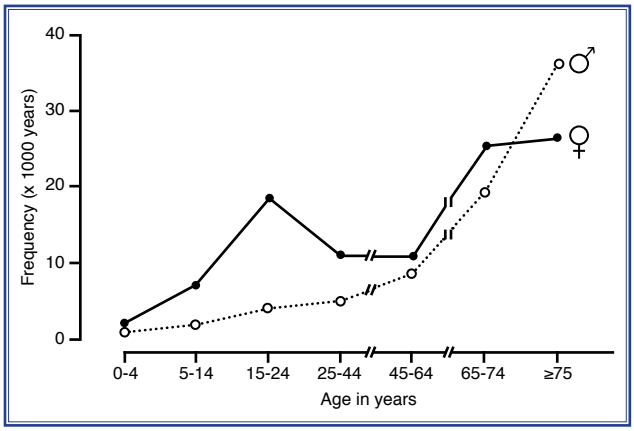

Figure 1. Frequency of the complaint syncope as reason for encounter in general practice in the Netherlands. Data are obtained from the general practitioners' transition project. It concerns an analysis of 93,297 patient-years. The arrow around 1 year is to indicate that a small peak occurs between 6–18 months (breath-holding spells) (Ref. 38, with Editorial permission).

Recently, Wieling et al.[39] reported that there are 2 peaks of incidence during life, with the first at approximately 15 years of age, and predominantly among female patients, and the second in older patients, >65 years, with an even gender distribution. This is a similar pattern to that observed in the general population (Fig.1).[39] If syncope data are examined according to VVS, most presentations are seen to be related to the reflex mechanism in any setting. In patients under the age of 40, 51% of syncope cases are related to the reflex mechanism.[40] The frequency of reflex syncope declines 37% for patients aged 40–60 years. Importantly, in patients <40 years, orthostatic hypotension is a rare cause of syncope; orthostatic hypotension is frequent in elderly patients.

Evaluation of all of these data reveal there is no single, acceptable, logical modality to be used for patients with cardioinhibitory syncope under the age of 40. Thus, an effective strategy should be investigated and found for this population.

Determination of Possible Alternative Intervention(s)

According to the PICO framework, the next question should be what is (are) the main alternative(s) to compare with the intervention being considered.[11] A search strategy can be constructed for terms related to the population, and this can be combined with terms related to the interventions and comparators (other main treatment options) to be evaluated. During the design of a well-formulated review question on the

effectiveness of a new intervention using the PICO framework, the following questions should be asked and answered for new interventions and comparators: (1) What is important for the patient? (2) Which outcomes should be considered? For example, there has been no increased risk of cardiovascular morbidity or mortality associated with VVS. Thus, the effect on mortality is not a primary endpoint for VVS intervention studies. The goal of treatment should be to prevent recurrence with the aim of improving the quality of life and reducing morbidity.

Another essential question should be whether any intervention reduces prodromal symptoms or improves health-related quality of life in patients with severe VVS. Rose et al.[41] used EuroQol-5D to evaluate the quality of life of 136 syncope patients. Compared with the general population, the quality of life of syncope patients was lower in all subscales of the EuroQol-5D. Importantly, prodromal symptoms decreased the quality of life more than syncope alone. Thus, the selection of a reduction in the frequency of syncope recurrence or prodromal symptoms might be a rational approach when evaluating the effectiveness of any intervention.

In the next part of the article, we will try to discuss the possible role of CNA strategy in patients with VVS.

Reviewing the Evidence for an Alternative Strategy

In order to reveal a potential role for an alternative strategy, the most important steps during literature searches are the selection of relevant studies, assessment of their quality, and the interpretation of the results.[11]

Selection of Relevant Studies

During selection of the studies, all of the process should be clearly documented, giving details of the inclusion and exclusion criteria that were applied. Decisions about which studies to include in a review are among the most influential. Provided that these judgments are reproducible, the same process should be repeated by more than one author.

First, the titles of the retrieved citations should be scanned using well-selected keywords, and those that fall outside the topic of the guideline should be excluded. Then, a quick check of the abstracts should be performed to determine if they are relevant to the review questions. Once the abstract selection is complete, full versions of the selected studies can be acquired for assessment. Studies that fail to meet the inclusion criteria should be excluded. Conference abstracts should not be excluded in the search strategy as they may point to published trials that may be missed.

Relevant articles may be obtained and screened from a search of well-accepted databases using the keywords “CNA,” “vagal” AND “denervation,” “vagal” AND “ablation,” “syncope,” AND “ablation,” and “GPs” AND “ablation” as search terms.

Assessment of Quality of Studies

The Cochrane handbook for systematic reviews of interventions should be used to determine the study design, such as randomized or non-randomized. In the current syncope guidelines, the question of whether there is an effective strategy in patients with VVS under the age of 40 cannot be answered with randomized trials. So, during the review process, the inclusion of non-randomized studies should be justified by the review authors. It is well-known that potential biases are a bigger problem for non-randomized studies than randomized trials.[42] However, interpretation of data with caution may resolve this problem. Except for cardiac pacing therapy, the vast majority of trials investigating the usage of intervention in patients with VVS are non-randomized. Therefore, it is likely that non-randomized studies will be considered during the evaluation of an innovative strategy.

The clinical efficiency of a CNA strategy in patients with VVS has so far been evaluated in 6 cohorts with before and after studies/[9,43] As a targeted clinical endpoint, the data related to freedom from syncope and freedom from prodrome was investigated in all studies. The duration of follow-up, which was 12.3±3 months in the study with the shortest follow-up time, was presented in 5 of the 6 studies. Three studies consist of not only VVS cases, but also patients with a functional atrioventricular block and sinus node dysfunction. Despite this confounding factor, it was clearly indicated how to diagnose syncope and which patients are excluded.

Interpretation of the Results

The guidelines for data collection favor head-to-head randomized or non-randomized controlled studies. When data from head-to-head studies of the options (and or comparators) of interest are not available, in-

direct treatment comparison analyses or a qualitative overview that critically appraises individual studies should be considered. However, the results of this type of analysis should be approached with particular caution.

At this point, we should start to evaluate clinical data for a CNA strategy in patients with VVS. To facilitate the assessment, all of the clinical data might be divided into 3 groups: studies consisting of mixed patient groups, studies consisting only of cases with VVS, and case reports and series. The first study consisting of mixed patient groups of VVS, functional atrioventricular block, and sinus node dysfunction was presented by Pachon et al.[6] In VVS cases, only patients demonstrating a cardioinhibitory response on a tilt table test were included in the study. The results after 9.2±4.1 months of follow-up indicated 100% freedom from syncope and prodrome. A similarly designed prospective study was conducted by our group.[8] In the VVS group, cases demonstrating type IIB or type I response with more than 3 seconds asystole, according to the new VASIS classification, underwent the procedure. Freedom from syncope and prodrome were 100% and 75%, respectively, at the end of 12.3±3 months. In the last study consisting of mixed groups, only patients who demonstrated type I (asystole) response based on the ISSUE classification were included in the study.[44] Freedom from syncope was constant, remaining at 100% in long-term follow-up (23±14 months). There were no data for prodromal symptoms in that study. When all of the data were evaluated together, there was no new syncope in any of the 18 VVS cases.

The clinical efficacy of CNA was investigated in 3 studies consisting only of cases with VVS. A total of 110 patients were included in the first study according to not only clinical findings, but also positive TT results. The clear majority of cases demonstrated cardioinhibitory response to TT. Pachon et al.[45] presented long-term follow-up (45.1±22 months) results of patients and demonstrated a 93% freedom from syncope rate. In the next study, the mean follow-up duration and freedom from syncope rates were 30±16 months, and 100%, respectively.[7] In the last and largest study, the anatomically guided approach was compared with the HFS-guided approach in 57 patients.[46] At the end of a mean 36.4±22 months of follow-up, freedom from syncope was detected as 100% and 89%, respectively.

To compare the potential role of CNA in patients with VVS, a comprehensive review was conducted using the keywords "CNA," "vagal denervation," "reflex syncope," "vagal ablation," and "GPs ablation in accordance with the recent Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement" by our group.[9,47] The retrieved citations were first screened independently by 2 reviewers for inclusion and exclusion criteria.[9] Freedom from syncope and freedom from prodrome were 100% and between 50% and 100%, respectively, in the studies. Ablation was performed via both atria in 3 studies; only the left atrial approach was used in the remaining studies. No major complication related to the procedure was reported.

Interpreting the Evidence to Make Recommendations

After completion of the review questions, we should decide what recommendations can usefully be made to healthcare and other professionals in the next and most important step. During this process, how we go from the evidence to the recommendation should be easily identified. The concept of the strength of a recommendation should take into account not only the quality of the evidence, but also whether there are any other alternatives and an effective strategy. A key stage in moving from the evidence to recommendations weighs up the magnitude and importance of the potential benefits and harm of an intervention. For CNA strategy, we may do it qualitatively (for example, the evidence of a reduction in syncope rates outweighed a small/no increase in adverse effects. Current guidelines use the classifications of I, II, and III to indicate the strength of a recommendation. The levels of evidence and the quality of evidence are indicated with A, B, and C.

The strength of the recommendation is described in 3 levels of certainty in the Guidelines Manual of NICE: interventions that must (or must not) be used, interventions that should (or should not) be used, and interventions that could be used. For recommendations on interventions that "could" be used, the intervention should do more good than harm for most patients. The decision may vary depending on a person's values and preferences, and so the healthcare professional should spend time considering and discussing the options with the patient. For CNA, it may be possible to make strong recommendations for subgroups

of people of a young age and with the cardioinhibitory type of VVS.

Our Recommendations for CNA Strategy

Consider CNA strategy to treat patients with VVS regardless of age in the coexistence of the following criteria: more than 3 syncopal episodes preceding the procedure after failure of conventional therapies such as optimal fluid intake and physical counterpressure maneuvers, confirmation of syncope with a VASIS type IIB or type I response with more than 3 seconds asystole, and the absence of structural cardiopathy. As with all ablation procedures, it should be kept in mind that clinical experience is an absolute necessity not only for the success of the procedure, but also for the safety of the procedure. A larger patient cohort and randomized controlled trials are needed to confirm the safety and efficacy of this new treatment option in patients with VVS.

Conclusion

CNA may be a potential alternative to pacemaker implantation in carefully selected cardioinhibitory type VVS cases. In contrast to pharmacological therapy and pacemaker implantation, this strategy aims to get to the root of the problem: disturbances in the intrinsic cardiac autonomic nervous system. When a CNA strategy is considered for young patients with VVS, the discussion of uncertainties may include evaluation of whether the uncertainty is sufficient to justify delaying making a recommendation to await further research, taking into account the potential harm of failing to make a clear recommendation. Large-scale, randomized, controlled trials are needed to increase the level of evidence for the technique.

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