INVITED REVIEW / DAVETLİ DERLEME

What might be the place of cardioneuroablation strategy 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. No optimal treatment strategies are currently available especially for the cardioinhibitory type of VVS. Cardioneuroablation (CNA) is a relatively novel technique which intends to abolish the vagal efferent output during VVS. We aimed to find a possible answer to following question: what might be the place of CNA strategy in syncope guidelines in this review article.

Özet– Vazovagal senkop (VVS) senkopun en yaygın tipidir. Mortalite riskinde artış ile ilişkili olmamasına rağmen tekrarlayan senkop epizodları ciddi sakatlanmalara ve yaşam kalitesinde azalmaya neden olabilir. Günümüzde etkin ve önerilen bir tedavi stratejisi bulunmamaktadır. Bu durum özellikle kardiyoinhibitör tip VVS vakaları 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 aim to present all the relevant evidence on a wide range of cardiovascular 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 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. Especially, analyzing medical literature in an unmethodical way biased conclusions may result.[2] Moreover, it may lead to 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 classified into three 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.[5] Despite its benign course, recurrent VVS may be disabling.

Abbreviations:

BJR	*Bezold-Jarisch reflex*
CNA	*Cardioneuroablation*
GPs	*Ganglionated plexi*
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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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 altering the quality of life, recurrent syncope without prodromal symptoms which exposes the patient to a risk of trauma, and syncope occurs 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, a rationale recommendation for cardiac pacing cannot be given in patients aged <40 years.[5]

As a new treatment strategy, in some observational studies and case reports radiofrequency catheter ablation (RFCA) of ganglionated plexi (GPs) located close to the sinus, and atrioventricular nodes were reported to abolish the vagal efferent output during VVS.[6–9] The technique was named as cardioneuroablation (CNA) by the operators who made the first application.[6] Because of the small nature of the studies and lack of control groups, the CNA treatment strategy could not get any indication on 2018 ESC and 2017 AHA, ACC, HRS syncope guidelines.[5,10]

The present review dedicated to finding a possible answer to following questions: What might be the place of CNA strategy in syncope guidelines.

The Development Process for Clinical Guidelines and Expert Consensus Documents

Initially, the key clinical issues should be identified that must be included. Next, an overview of what the clinical guidelines will include and excluding should be provided. At that point, the key clinical issues listed in the scope need to be translated into review questions. All these questions must be clear, focused and closely defined the boundaries of the main topic. Then, a search strategy should be developed for each review questions in the relevant database. To correctly identify the evidence, ensuring of sensitivity and specificity of search terms is the most important step. In the following part of the article, we try to describe how review questions should be developed and formulated to describe 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 one 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]

Chosen of the Target Population

At first, the population of interest should be well chosen. VVS is a neurally mediated condition and is characterized by an abrupt failure of the autonomic nervous system in maintaining adequate blood pressure and or heart rate for cerebral perfusion.[3] The Bezold-Jarisch reflex (BJR) is still used as the most accepted explanation for the pathogenesis of vasovagal syncope.[12] According to the BJR, the activation of mechanoreceptors in the left ventricle depending on a trigger such as a decrease in venous return from volume depletion or prolonged standing cause an increase on cardiac contractility from sympathetic activation which stimulates C fibers. Finally, the reflex leads to vagal activation and withdrawal of sympathetic outflow which causes a fall in cerebral perfusion and syncope. There are three well-defined responses due to the BJR: a cardioinhibitory response (due to vagal activation; manifested by persistent bradycardia or prolonged pauses and 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, while we select our target population, we should exclude other syncope reasons such as syncope due to orthostatic hypotension and cardiac syncope.

In line with the most recent ESC guidelines, the cornerstone of management of VVS patients was defined as non-pharmacological treatment, including education, lifestyle modification, and reassurance regarding the benign nature of the condition.[4] Additional treatment was only suggested in patients with severe forms, as defined before when very frequent syncope alters the quality of life; when recurrent syncope without, or with a very short, prodrome 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 forms, 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

The questions like which intervention, treatment or approach is used for VVS should be asked and answered for the next steps. Following treatment strategies were discussed and suggested by the guidelines: (1) physical counter-pressure maneuvers; (2) tilt training; (3) pharmacological therapy; and (4) cardiac pacing (4).

What is the Effectiveness of Physical CounterPressure Maneuvers in Patients with VVS in Adults?

It was demonstrated that isometric handgrip exercises or other physical counter-pressure maneuvers might induce a significant blood pressure increase in normal and even hypertensive subjects. So, the main theoretical background of these strategies is to counter with the decrease in venous return from volume depletion or prolonged standing in the first part of the BJR. Also, 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 counter-pressure maneuvers was assessed in three clinical studies and one prospective multicentre randomized trial.[15–18] Despite promising results and a better recurrence-free survival rates, only two of these studies consisted of 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. Active and placebo-controlled groups were compared for only acute tilt testing (TT) results. In the follow-up, the arm-tensing maneuver was used in all patients. During a mean follow-up of 9±3 months, 11 patients experienced an impending syncope. Two patients had a syncopal relapse but were unable to perform the maneuver. In one 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 demonstrated a cardioinhibitory type response in only 26% of the cases. Considering all data related to physical counter-pressure maneuvers, it seems to be 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 tilt testing may affect more than one mechanism in concert in the same patient.[19] Clinical studies have revealed that tilt training therapy may restore orthostatic tolerance to a level that prevents syncope in some of the patients.[19–21] Verheyden et al.[22] investigated underlying mechanisms by which tilt training improved symptoms in patients with a clinical diagnosis of VVS and demonstrated that daily repeated tilt testing or training restores orthostatic tolerance by increasing the degree of vasomotor reserve available for vasoconstriction. Jang et al.[22] studied the prognosis after tilt training in 119 patients with recurrent VVS and to determine the predictors of recurrence after tilt training. Of 119 patients, 81 patients (68%) were found to show vasodepressive type, 9 patients (7.7%) showed cardioinhibitory type, and 29 patients (24.3%) showed mixed type. Syncope recurred in 26.1% of VVS patients.

Between the two groups of tilt training patients according to recurrence of VVS, there were significant differences in age (years) and time-to-tilt syncope (min). The recurrence group was younger than the nonrecurrence group and had a longer the time-to-tilt syncope (min) compared to the non-recurrence group.

Due to conflicting results of studies and the low compliance of patients in continuing the training programme for an extended period, tilt training strategy should only be offered in highly motivated young patients with recurrent vasovagal symptoms triggered by orthostatic stress. Also, as it mentioned for physical counter-pressure maneuvers, the vast majority of positive results related to mixed and vasodepressive type VVS cases. It might not be reasonable to adopt the same results to cardioinhibitory VVS patients.

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

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

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 the recently published placebo-controlled study, the benefit of fludrocortisone was assessed in preventing VVS.[23] The patients were included in the study if they 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 despite followed in the study. 14 patients lost the follow-up due to patients' refusal. There was no significant difference for the 12-month syncope event rate was between the fludrocortisone and placebo arms. Although fludrocortisone is frequently used in patients with orthostatic hypotension, it is less well studied in recurrent VVS without orthostatic hypotension. There was no sub-group analysis for different types of VVS such as cardioinhibitory, vasodepressor, and mixed.

Beta blockers were previously suggested to prevent the increase on cardiac contractility from sympathetic activation in the first of reflex arc. The Prevention of Syncope Trial (POST) assessed the effectiveness of metoprolol in treating VVS. While the overall results of the trial were disappointing, sub-group analyses demonstrated that it might be useful in suppressing VVS in patients older than 42.[25,26]

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

As a different medication group, Kaya et al.[29] investigated the effect of amitriptyline, a tricyclic antidepressant drug, by using its anticholinergic effects in preventing syncopal episodes in 74 patients with VVS. At the end of the 6th month follow-up period, 67 patients (91%) were free from symptoms. Only two patients (0.3%) did not tolerate amitriptyline due to side effects.

Due to contrasting results from multiple trials, the medications should only be suggested in patients with the orthostatic form of VVS.

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

Between four suggested treatment strategies, the only cardiac pacing seems as effective if asystole is a dominant feature of VVS. In order to identify the patients who gain benefit from pacing, the relationship between symptoms and bradycardia should be revealed by the clinical evaluation and serial ECGs.

In the first study of 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; tilt-testing 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 patients were seen at the outpatient clinic every three months until the primary endpoint was reached or the study ended. The authors emphasized following points as study's important results: (1) the patients with isolated unexplained syncope and those with a positive response to tilt-testing had similar clinical characteristics and outcome; (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 tilt-testing. Despite authors' these comments, a correlation between the type of responses observed during tilt-testing and the casually documented events was made in only eight patients. Furthermore, the asystolic episode was not detected in any patients demonstrating vasodepressor response on TT.

In the second study of same group, the patients who were at least 30 years of age and had suffered, in the prior 2 years, three or more syncope episodes of suspected neurally mediated syncope which was considered by the attending physician to be a severe clinical presentation (because of high number of episodes that affect patient's quality of life or high risk for physical injury due to unpredictable occurrence) requiring treatment initiation included in the study.[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, respectively. 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% 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 ISSUE group was a double-blind, randomized placebo-controlled study.[32] Patients included in this study were ≥40 years and had experienced, in the previous 2 years, ≥3 syncopal episodes of likely neurally mediated syncope etiology. Pacemaker implantation criteria were documentation of syncope with ≥3 s asystole or ≥6 s asystole without syncope. The patients who met 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 aged ≥40 years affected by severe, unpredictable, recurrent, reflex syncope included in the study.[33] Syncopes were defined as 'severe' when they impaired the patient's quality of life due to high frequency and their occurrence was 'unpredictable', thus exposing patients to a risk of trauma. Syncopes were defined as 'recurrent' when the patient had had at least two episodes during the previous year or three episodes during the previous two years. During enrolment, patients initially underwent carotid sinus massage; if a diagnosis of cardio-inhibitory carotid sinus syndrome was made, a dual-chamber pacemaker was proposed, and follow-up immediately started. If carotid sinus massage was negative or the response was vasodepressor, the patient underwent TT. If a diagnosis of cardio-inhibitory form according to new Vasovagal Syncope International Study (VASIS) classification was made, a dual-chamber pacemaker was proposed, and follow-up immediately started.[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 cardio-inhibitory form was similar to the ISSUE-3 study.[31] Of 281 patients who met the inclusion criteria, 137 (49%) received a pacemaker: syncope recurred in 18% of them. At three years, the actuarial syncope recurrence rate was significantly lower than in 142 patients who did not receive a pacemaker and was observed using an ILR [43% (95% CI 29–57), p=0.01]. Surprisingly, the probability of recurrence of syncope was lower among patients who had had a negative response during TT than in those who had had a positive response (asystolic or not asystolic) or those who had not undergone TT. In patients demonstrating negative response on TT but asystolic response with ILR, the recurrence rate after cardiac pacing was very low, being around 5% at three years.

In a sub-group analysis of the ISSUE-3 study, the role of TT in predicting recurrences was investigated.[35] By using 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 2B 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 two groups had similar clinical characteristics. Syncope recurred in 8 (31%) TT+ and in 1 (4%) TT– patients. At multivariable analysis, TT+ and a total number of events were the only independent predictor 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 paced patients was much higher 63±14 and 73±11 years, respectively.

By all these data, the dual-chamber cardiac pacing is suggested to reduce 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 mentioned in the previous sections, there is still no well-defined and effective strategy for all recurrent VVS cases. The studies investigating the effectiveness of physical counterpressure maneuvers and tilt training revealed conflicting results and low compliance rates. The second important point is that the vast majority of positive results related to mixed and vasodepressive type VVS cases. Thus, there is 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 two widely studied medications. Although the results seem promising for orthostatic hypotension cases, the data is not enough to say the effectiveness of these medications in classic VVS cases which applies in particular to the cardioinhibitory type.

Considering these limited data in patients with cardioinhibitory type VVS, prevention of bradycardia or asystole episodes by 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 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 of such a definition of indication is that the patients under the age of 40 were not included in the studies, even in the studies demonstrating positive results like ISSUE-3 and SUP 2.[32,34] The other relatively well-designed trials such as the Vasovagal Pacemaker Study (VPS)-2 and the vasovagal syncope and pacing trial (SYNPACE) showed no benefit of pacing in those with the pacemaker on compared with those who had the pacemaker off.[36,37]

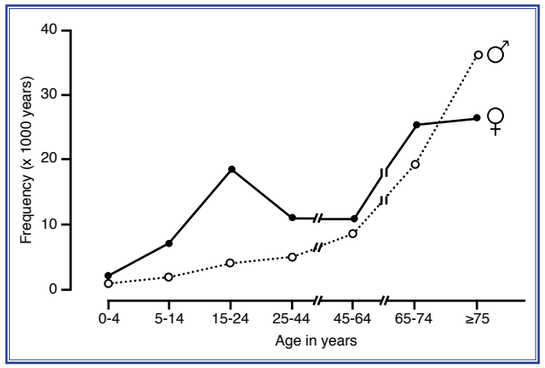

Figure 1. Frequency of the complaint syncope as reason for encounter in general practice in the Netherlands. Data are obtained from the general practitioners' transition project. It concerns an analysis of 93,297 patient-years. The arrow around 1 year is to indicate that a small peak occurs between 6–18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

Recently, in a report by Wieling et al. it has been shown that there are two peaks of incidence during life, with the first at approximately 15 years of age, predominantly female, and the second in older patients, >65 years, with an even gender distribution, a similar pattern to that observed in the general population (Fig. 1).[38,39] If the data are examined by VVS, most presentations of syncope are 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 reduces 37% for subjects aged 40–60 years. Importantly, in patients <40 years orthostatic hypotension is a rare cause of syncope; orthostatic hypotension is frequent in very old patients.

If all these data evaluate together, there is no acceptable and rational modality 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] By this way, a search strategy can be constructed for terms relating to the population; this can be combined with terms relating to the interventions and comparators (other main treatment options) to be evaluated. During designing of a well-formulated review question on the effectiveness of a new intervention using the PICO framework, 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 was no increased risk of cardiovascular morbidity or mortality associated with VVS. Thus, the effect on mortality is not an primary endpoint for VVS intervention studies. The goal of treatment should be to prevent recurrences 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 136 syncope patients. Compared with the general population, quality of life of syncope cases was lower in all subscales of EuroQol-5D. Importantly, prodromal symptoms decreased the quality of life more than syncope alone. Thus, the selection of 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 the patients with VVS.

Reviewing the Evidence for an Alternative Strategy

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

Selection of Relevant Studies

During selection of the studies, all 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 decisions. Providing 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 by 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 perform to put forth whether 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 because it may give a chance in pointing to published trials that may be missed.

Relevant articles may be obtained from a search of well-accepted databases by using the keywords "CNA," "vagal" AND "denervation," "vagal" AND "ablation,"" syncope," AND "ablation," and "GPs" AND "ablation" as search terms. Finding additional eligible studies, review articles should also be screened.

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. As is the case in the current syncope guideline, the question of whether there is an effective strategy in patients with VVS under the age of 40 cannot be answered by randomized trials. So, during the review process, the inclusion of non-randomized studies should be justified by review authors. It is well-known that potential biases are a bigger problem for non-randomized studies compared with 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 should not be a big deal to consider non-randomized studies during the evaluation of an innovative strategy.

Clinical efficiency of CNA strategy in patients with VVS has been evaluated in 6 cohorts before and after studies, so far.[9,43] As a targeted clinical endpoint, the data related to freedom from syncope and freedom from prodromes was investigated in all studies. Duration of follow-up which was 12.3±3 months in the study with the shortest follow-up time was presented in five of six studies. Three of six studies consist of not only VVS cases, but also the 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 in the studies.

Interpretation of the Results

The guidelines for data collection prefer 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 as in a case in VVS, indirect 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 of CNA strategy in patients with VVS. Facilitating assessment, all clinical data might be divided into three 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 such as VVS, functional atrioventricular block, sinus node dysfunction was presented by Pachon et al.[6] In VVS cases, only patients demonstrating cardioinhibitory response on a tilt table test were included in the study. Freedom from syncope and prodromes was presented as 100% at the end of 9.2±4.1 months follow-up period. A similarly designed prospective study was conducted by our group.[8] In VVS group, the cases demonstrating type 2B or type 1 response with more than 3 seconds asystole, according to new VASIS classification on TT, underwent the procedure. Freedom from syncope and prodromes 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 1 (asystole) response based on the ISSUE classification were included in the study.[44] Freedom from syncope was constant with %100 in long-term follow-up (23±14 months). There was no data for prodromal symptoms in that study. When all data were evaluated together, there was no new syncope in any of 18 VVS cases.

Clinical efficacy of CNA was investigated in three studies consisting only of cases with VVS. A total of 110 patients were included in the study according to not only to clinical findings but also to positive TT results. The vast majority of cases demonstrated cardioinhibitory response on 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, mean follow-up duration and freedom from syncope rate 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 follow-up period, freedom from syncope was detected as 100% and 89%, respectively.

To compare 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] Retrieved citations were first screened independently by two 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 three studies; only left atrial approach was used in the remaining studies. There was no major complication related to the procedure reported.

Interpreting the Evidence to Make Recommendations

After completion of the review questions, we should decide what recommendations can usefully be made to health care 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 effective strategy. A key stage in moving from evidence to recommendations weighs up the magnitude and importance of the benefits and harms of an intervention. For CNA strategy, we may do it qualitatively (for example, 'the evidence of a reduction in syncope rates outweighed a small or none increase in adverse effects. Current guidelines use classification of I, II, and III to indicate the strength of recommendation. Levels of evidence and quality of evidence are indicated with A, B, and C.

The strength of the recommendation is described in three levels of certainty in the Guidelines Manual of NICE such as the interventions that must (or must not) be used, the interventions that should (or should not) be used, and the 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 more time considering and discussing the options with the patient. For CNA, it may be possible to make 'strong' recommendations for subgroups of people with young age and cardioinhibitory type.

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 three 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 2B or type 1 response with more than three seconds asystole, 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 a 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 the issue is the usage of CNA strategy in young patients with VVS, the discussion of uncertainty may include consideration 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. Increasing the level of evidence of technique, large-scale, randomized, controlled trials are needed.

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