Cardioneuroablation in the treatment of neurally mediated reflex syncope: a review of the current literature

Nöral aracılı senkop tedavisinde kardiyonöroablasyon: Mevcut literatürün gözden geçirilmesi

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ABSTRACT

Objective: An imbalance between parasympathetic and sympathetic tone is a main cause of neurally mediated reflex syncope (NMRS). These patients may be very symptomatic and the condition may require cardiac pacemaker implantation. Cardioneuroablation (CNA) is a relatively novel technique based on radiofrequency ablation of vagal ganglia that can be used in treatment of NMRS. The aim of this analysis was to compare potential role of CNA in patients with NMRS.

Methods: In accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement, literature search was conducted using the keywords "cardioneuroablation," "vagal denervation," "reflex syncope," "vagal ablation," and "ganglionic plexi ablation." Retrieved citations were first screened independently by 2 reviewers for inclusion and exclusion criteria.

Results: 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 left atrial approach was used in the remaining studies. There was no major complication related to the procedure reported.

Conclusion: Focused or extensive vagal ganglia ablation may be a potential alternative to pacemaker implantation in a carefully selected patient population. In contrast to pharmacological therapy and pacemaker implantation, ganglia ablation is designed to get to the root of the problem: disturbances in the intrinsic cardiac autonomic nervous system. This novel technique should be evaluated in large-scale, randomized, controlled trials.

ÖZET

Amaç: Parasempatik ve sempatik tonüs arasındaki denge bozukluğu nöral aracılı refleks senkobun (NARS) ana nedenlerinden biridir. Bu hastalar çok semptomlu olabilir ve durum kalp pili takılmasını gerektirebilir. Kardiyonöroablasyon (KNA) vagal gangliyonların radyofrekans kateter ablasyonuna dayanan ve NARS'li hastalarının tedavisinde kullanılabilen göreceli olarak yeni bir tekniktir. Bu çalışmada, NARS'li hastalarda KNA'nın rolü ile ilgili mevcut bilgiler karşılaştırıldı.

Yöntemler: PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) beyanına uygun olarak 'cardioneuroablation', 'vagal denervation', 'reflex syncope', 'vagal ablation' ve 'ganglionic plexi ablation' kelimeleri ile literatür taraması yapıldı. Tüm yayınlar dahil edilme ve dışlanma kriterleri açısından iki yorumcu tarafından bağımsız olarak değerlendirildi.

Bulgular: Toplam beş gözlemsel çalışma ve beş olgu sunumu çalışmaya kabul edildi. Senkopsuz sağkalım %100 iken herhangi bir prodromsuz sağkalım %50 ile %100 arasında bulundu. Üç çalışmada her iki atriyumdan ablasyon uygulanırken iki çalışmada sol atriyum yaklaşımı kullanılmıştı. İşleme bağlı ciddi komplikasyon izlenmedi.

Sonuç: Odaklanmış ya da geniş vagal ganlİyon ablasyonu dikkatli seçilen hastalarda kalp pili takılmasına bir seçenek olabilir. Farmakolojik tedavi ve kalp pili takılmasından farklı olarak gangliyon ablasyonu problemin kökenini yani kalbin otonom sistemindeki bozukluğu hedeflemektedir. Bu yeni teknik geniş kapsamlı randomize çalışmalarda değerlendirilmelidir.

Received: August 23, 2016 *Accepted:* October 28, 2016

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Neurally mediated reflex syncope (NMRS) traditionally refers to a heterogeneous group of conditions in which cardiovascular reflexes that are normally useful in controlling circulation are intermittently inappropriately activated. It is the most common cause of transient loss of consciousness and considerably reduces quality of life.[1] Occurrence of vasodilatation and/or bradycardia in response to a trigger may result in drop in arterial blood pressure and global cerebral perfusion.[2] The term "cardioinhibitory" is commonly used when bradycardia or asystole predominates, and "vasodepressor" refers to predominance of clinical picture with loss of upright vasoconstrictor tone. "Mixed" is used if a combination of these 2 responses in different ratios predominates.[3] At this time, there are only non-pharmacological physical treatments; no proven effective pharmacological therapy exists for NMRS.[4] Possible efficacy of pacing to prevent NMRS episodes has been investigated in some major multicenter, randomized, controlled trials. Unfortunately, results have been conflicting.[5–9] It has been demonstrated in animal studies that parasympathetic postganglionic neuron bodies are primarily located in epicardial areas.[10–12] Radiofrequency catheter ablation (RFCA) of these epicardial ganglia from endocardial surface was suggested by Pachon et al.[13] as a potential therapeutic strategy. Data indicate that this novel technique could be effective, but the number of published studies is limited and the majority are observational and small-scale. The present study is a review of the current evidence about use of this technique in cases of NMRS.

METHODS

The current study was conducted in accordance with the recent Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement.[14] Relevant articles were obtained from search of PubMed and MEDLINE databases through August 20, 2016. Search was performed using the keywords "cardioneuroablation," "vagal denervation," "reflex syncope," "vagal ablation," and "ganglionic plexi ablation" as search terms, according to published recommendations.[15] Titles and abstracts of all returned articles were screened for exclusion. To find additional eligible studies, review articles were also screened.

Retrieved citations were first screened independently by 2 reviewers (T.E.G. and S.B.). If the citations were deemed potentially pertinent, they were then appraised as complete reports according to the following selection criteria: (1) human studies, (2) published through June 30, 2016, (3) investigation of patients undergoing cardioneuroablation (CNA) or vagal denervation for reflex syncope using RFCA, and (4) published in English. Exclusion criteria were as follows: (1) non-human setting, (2) duplicate reporting (in which case, manuscript reporting the largest sample of patients was selected), (3) studies without comprehensive follow-up description, (4) vagal denervation for atrial fibrillation (AF), functional atrioventricular (AV) block or sinus node dysfunction or sinus bradicardia, or (5) letter to the editor articles.

Abbreviations:

AA	Anatomical approach
AF	Atrial fibrillation
AV	Atrioventricular
CNA	Cardioneuroablation
FFT	Fast Fourier transform
HFS	High frequency stimulation
HR	Heart rate
HUT	Head-up tilt table test
LA	Left atrium
NMRS	Neurally mediated reflex syncope
RA	Right atrium
RFCA	Radiofrequency catheter ablation
RV	Right ventricle
SA	Spectral analysis
SDNN	Standard deviation normal-normal

Search results

The first search identified 7 articles; from among this group, 4 were excluded following application of the inclusion and exclusion criteria, and 3 observational studies were selected and enrolled.[13,16,17] Details of selection flowchart are summarized in Figure 1. Second search identified 2901 articles; 2897 were excluded following application of the inclusion and exclusion criteria. Four were selected: 2 observational studies[16,18] and 2 case reports.[19,20] Third search identified 2854 articles; 2845 from this group were excluded following application of the inclusion and exclusion criteria. Nine were selected: 5 observational studies[13,16–18,20] 2 case reports, and 1 report of 2 cases.[19,21,22] Fourth search identified 328 articles; 322 of which were excluded following application of the inclusion and exclusion criteria. Total of 6 were selected: 4 observational studies[16–18,20] and 2 case reports.[19,21] Last search identified 70 articles; from among this group, 68 were excluded following application of the inclusion and exclusion criteria and 2 case reports were selected.[23,24] After elimination of same research results, total of 5 observational studies and 4 case reports remained. Current evidence was examined in 2 groups: observational studies and case reports. Efforts

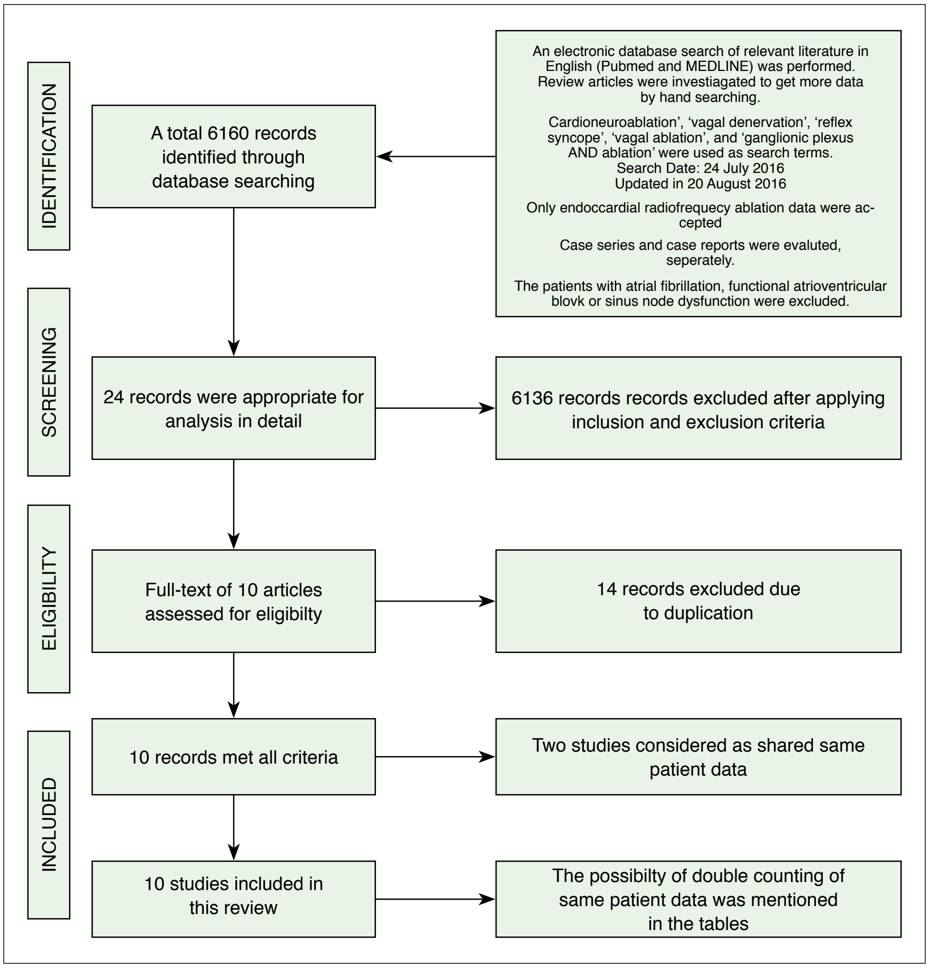

Figure 1. Flowchart of study selection and enrollment process for present systematic review.

were made to group the 3 main variations of this procedure, and provide comparison of outcomes.

RESULTS

Observational studies

As detailed in Table 1, total of 5 observational studies were included in the present analysis. Two of these studies were mixed case series consisting of patients with NMRS, functional AV block, and sinus node dysfunction.[13,17] Two of the studies were conducted by same group.[13,16]

Study prepared by Sun et al. was the only intervention comparison trial of high frequency stimulation (HFS) versus anatomical approach (AA). Remaining 4 studies primarily consisted of consecutive enrollment of patients with same single approach and evaluation of outcome measures. Yao et al. used HFS, while Pachon et al. used sequential combination of spectral analysis (SA) and AA. The first study to define combined use of all 3 approaches was conducted by our group.[17]

Follow-up ranged from 9 to 36 months in studies. Freedom from syncope and freedom from prodrome was 100% and between 50% and 100%, respectively, in the studies. Ablation was performed via both atria in 3 studies.[13,16,17] Only left atrial approach was used in remaining studies.[18,20] There was no major complication related to procedure. Outcome measures in observational studies are summarized in Table 2.

Case reports

A total of 6 patients were presented in 5 articles. Inclusion criteria of cases were similar and consisted of cardioinhibitory type, positive tilt test, syncope resistant to pharmacological treatment and physical coun-

Table 1. Baseline characteristics of patients for observational studies included in systematic review

First author, year	Pachon, 2005[13]	Pachon, 2011[16]	Yao, 2012[18]	Aksu, 2016[17]	Sun, 2016[20]
Study design	Single center, prospective, mixed patient population	Multicenter, prospective	Single center, prospective	Single center, prospective	Single center, prospective, mixed patient population
Inclusion criteria	Cardioinhibitory, positive tilt test	Cardioinhibitory or mixed, positive atropine test, positive tilt test	Cardioinhibitory or mixed, more than 3 syncopal episodes, positive tilt test,	Cardioinhibitory or mixed, more than 3 syncopal episodes, positive atropine test, positive tilt test	Cardioinhibitory or mixed, more than 3 syncopal episodes, positive tilt test
Number	6*	43†	10	8**	57 (10 vs 47)††
Method of localizing ganglionic plexi	SA+AA	SA+AA	HFS	SA+HFS+AA	HFS vs AA
Ablation area guidance	Fluoroscopy	EnSite system	EnSite system	EnSite system	EnSite system
Mean follow-up duration (months)	9.2	45	30	11	36

*The study population consisted of patients with neurally mediated reflex syncope, functional atrioventricular block, and sinus node dysfunction. Only patients with neurally mediated reflex syncope were included in the evaluation. Results of the procedure were defined for 5 patients in original study. The procedure was not performed in 1 patient due to anatomical anomaly. The study population consisted of patients with neurally mediated reflex syncope, functional atrioventricular block, and sinus node dysfunction. Only patients with neurally mediated reflex syncope were included in the evaluation. †This study population may include patients from reference 13. ††This study population may include patients from reference 19.
AA: Anatomical approach; HFS: High frequency stimulation; SA: Spectral analysis. EnSite cardiac mapping system; St. Jude Medical, Inc., St. Paul, MN, USA.

Table 2. Occurence of commonly reported outcomes according to technique and approach in observational studies

Technique	Approach	Procedure time (minutes)	Follow-up duration (months)	Syncope recurrence	Prodrome-pre	Prodrome-post	HUTpre	HUTpost	Heart rate variability (SDDN)	Reference
SA+AA	BA	–†	9.2	1/5 (20%)	5/5 (100%)	0/5 (0%)	5/5 (100%)	0/5 (0%)	SD	(13)
SA+AA	BA	–†	45	3/43 (6.9%)	–†	5/43 (11.6%)	43/43 (100%)	4/43 (9.3%)	SD	(16)
HFS	LA	–†	11	0/10 (0%)	7/10 (70%)	5/10 (50%)	10/10 (100 %)	2/10 (20%)	SD	(19)
HFS*	LA	50.2	10	0/10 (0%)	7/10 (70%)	5/10 (50%)	–†	–†	–†	(21)
AA*	LA	43.7	47	5/47 (10.6%)	40/47 (85.1%)	11/47 (23.4%)	–†	–†	–†	(21)
SA+AA+HFS	BA	121.2	11	0/8 (0%)		6/8 (75%)	–†	–†	SD	(17)

*These data were taken from the same study.[20] †These outcome measures were not reported as a discrete value in this reference.
AA: Anatomical approach; BA: Biatrial approach; HFS: High frequency stimulation; LA: Left atrial approach; RA: Right atrial approach; SA: Spectral analysis; SD: Significantly decreased.

ter pressure maneuvers, except for case 6, in which syncope was mainly related to high degree AV block (Table 2). Different catheters were used for ablation. Although non-irrigated catheters were used in earlier 3 cases,[21,23] irrigated catheters were used in the last 3 cases.[19,22,24]

Outcome measures

Adjunctive pharmacotherapy

Postablation adjunctive pharmacological treatment, which is a potentially complicating factor, was not described in detail in most of the studies. Warfarin with target prothrombin time international normalized ratio (INR) value of between 2 and 3 for 2 months was used in 1 study in which adjunctive antiarrhythmic or antidepressant treatment was not mentioned.[13] In the second study reported by the same group, 100 mg/day aspirin was used following warfarin for 1 month. They treated 1 patient with recurrent neurally mediated syncope and positive head-up tilt table test (HUT) with

Table 3. Baseline characteristics of patients for case reports included in systematic review

First author, year	Scavanacca, 2009[21]	Liang, 2012[19]	Rebecchi, 2012[23]	Suenaga, 2015[22]*	Fukunaga, 2016[24]**
Age	15	57	31 and 45	17	35
Patient characteristics	Syncope resistant to medications and physical counterpressure maneuvers, cardioinhibitory, positive tilt test	Syncope resistant to medications and physical counterpressure maneuvers, cardioinhibitory, positive tilt test	Syncope resistant to medications and physical counterpressure maneuvers, cardioinhibitory, positive tilt test	Syncope resistant to medications and physical counterpressure maneuvers, cardioinhibitory, positive tilt test	Recurrent syncope due to intermittent advanced atrioventricular block
Determination method of ganglionic plexi	HFS	HFS	AA	AA	AA
Guidance of ablation area	Carto system	HFS	Carto system	Carto system	Carto system
Ablation site	Both atria	Both atria	Right atrium	Right atrium	Both atria
Follow-up duration (months)	9	12	8 and 5	12	10

*Patient has dextrocardia. **Main cause of syncope was advanced atrioventricular block.
AA: Anatomical approach; HFS: High frequency stimulation.ARTO mapping system; Biosense Webster, Inc., Diamond Bar, CA, USA.

disopyramide and venlafaxine, prescribed hormonal treatment for another patient with premenstrual syndrome-associated prodromal symptoms, and fluoxetine or venlafaxine in 5 patients with positive HUT.[16] Postprocedural anticoagulation with warfarin and target INR of between 2 and 3 for 3 months was applied in,[17] without additional pharmacological treatment. They tried nonpharmacological treatments comprising patient education, avoidance of possible triggers, early recognition of prodrome, and techniques to terminate episodes (e.g., supine positioning and counterpressure maneuvers). Only warfarin, and only in 2 patients with concomitant AF, was used in Yao et al. study.[18] Sun et al. discontinued all pre-ablation medication for their patients, which included beta-blockers, fludrocortisone in 2 patients and 10 mg daily midodrine in 10 patients.[20] Pharmacological pretreatment might affect procedural success, and postprocedural adjunctive treatment might affect outcomes. Thus, these points should be made clear for enrollment, periprocedural period, and follow-up, and decision-making algorithm should also be clearly defined.

Intraprocedural outcomes

We defined intraprocedural indicators of procedural success as complete elimination of AV block and persistent increase in Wenkebach point, increase in sinus rate in elimination of response to parasympathetic response to HFS, and elimination of atrial fractionated potentials above 300 Hz with residual potentials below 1 mV.[17]

Stress test

Basal heart rate (HR), maximal HR, and chronotropic response were the assessed variables in some studies. No significant changes in parameters of initial HR, maximal HR, or chronotropic incompetence percentage were detected in this study.[16]

Rhythm Holter data

Holter recordings prior to procedure and in follow-up period were available in majority of the studies. Assessed and reported outcome variables consisted of: HR variability variables: standard deviation normal-normal (SDDN); degree of increase in maximal, mean and minimum HR; and presence or absence of pauses or dysrhythmia.[13,16–18] There were significant increases in minimal and mean HR parameters, while SDDN parameter demonstrated statistically significant decreases with CNA in studies.[16] Sun et al. demonstrated that in long-term follow-up, changes in SDDN and mean HR lost statistical significance, while changes in minimum HR preserved their significance.[20] Another variable derived from 24-hour rhythm Holter data used in some studies was deceleration capacity. This parameter was associated with syncope recurrence following CNA.[16]

Head-up tilt table test

Follow-up tilt table testing was performed in majority of the studies to assess efficacy of the procedure. Changes in HUT results interpreted as favorable outcomes of CNA were as follows: (1) change in detected hemodynamic response from cardioinhibitory to vasodepressor, milder cardioinhibitory (i.e., mild sinus bradycardia) or completely negative test result, and (2) increase in time-to-symptom or syncope onset. Sun et al. demonstrated significant decreases in time-to-symptom onset with CNA and comparable decreases with AA versus HFS.[20] Drifting of prodromal symptoms or syncope from tilt table phase to extended pharmacological challenge phase was also seen as favorable outcome. Pachon et al., interpreting HUT test results for CNA, found that cardioinhibitory responses with transient AV block were observed when AV node was not targeted. The same study group demonstrated milder cardioinhibitory responses postablation.[16]

Prodromal events

Prodromal events were reported as distinct outcome in some studies,[13] while reported together with all syncopal events in others. There was wide variation in reported rates of prodromal events during postprocedural follow-up (0%–85.1% in AA group of Sun et al. study). This may be due to sample size, adjunctive pharmacotherapy, or implementation of other preventive measures.

Syncopal events

Recurrence of syncopal events was main outcome in most of the studies. Recurrence rate was 10.6% in study conducted by Pachon et al.,[16] in which they used SA and AA approach together, and 6.9% in study reported by Sun et al.,[20] in which they used AA approach. Kaplan-Meier survival plot was drawn with the available follow-up data. Maximum, minimum, and average follow-up times were used whenever event-free survival data was not available for individual cases from the studies. Quantitative statistical measures of significance of the difference between groups with regard to event-free survival would not be applicable due to heterogeneity of the studies. It can be said however, based on the survival plot, that methodologies incorporating HFS into CNA are associated with lower rates of syncopal events, and anatomical-only approaches were associated with early recurrence and higher rates (Figure 2).

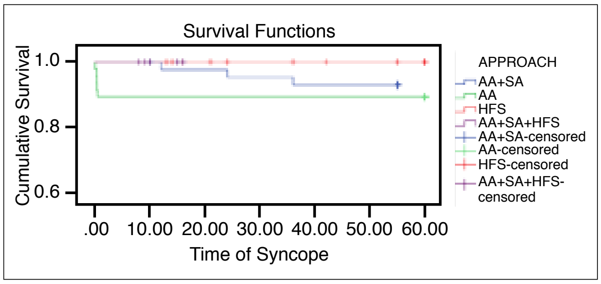

Figure 2. Survival graph of new syncopal events during postprocedural follow-up. AA: Anatomical approach; HFS: High frequency stimulation; SA: Spectral analysis.

DISCUSSION

In great majority of NMRS cases, it may be impossible eliminate syncopal episodes and control prodromal symptoms. Furthermore, there is no accepted single treatment modality for all patients according to relevant guidelines.[1] On the basis of conflicting study results, endocardial pacing plays a small role in therapy for reflex syncope, unless severe spontaneous bradycardia is detected during prolonged monitoring.

Vagal pathways to the sinus and AV nodes have been extensively studied.[10–12] Basically, vagal postganglionic neurons to the sinus node are located in a fat pad (ganglionic plexus) adjacent to the right pulmonary vein-atrial junction, while vagal postganglionic neurons to the AV node are located in a fat pad at the junction of the inferior vena cava and LA. In 1997, Chiou et al.[12] investigated the functional pathways of efferent vagal innervation to the atria by measuring effective refractory period, HR, and AV nodal conduction changes during vagal stimulation before and after application of phenol or RFCA to selected areas of the heart to interrupt efferent vagal fibers that may travel through that site. At the end of study, they found a new, additional fat pad between the aorta and the superior vena cava. The major importance of this fad pat is that bilateral vagal fibers to the sinus and AV nodes converge first at this area and then project to the other ganglia.

The autonomic nervous system consists of parasympathetic, sympathetic, and sensory components residing in different anatomical localizations in target organ. It is well known that parasympathetic and sympathetic systems reach end organ via pre- and postganglionic fibers. Unlike the sympathetic system, the body of postsynaptic parasympathetic neurons is very close to target organ.[14,15] This is also the case for the heart. Therefore, ablation of these postganglionic neuronal cell bodies may be achieved with endocardial RFCA, whereas ablation effect is not permanent in sympathetic and sensory neurons due to distinct localization of postganglionic neuron bodies from the heart.[25,26]

After demonstration of selective vagal denervation of sinus and AV nodes achieved with surgical dissection of vagal ganglia, human studies began to aim for permanent vagal denervation.[25] The first studies were related to vagally induced AF.[27,28] To define exact localization of these fat pads, 2 different approaches were used by investigators. First, Scanavacca et al.[27] used HFS and evaluated whether selective RFCA of atrial sites in which HFS-induced vagal reflexes prevented paroxysmal AF. Then, Pachon et al.[28] successfully used fast Fourier transform (FFT) analysis to define ganglionic plexi.

These promising results initiated a new era in treatment of patients with vagally induced bradyarrhythmias. Pachon et al. presented the first results of CNA procedure in human in a mixed study population consisting of NMRS, intermittent high degree AV block, and sinus node dysfunction.[13] Using FFT, they demonstrated significant relief of syncope episodes and prodromal symptoms at mean follow-up duration of 9.2±4.1 months. Recently, we presented promising results in a similar patient population.[17] However, we investigated effectiveness of selective and/or stepwise RFCA of these areas via right atrium (RA) and/or LA rather than use standard approach in all patients. Additionally, we used both FFT analysis and HFS to define vagal innervations sites. Although we ablated both atrial vagal myocardium sites in patients with NMRS and sinus node dysfunction, procedure was performed via RA in patients with AV block, followed by RFCA of all ganglia via LA, if AV conduction disorder persisted. We found significant relief of symptoms at follow-up duration of 9.5±3.1 months.

As of now, main question is whether AA is enough to achieve satisfactory results or not. Recently, Sun et al.[20] compared HFS and anatomically guided ganglionic plexus ablation in 57 patients with NMRS. In AA, in addition to the 4 previously defined ganglionic plexus sites, left lateral fat pad located between left inferior pulmonary vein and left auricular appendage was integrated into ablation protocol. In HFS group, they ablated only sites demonstrating vagal response during HFS. At the end of the study, no statistical differences were found between groups in either freedom from syncope or recurrent prodrome events; however, procedure time was significantly decreased with anatomical approach.[20]

To overcome requirement of transseptal puncture and LA ablation, selective RA vagal denervation was recently studied by Rebecchi et al.[23] in 2 patients with NMRS. They used AA to ablate ganglionated plexi. Ablation procedure consisted of radiofrequency delivered to RA anatomical sites where underlying presence of ganglionic plexus clusters was regarded as highly probable on the basis of anatomical studies. Superior RA, posterior RA, and inferior RA ganglionic plexi were targeted empirically. Procedure was successful in both cases. In our previously published case, we demonstrated that RA approach alone may be sufficient in patients with functional AV block.[29,30]

Lastly, therapeutic effects of CNA may be not limited to cardioinhibitory type of vasovagal syncope, but may also encompass mixed-type syncope, and even situational syncope. In our study, we demonstrated that the procedure may be used in patients with situational syncope.[17] It is well known from implantable loop recorder experience that only half of spontaneous NMRS episodes are asystolic in nature.[31] As a result, ablation of cardiac vagal ganglia may not guarantee success in all NMRS cases. Three different measures have been suggested by authors (1) as a means of aiding decision of eligibility for CNA and (2) evaluating effectiveness of CNA and predicting recurrent syncopal events following the procedures.

Atropine test was performed by Pachon et al.[16] to decide eligibility for CNA. They defined a greater than 25% increase in HR after atropine administration as positive atropine test result and only enrolled patients with positive atropine test results. They also demonstrated significant decrease in atropine test positivity following CNA in their patient group. The same study group showed partially positive atropine test results in long-term follow-up, suggesting a limited reinnervation and/or partial ablation.[16] Refining patient selection with implantable loop recorder as well may increase clinical benefit derived from this procedure.

Our review has clearly demonstrated that there is very limited evidence on use of this potentially effective treatment. Despite evolution of various methodologies for performing this procedure, success rates seem to be at comparable levels. Interpretation of the current data is very difficult due to lack of standardization of outcomes and side-by-side, randomized, controlled intervention trials in the field.

Limitations

The studies involved in this review lack (1) standardization of the periprocedural and postprocedural optimal medical therapy, (2) standardization of the decision-making process in case selection, (3) standardization of the procedure (SA, AA, HFS, and various combinations of these; LA, RA, and biatrial approaches), (4) standardization of outcome measures and follow-up time, and (5) adequate sample size and randomization.

Conclusion

All these results provide important insight into the complicated nature of autonomic innervation of the heart that comprises seemingly contradictory responses. Focused or extensive vagal ganglia ablation may be a potential alternative to pacemaker implantation in a carefully selected patient population. In contrast to pharmacological therapy and pacemaker implantation, ganglia ablation is designed to get to the root of the problem: disturbances in the intrinsic cardiac autonomic nervous system. This novel technique should be evaluated in large-scale, randomized, controlled trials.

Conflict-of-interest issues regarding the authorship or article: None declared

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Keywords: Ablation; bradycardia; denervation; syncope; parasympathetic; vagus.

Anahtar sözcükler: Ablasyon; bradikardi; denervasyon; parasempatik; senkop; vagus.