Closed-looped stimulation cardiac pacing for recurrent vasovagal syncope: A systematic review and meta-analysis

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Abstract

Background: Vasovagal syncope (VVS) is defined by transient loss of consciousness with spontaneous rapid recovery. Recently, a closed-loop stimulation pacing system (CLS) has shown superior effectiveness to conventional pacing in refractory VVS. However, systematic review and meta-analysis has not been performed. We assessed the impact of CLS implantation and reduction in recurrent VVS events by a systematic review and a meta-analysis.

Methods: We comprehensively searched the databases of MEDLINE and EMBASE from inception to September 2017. Included studies were published prospective or retrospective cohort, randomized controlled trial, and case–control studies that compared VVS events between recurrent, severe, or refractory cardioinhibitory VVS patient implanted with CLS and conventional pacing. Data from each study were combined using the random-effects, generic inverse variance method of DerSimonian and Laird to calculate odds ratios and 95% confidence intervals.

Results: Six studies from November 2004 to October 2017 were included in this meta-analysis involving 224 recurrent, severe, or refractory cardioinhibitory VVS patients implanted with CLS and 163 recurrent, severe, or refractory VVS patients implanted with conventional pacing. CLS significantly reduced recurrent VVS events compared to conventional pacing (pooled odds ratio = 0.23, 95% confidence interval: 0.13-0.39, P = 0.000, I² = 36.5%) as well as subgroup of four randomized controlled trial studies (pooled odds ratio = 0.28, 95% confidence interval: 0.17-0.44, P = 0.000, I² = 39.2%).

Conclusion: Closed-loop stimulation significantly reduced recurrent VVS events up to 80% when compared to conventional pacing. Our study suggests that CLS is an effective tool for preventing syncope recurrences in patients with recurrent, severe, or refractory cardioinhibitory VVS.

Keywords: bradycardia, closed-loop stimulation, pacemaker, syncope, vasovagal
1 | INTRODUCTION

Syncope is a clinical syndrome defined by abrupt transient loss of consciousness, loss of postural tone and rapid spontaneous recovery. It is believed to be from decreased blood flow to the brain. Vasovagal syncope (VVS) is the most common type of reflex syncope which is precipitated by emotional stress or orthostatic stress causing arterial hypotension and loss of consciousness. The most frequent mechanism of VVS is mixed cardioinhibitory and vasodepressor responses from abnormality in autonomic system regulation. Cardioinhibitory response may lead to inappropriate bradycardia or prolonged asystole, while vasodepressor response is caused by decreased sympathetic activity that may lead to symptomatic hypotension. Classically, patients may find the episode related to exposure to emotional or orthostatic stresses and may experience warmth, pallor, nausea, and diaphoresis. Diagnosis of VVS is on clinical basis. History and physical examination are sufficient to make a diagnosis in most cases. A head-up tilt test (HUTT) is recommended in patients with suspected VVS but initial evaluation gives unclear diagnosis. Severe recurrent VVS can lead to physical injury, limited daily activities, and decrease in quality of life in those who are affected. A previous study showed that conventional pacemaker implantation in severe recurrent VVS was an ineffective treatment. Permanent DDI pacing with rate-drop and rate hysteresis algorithm were reported to be effective in selected patients who presented with cardioinhibitory VVS. However, a recent study showed that the conventional pacemaker algorithm does not significantly reduce syncopal episodes and might act “too late” in the VVS process since patients develop decrease in blood pressure before bradycardia which is picked up by the conventional pacemaker.

Closed-loop stimulation (CLS) is a pacemaker system with a developed impedance censor in the right ventricle which reflects contractility and responds with rapid atrioventricular pacing. CLS is a rate-adaptive pacing which detects increased myocardial contractility by measuring the right ventricular intracardiac impedance and activates a high-rate atrioventricular sequential pacing that may anticipate withdrawal of sympathetic tone and may counterbalance the increase in vagal tone. There are some studies that suggest that this pacing algorithm is effective in preventing arterial hypotension and syncope in cardioinhibitory VVS. However, the previous studies have small sample sizes with no more than 50 subjects included. Recently, more studies have shown superior efficacy of CLS compared to conventional pacing. In this systematic review and meta-analysis, we investigated the impact of CLS implantation on reduction in recurrent VVS events.

2 | METHODS

2.1 | Search strategy

Two investigators (NP and NL) independently searched for published studies indexed in MEDLINE and EMBASE databases from inception to June 2017 using a search strategy (Figure 1) that included the terms “Closed-loop stimulation,” “pacemaker,” and “syncope.” Only English language publications were included. A manual search for additional pertinent studies and review articles using references from retrieved articles was also completed.

2.2 | Inclusion criteria

The eligibility criteria included the following:

1. Cohort, case–control study (prospective or retrospective), or randomized controlled trial study reporting incident of recurrent, severe refractory cardioinhibitory syncope in VVS patients with and without CLS implantation
2. Relative risk, hazard ratio, odds ratio, incidence ratio, or standardized incidence ratio with 95% confidence intervals or sufficient raw data for the calculation were provided.
3. Recurrent, severe, or refractory cardioinhibitory VVS participants without CLS implantation were used as controls.

Study eligibility was independently determined by two investigators (NK and PC), and differences were resolved by mutual consensus. The Newcastle-Ottawa quality assessment scale was used to evaluate each study in three domains: recruitment and selection of the participants, similarity and comparability between the groups, and ascertainment of the outcome of interest among cohort studies.

2.3 | Data extraction

A standardized data collection form was used to obtain the following information from each study: title of study, name of first author, year of study, year of publication, country of origin, number of participants, demographic data of participants, method used to identify cases and controls, method used to diagnose the outcomes of interest (VVS and recurrent syncope events), and average duration of follow-up with confounders that were adjusted and adjusted effect estimates with 95% confidence interval 95% confidence intervals and covariates that were adjusted in the multivariable analysis. To ensure accuracy, all investigators independently performed these data extraction process. Any data discrepancy was resolved by referring back to the original articles.

2.4 | Statistical analysis

We performed a meta-analysis of the included cohort studies using a random-effects model. The extracted studies were excluded from the analysis if they did not present an outcome in each intervention group or did not have enough information required for continuous data comparison. We pooled the point estimates from each study using the generic inverse-variance method of Der Simonian and Laird. The heterogeneity of effect size estimates across these studies was quantified using the I² statistic. The I² statistic ranges in value from 0 to 100% (I² < 25%, low heterogeneity; I² = 25%-50%,...
A sensitivity analysis was performed to assess the influence of the individual studies on the overall results by omitting one study at a time. Publication bias was assessed with funnel plot and Egger’s regression test (P < 0.05 was considered significant). All data analyses were performed using the Stata SE 14.1 software from StataCorp LP.

2.5 | Sensitivity analysis

We used a sequential exclusion strategy, as described by Patsopoulos and colleagues, to examine whether overall estimates were influenced by the substantial heterogeneity observed. We sequentially and cumulatively excluded studies that accounted for the largest share of heterogeneity until $I^2$ was less than 50%. We then examined whether relative risk estimates were consistent. In accordance with Cochrane, evidence of publication bias was examined through Egger’s test. Potential bias from clinical characteristics was analyzed with subgroup analysis and was compared with meta-regression among cohort study design vs randomized controlled trial.

### RESULTS

3.1 | Description of included studies

Our search strategy yielded 17 potentially relevant articles (10 articles from EMBASE and 7 articles from MEDLINE). After exclusion of 6 duplicated articles, 11 articles underwent title and abstract review. Three were excluded at this stage as they were not cohort studies. One study was excluded as they were abstract presentation, and one study was excluded because of potential duplicated studied population. Therefore, 4 randomized controlled trial and 2 retrospective cohort studies (224 VVS with CLS and 163 VVS without CLS).
| First Author       | Occheta | Kanjwal | Palmisano | Russo | Palmisano | Baron-Esquivias |
|-------------------|---------|---------|-----------|-------|-----------|----------------|
| Country of Origin | Italy   | USA     | Italy     | Italy | Italy     | Spain          |
| Year              | 2004    | 2010    | 2012      | 2013  | 2017      | 2017           |
| Study Type        | Randomized, single blind | Retrospective cohort | Retrospective cohort | Randomized single blind study, crossover design | Randomized, single-blind, multicentre study | Randomized, double-blind, controlled study |
| Participant description | Implanted dual-chamber pacemaker for VVS (DDD-CLS vs DDD) | Recurrent neurocardiogenic syncope (DDD-CLS vs DDD-conventional pacing) | Dual-chamber pacemaker implantation for recurrent, severe, cardioinhibitory VVS (DDD-CLS vs DDD-conventional pacing) | Refractory vasovagal syncope VVS and a cardioinhibitory response to HUTT (DDD-CLS on vs DDD-CLS off) | Implanted dual chamber-pacemaker for VVS (DDD-CLS vs DDD-conventional pacing) | Patients older than 40 y with high VVS burden and a cardioinhibitory head-up tilt test (DDD CLS vs sham DDI) |
| Indication for pacemaker implantation | Refractory cardioinhibitory both with and without asystole | Severe cardioinhibitory both with and without asystole | Refractory cardioinhibitory with asystole | Refractory and recurrent cardioinhibitory both with and without asystole | Recurrent cardioinhibitory both with and without asystole | Refractory and recurrent cardioinhibitory both with and without asystole |
| Exclusion criteria | Structural heart disease, severe underlying disease | N/A | Heart conduction defect, structural heart disease, psychiatry, hypertension | Underlying heart disease, kidney disease, hypertension, impaired glucose | Unable to perform a HUTT | Syncope from other causes, pregnant women and breastfeeding |
| Total Population  | 50      | 44      | 41        | 50    | 30        | 46            |
| CLS (events)      | 41 (0)  | 17 (0)b | 32 (7)    | 25    | 50 (2)    | 30 (9)        |
| Control (events)  | 9 (7)   | 9 (7)b  | 12 (9)    | 16    | 50 (15)   | 30 (23)       |
| Male (%)          | 54      | 14.3    | 44        | 44    | 66        | 60            |
| Mean age (y)      | 59 ± 18 | 41 ± 11 | 53 ± 16   | 53 ± 5.1 | 62.2 ± 13.5 | 56.30 ± 10.63 |
| Mean Duration of Follow-up (mo) | 18.9 ± 4.2 | 9 ± 3 | 52.8 ± 36 | 36 | N/A | 24 |
| Outcome Definition| Recurrent syncope | Recurrent neurocardiogenic syncope | Recurrent syncope | Number of syncopal episodes | Recurrent VVS induced by HUTT | Recurrent syncope |
| Conclusion by authors | The study demonstrates the effectiveness of CLS pacing in preventing cardioinhibitory VVS | Dual-chamber CLS pacing may be promising therapy for refractory NC | CLS pacing was more effective than dual-chamber pacing with conventional algorithms for syncope prevention in preventing bradycardia-related syncope | CLS is an effective algorithm for preventing syncope recurrences in healthy patients with tilt-induced vasovagal cardioinhibitory syncope. | CLS reduces the occurrence of syncope induced by HUTT | DDD-CLS pacing significantly reduced syncope burden and time to first recurrence |

| NOS | N/A | 7 | 9 | N/A | N/A | N/A |

CLS, close loop simulation; HUTT, head-up tilt test; NC, neurogenic syncope; NOS, Newcastle-Ottawa quality assessment scale; VVS, vasovagal syncope.

*Patient underwent CLS implantation and DDD-CLS on mode was compared with DDD-CLS off mode.

*Number of patient and events that was randomized and was used to calculate pooled odds ratio in randomized controlled trial subgroup.
were included in this meta-analysis. The clinical characteristics are described in Table 1.

3.2  Quality assessment of included studies

Quality of each study was evaluated by two independent authors (PK, WV). The Newcastle-Ottawa scale (0-9) was used in cohort studies to evaluate included studies on 3 domains: selection, comparability, and outcomes. Higher scores represent higher study quality. The score of each study ranged from 7 to 9 which reflected high quality of included studies (Table 1). For randomized controlled trial studies, the Cochrane Collaboration’s tool for assessing risk of bias in randomized trials was used (Figure 2) on the following items: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, and selective reporting (each component was categorized as having high, low, or unclear risk of bias). Discrepant opinions between authors were resolved by consensus.

3.3  Meta-analysis results

Six studies (224 VVS with CLS and 163 VVS without CLS) were included in our meta-analysis. Every study revealed a decreased risk of recurrent syncope events in VVS patients meeting statistical significance. CLS significantly reduced recurrent VVS events compared to conventional pacing (pooled odds ratio = 0.23, 95% confidence interval: 0.13-0.39, P = 0.000, I² = 36.5%) in our meta-analysis as well as in subgroup of four randomized controlled trial studies (pooled odds ratio = 0.28, 95% confidence interval: 0.17-0.44, P = 0.000, I² = 39.2%) (Figure 3). The statistical heterogeneity was moderate with I² of 36.5% and 39.2% for the overall and randomized controlled trial subgroup, respectively. Publication bias was found from Egger test (P = 0.002 and P = 0.022, respectively) and funnel plot (Figure 4). Sensitivity analysis to explore heterogeneity showed no significant change in our findings when omitting each study (Figure 5). For exploratory subgroup analysis by meta-regression, we found no difference among randomized controlled trial and cohort studies (P = 0.884).

(A) Random sequence generation (selection bias)
Allocation concealment (selection bias)
Blinding of participants and personnel (performance bias)
Blinding of outcome assessment (detection bias)
Incomplete outcome data (attrition bias)
Selective reporting (reporting bias)
Other bias

(B) Baron-Esquivias 2017
Occheta 2004
Palmisano 2017
Russo 2013

FIGURE 2  Risk of bias (A) and summary risk of bias (B) among randomized controlled trial studies
**4 | DISCUSSION**

Our meta-analysis suggests that dual-chamber CLS pacing is effective in preventing recurrent bradycardia-related syncopal episodes in patients with severe VVS.

Vasovagal syncope is the most common cause of fainting. Clinical outcome of VVS is usually benign. Pathophysiology of VVS starts with shifting of blood to lower extremities causing decrease in right ventricular filling and stroke volume. Then, sympathetic tone is activated leading to increase in cardiac contractility. Afferent signals from the left ventricle cause sympathetic tone withdrawal and increased vagal reflex leading to peripheral vasodilation, arterial hypotension, and bradycardia. The conservative treatment options are increase salt and fluid intake, counter pressure maneuvers, and...
medications including fludrocortisone, midodrine, beta blocker, and serotonin reuptake inhibitor. However, in severe recurrent VVS cases that affect daily function, permanent pacemaker is introduced into management of choice. The VVS patients have a fall in blood pressure preceding the fall in heart rate. Several studies reported that dual chamber pacing with either rate drop or rate hysteresis algorithms showed reduction in the frequency of syncope in VVS patients. These algorithms pace at an accelerated rate during impending syncope. Hysteresis algorithm allows the pacing rate to surpass the lower limit of heart rate for a programmable period of time. Rate drop algorithm is more complicated as it introduces rapid dual chamber pacing if the device detects a rapid reduction in heart rate. Ammirati et al suggested that dual chamber pacing with a rate-drop algorithm was more effective than dual chamber pacing with hysteresis algorithm. However, a recent study showed that the conventional pacemaker algorithm does not significantly reduce syncope episodes and the rate-only sensing algorithm of conventional pacemaker results in sensing the VVS process when it is well underway and provides the behind time pacing. Therefore, a newer dual-chamber CLS algorithm has been developed.

According to the latest guideline for evaluation and management of patients with syncope, treatments for first-episode VVS include adequate patient education, counter-pressure maneuvers, salt and fluids intake. For recurrent VVS, Midodrine (class IIa), Fludrocortisone (class IIIb), beta-blockers (class IIb), orthostatic training (class IIb), selected serotonin reuptake inhibitors (class IIb), and dual-chamber pacemaker therapy (class IIb) are indicated. The pacemaker therapy is beneficial particularly in patients with tilt-table test-positive cardioinhibitory response and not as effective in patients with vasodepressor response. However, it remains challenging to identify the underlying mechanism of VVS in each individual, even with tilt-table test. Currently, it is suggested that dual chamber pacing be used in a highly specific group of patients (class IIb), which includes patients ≥40 years of age with recurrent syncope and documented spontaneous pauses ≥3 seconds correlated with syncope or an asymptomatic pause ≥6 seconds.

Closed-loop stimulation pacemaker detects variation in myocardial contractility, which is caused by altered sympathetic and parasympathetic tone, at the beginning of VVS via increase in right ventricular intracardiac impedance, which then triggers high-rate atrioventricular sequential pacing. Studies show that the CLS provides timely intervention to prevent hypotension related to decrease venous return by maintaining cardiac output through heart rate (Cardiac Output = Heart Rate x Stroke Volume). Palmisano et al showed that CLS pacing starts 8 minutes before the maximum fall in blood pressure induced by vasovagal reaction and has reduced the maximum fall in systolic blood pressure and has increased the minimum value of mean systolic blood pressure by about 20 mm Hg compared with patients with conventional pacemaker. In the situations where VVS could not be aborted, CLS provides prodromal symptoms and delays loss of consciousness. Therefore, patients have earlier awareness and have time to prevent physical injury that might result from syncope. Most importantly, Occheta et al proves that CLS pacemaker improves quality of life for VVS patients.

5 LIMITATION

There are some limitations that could limit this meta-analysis validity. First of all, the included studies are all small populations with total of only 224 CLS participants and short follow-up duration compared to natural history of cardioinhibitory VVS. There should be studies with long-term follow-up in order to confirm lifetime benefit of the close loop stimulator. Secondly, there is heterogeneity among those included studies. There are differences in definition of outcomes including using recurrent syncope or occurrence of syncope induced by HUTT. The control groups are diverse among the included studies. There are differences in definition of outcomes including using recurrent syncope or occurrence of syncope induced by HUTT. The control groups are diverse among the included studies with differences in conventional pacemaker algorithm. However, after the analysis, CLS has a statistical significant improvement in outcome. In addition, there is concern for the poor reproducibility of an asystolic response during HUTT in patients with neurocardiogenic syncope. This raises issues about its clinical

FIGURE 4 Funnel plot of fragmented syncope events and closed-loop stimulation (CLS) implantation. Circles represent observed published studies of overall studies (A) and randomized controlled trial studies (B)
relevance and study validity.\textsuperscript{29,30} Anyhow, the studies that used occurrence of spontaneous recurrent syncopal event as an outcome of interest have consistent results with those that used HUTT as the outcome. Lastly, there is significant publication bias from Egger's test and funnel plot, indicating that there are a limited number of negative studies in this meta-analysis. Thus, we support publishing negative studies for further reference to ensure validity of the association.

6 | CONCLUSION

In summary, CLS pacing is considered as the optimal treatment for patients with recurrent, severe, or refractory VVS. Further studies should conduct long-term follow-up with assessment of clinical outcome of spontaneous syncopal events to confirm lifetime benefit.

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CONFLICT OF INTEREST

Authors declare no conflict of interests for this article.

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