



KEMENTERIAN KESIHATAN MALAYSIA

# INFORMATION BRIEF (RAPID REVIEW)

## CARDIONEURAL ABLATION IN TREATING MALIGNANT VASOVAGAL SYNCOPE

Malaysian Health Technology Assessment Section (MaHTAS)  
Medical Development Division  
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Please contact [htamalaysia@moh.gov.my](mailto:htamalaysia@moh.gov.my) if further information is required.

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## **TITLE: CARDIONEURAL ABLATION IN TREATING MALIGNANT VASOVAGAL SYNCOPE**

### **PURPOSE**

To provide brief information on cardioneural ablation in treating malignant vasovagal syncope.

### **BACKGROUND**

A vasovagal episode, also known as vasovagal syncope (VVS), is the most common type of reflex syncope. Reflex syncope is a general term for several types of syncope caused by a failure in autoregulation of blood pressure and cerebral perfusion pressure, resulting in transient loss of consciousness. More than 85% of syncopal events in people younger than 40 years are attributable to vasovagal syncope. Even in older people, vasovagal syncope causes more than 50% of syncopal episodes. The complex mechanisms drive this, involving a decrease in cardiac output and vascular tone.<sup>1</sup>

Vasovagal syncope can occur with upright posture (standing or seated or when exposed to emotional stress, pain, or medical settings) and is often defined by diaphoresis, warmth, nausea, and pallor. Vasovagal syncope is associated with vasodepressor hypotension and inappropriate bradycardia and is usually followed by fatigue. Typical features may be absent in older patients. Recognisable triggers and a distinct prodrome frequently precede an episode. The diagnosis is made mainly based on a comprehensive history, physical examination, and, if available, firsthand observation.<sup>2</sup>

Recurrent and severe VVS that is accompanied by significant hypotension and bradycardia may cause prolonged asystole (from 3 seconds to more than 60 seconds). In these cases, the VVS is defined as malignant VVS and can cause a serious physical injury (e.g., cranial trauma or bone fractures following a fall or an accident) and psychological impairment, including a substantial limitation of the patient's social and working life.<sup>3</sup>

The therapy of VVS is challenging. Given the benign nature of VVS and its frequent remissions, medical therapy is usually unnecessary unless conservative treatments are ineffective. In patients with malignant VSS, effective treatment is needed, as syncopal events without prodromes may cause serious trauma and impair quality of life (QoL).<sup>2</sup> Recently, cardioneuroablation (CNA) is an emerging strategy for treating conditions associated with hypervagotonia such as vasovagal syncope that is being studied but not yet advised for therapy due to a limited number of patients and a lack of findings from particular population-based research.<sup>4</sup> Cardioneuroablation of the parasympathetic ganglionated plexi (GP) has been demonstrated to produce excellent short- and middle-term effects in the treatment of VVS as these GPs play an important role in the genesis of VVS, and symptomatic bradycardia. Four major GP sites are located in the left atrium. The ablation of the GPs led to an increase in

resting sinus rhythm in patients (ranging from 55 to 80 bpm) and complete disappearance of cardioinhibitory response associated with hypervagotonia such as VVS.<sup>5</sup>

## EVIDENCE SUMMARY

A total of 40 titles were retrieved from scientific databases such as Medline, EBM Reviews, and EMBASE via OVID and PubMed. Google was used to search for additional web-based materials and information. The last search was conducted on 1 November 2023. One systematic review, one randomised controlled trial, and two pre-post studies were found to be relevant and included in this review.

A systematic review (SR) of CNA in VVS was carried out to determine a freedom from syncope estimate for CNA. Based on the SR, CNA significantly improved the freedom from syncope recurrence. Overall mean follow-up was  $24.0 \pm 11.3$  months, and 94.0% of patients were free from syncope at the end of the study. The reported freedom from syncope prodromes was 86.0% (eight studies;  $n=301$ ). A study by Sun et al. (mean follow-up of  $36.4 \pm 22.2$  months) observed that the time to recurrence ranged between 2 and 17 days, while a study by Pachon et al. (mean follow-up of  $45.1 \pm 22.0$  months) documented three recurrences that occurred after one year, two years, and three years, respectively. Subgroup analysis for ablation technique showed significantly lower freedom from syncope in patients with right atrial ablation exclusively (81.5%; 95% CI 51.9% - 94.7%;  $p < 0.0001$ ) vs left atrial ablation only (94.0%; 95% CI 88.6% - 96.9%) and biatrial ablation (92.7%; 95% CI 86.8% - 96.1%).<sup>6</sup>

A prospective, open, controlled, randomised, investigator-initiated trial was carried out to compare CNA with optimum nonpharmacologic therapy in individuals with cardioinhibitory VVS. A total of 48 patients with recurrent cardioinhibitory or mixed VVS were randomly assigned to the CNA or control groups (24 in the CNA group and 24 in the control group). After two years of follow-up, two patients (8%) in the CNA group had syncope recurrence, compared to 13 patients (54%) in the control group ( $p < 0.0001$ ). The majority of syncope recurrences in the control group ( $n=12$ ) occurred during the first year of follow-up, with the remaining one syncopal episode occurring during the second year of follow-up. Two syncope recurrences occurred in the CNA group after 17 and 24 months of follow-up. The probability of syncope was 95% lower in the CNA group than in the control group. The QoL significantly improved in the CNA group ( $p=0.0001$ ), whereas it remained stable in control patients ( $p=0.5501$ ).<sup>7</sup>

In Portuguese hospitals, a study assessed the safety and success rate of CNA guided by extracardiac vagal stimulation in removing recurrent VVS in a cohort of patients. In this study, 19 patients were recruited, and 21 ablations procedures were conducted. According to the study, only two individuals (11%) suffered syncope recurrence throughout a mean follow-up of  $21.0 \pm 13.2$  months (3 - 42 months). The incidence of syncope was lower after ablation compared to the previous year (2.8 vs. 0.3 episodes per patient,  $p < 0.001$ ). Patient A, who had five syncopal episodes in the year preceding ablation, initially underwent ablation in the right anterior GP and right superior GP. After six months of being symptom-free, this patient

experienced a recurrence of syncope. However, the underlying reason was unknown. Patient D remained asymptomatic for nearly a year following the procedure when an implantable loop recorder detected recurrent syncope with total atrioventricular block and a 19-second delay. Both patients had a second CNA procedure, and the initial positive vagal response (VR) was observed again. The same sequential and anatomically guided GP ablation strategy was used with excellent results. However, both experienced more syncopal episodes and required pacemaker implantation. One-third of patients reported a greater baseline heart rate in the weeks following the procedure and minor palpitations and exhaustion with exertion that subsided.<sup>8</sup>

A prospective, open-label, interventional, single-centre cohort study was aimed to evaluate the safety and efficacy of cardioneuromodulation in patients with neurally mediated reflex syncope (NMS) or functional sinus node dysfunction. Patients were assigned to group A if they had NMS and a positive tilt table test (TTT) result according to the modified version of the classification of NMS proposed by the Vasovagal Syncope International Study group (VASIS), and to group B if they had a documented sinus pause  $\leq 3$  seconds. The study included 50 patients, 31 in group A and 19 in group B. The study found that syncope burden was decreased (-95%) at 12-month follow-up for both groups compared to baseline ( $p < 0.001$ ). At the 12- and 30-month follow-ups, the syncope-free survival rate remained unchanged. During the study's 96 patient-year follow-up, no occurrences of complex syncope were reported. The nine patients in Group A who had a recurrence of syncope had 17 episodes in the 12 months following the surgery, compared to 254 at baseline (-93%;  $p = 0.008$ ).<sup>9</sup>

### Safety

Eleven studies ( $n = 337$ ) reported the occurrence of adverse events. An adverse event was observed in 43 patients (12.8%). Sun et al. found transient inappropriate sinus tachycardia in one patient (1.8%) following substantial left atrial ablation, and Aksu et al. described it in two patients (10.0%) after biatrial ablation. Furthermore, in the retrospective analysis by Pachon et al., 23.3% of patients receiving biatrial ablation were temporarily started on a beta-blocker for transient mild sinus tachycardia in the first three months post-ablation.<sup>6</sup> There were no other procedure-related complications, including malignant arrhythmias, cardiac tamponade, vascular access events, pericarditis, symptoms associated with delayed gastric emptying, or death.<sup>7</sup>

## CONCLUSION

Cardioneural ablation showed promising results for patients with VVS. The limited evidence showed CNA reduce syncope episodes in VVS patients. Well-designed clinical trials are required to provide robust data on the efficacy and safety of the CNA procedure in treating VVS patients for future guidance.

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Prepared by

Siti Aisah Fadzilah  
Senior Principal Assistant Director  
Health Technology Assessment Section (MaHTAS)  
Medical Development Division  
Ministry of Health Malaysia

Dr. Aidil M. Zarif  
Medical Officer  
Health Technology Assessment Section (MaHTAS)  
Medical Development Division  
Ministry of Health Malaysia

**Reviewed by**

Dr. Izzuna Mudla Mohamed Ghazali  
Public Health Physician  
Deputy Director  
Health Technology Assessment Section (MaHTAS)  
Medical Development Division  
Ministry of Health Malaysia

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