Review Article

Non-Pharmacological Management of Neurocardiogenic Syncope

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Neurocardiogenic syncope is a common disorder. It is diagnosed by obtaining a detailed history and performing a head-up tilt test, with or without drug provocation. Several studies have been performed pertaining to its management. However, no treatment, whether pharmacological or non-pharmacological, except for counterpressure maneuvers and daily orthostatic tilt training, has been proven effective. Randomized studies of therapies for neurocardiogenic syncope are needed.
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Introduction

Neurocardiogenic syncope, also known as vasovagal or neurally mediated syncope, is the most common cause of loss of consciousness.[1)] It is typically triggered by environmental, physical or mental stress, with an estimated life-time prevalence of 35%,[1–3)] and is diagnosed by head-up tilt testing.[4,5)] A wide variety of treatments for recurrent neurocardiogenic syncope has been proposed, including beta-adrenergic blockade,[4–6)] disopyramide,[7)] and cardiac pacing,[8)] though none is evidence-based.[9,10)] Therefore, the choices have been mostly empiric, on the basis of mechanisms commonly believed to cause neurocardiogenic fainting. However, these therapeutic interventions often fail to prevent recurrences of syncope. Widely accepted measures not confirmed to be effective include explanations of the underlying mechanisms, patient education, reassurance emphasizing the generally benign nature of the disorder, recognition of premonitory manifestations, and avoidance of triggers. Volume expansion by means of increased water and salt intake or medications is sometimes advised.[9–11)] Recently, home orthostatic self-training has been found highly effective in preventing recurrences of ordinary, drug-refractory neurocardiogenic syncope, as well as of the malignant form (defined as >5 sec asystole during syncope) of the disorder.[12–17)] However, the mechanisms of home orthostatic self-training have not been clarified with respect to its

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preventive efficacy during follow-up. Furthermore, the time spent by patients must be minimized in order for home orthostatic self-training to be a useful and accepted therapeutic option.

Pathophysiology and Pharmacological Therapies

The exact mechanism of neurocardiogenic syncope induced by head-up tilt testing is not clearly understood.[18] Blood pooling in the lower limbs during head-up tilt testing appears to initiate a sequence of events that may lead to profound arterial vasodilation and hypotension in susceptible individuals. This downward displacement of the intravascular volume causes a fall in cardiac output that activates the arterial baroreceptor reflexes, resulting in reflex sympathetic stimulation. The sympathetically-mediated increase in contractility of a preload-reduced left ventricular cavity is believed to activate unmyelinated vagal C-fibers by the ventricular mechanoreceptors. Stimulation of these receptors produces a large afferent signal to the brain stem and inhibits the outflow of sympathetic activity.[19] Morillo et al., in 1993,[7] observed a decrease in susceptibility to tilt-induced syncope in patients who underwent multiple head-up tilt tests to evaluate both their reproducibility and their therapeutic effects. A reconditioning of the baroreceptor or mechanoreceptor response was suggested to be responsible for the therapeutic effects. In normal subjects, during peripheral venous pooling, a compensatory cardiopulmonary baroreceptor reflex-mediated sympathetic activity is appropriately activated. In patients prone to neurocardiogenic syncope these compensatory mechanisms are followed by a paradoxical sympathetic withdrawal.

These proposed mechanisms of neurocardiogenic syncope have been the basis for the use of beta-adrenergic blockade to inhibit the activation of ventricular mechanoreceptors.[4,6] However, in a recent double-blind, randomized, placebo-controlled study, atenolol was no more effective than placebo in tilt-positive syncopal patients.[20] Disopyramide, which inhibits the positive inotropic activity of the heart and the efferent parasympathetic outflow, was expected to prevent neurocardiogenic syncope. As in the case of atenolol, however, disopyramide was ineffective, compared to placebo, in the prevention of tilt-induced neurocardiogenic syncope.[7] In a randomized, crossover trial of oral propranolol versus disopyramide performed by our group, propranolol prevented tilt-induced syncope in 6 (32%) and disopyramide in 5 (26%) of 19 patients, a statistically non-significant difference.[21] Tilt-induced syncope was prevented by either propranolol or disopyramide alone in only 9 (47%) patients, while in 10 patients syncope continued to be inducible by head-up tilt testing. Thus, in that randomized trial, oral propranolol and disopyramide, when administered alone, were both relatively and similarly ineffective in the prevention of tilt-induced neurocardiogenic syncope. These observations are consistent with those made in previous studies,[7,20] which were observational, open-label, underpowered, or of short duration and, ultimately, provided conflicting evidence regarding the efficacy of beta-adrenergic blockers in the prevention of neurocardiogenic syncope. However, the latest report from the double-blind, placebo-controlled Prevention of Syncope Trial (POST) provided strong evidence that metoprolol, compared to placebo, did not prevent neurocardiogenic syncope.[22] Therefore, there is currently no reliable pharmacological therapy for the prevention of neurocardiogenic syncope.

Non-Pharmacological Therapies

1. Physical counterpressure maneuvers

In absence of effective drug therapy, efforts have been made to develop non-pharmacologic treatments, including patient education and life-style modifications. Physical counterpressure maneuvers (PCM), including leg crossing, muscle tensing or isometric arm counterpressure maneuvers, have been shown to raise the blood pressure and control or abort syncopal episodes under laboratory conditions. In a multicenter, randomized clinical trial, which included 223 vasovagal syncopal patients, 170 patients were randomly assigned to standardized conventional therapy, and 106 patients received conventional therapy plus training in PCM.[23] The median yearly syncope burden during follow-up was significantly lower in the group trained in PCM than in the control group. During a mean follow-up of 14 months, 50.9% of patients assigned to conventional treatment and 31.6% of patients assigned to PCM had recurrent syncope. The authors concluded that PCM is a risk-free, effective, and low–cost intervention, which should be used as first-line treatment for patients with neurocardiogenic syncope and recognizable prodromes.

2. Cardiac pacing

Permanent pacing was introduced in the 1990s for the treatment of drug refractory neurocardiogenic syncope, particularly of the cardio-inhibitory type.[24–26] However, neither single nor dual chamber

pacing at rates between 60 and 70 bpm prevented syncope,[24] because the vasodepressor component was not eliminated at these pacing rates. In the late 1990s, reports were published of a decrease in rates of neurally mediated episodes of syncope by overdrive dual chamber pacing at 100 to 110 bpm, compared to non-paced patients with standard therapy.[27–29] However, in more recent trials, this was shown to be attributable to a placebo effect of pacemaker implants.[30,31] Thus, as in the case of drug therapy, the effectiveness of pacing for neurocardiogenic syncope has not been confirmed.

3. Home orthostatic self-training

Recent studies have found tilt training to be highly effective in the prevention of recurrent, refractory, ordinary or malignant neurocardiogenic syncope.[12–17] Ector et al. first described, in 1998, the continuation of a repetitive tilt-training program, consisting of one or two 30-min sessions daily, in 13 patients with neurocardiogenic syncope diagnosed with head-up tilt testing, who remained free of recurrences over a mean follow-up of 7.2 months.[12] They attributed the effects of tilt training to the repetitive and prolonged exposure of the cardiovascular system to gravitational stress, which might have a similar therapeutic effect in patients presenting with orthostatic intolerance. More recently, Di Girolamo et al. reported the results of a controlled study of a tilt-training program consisting of two 40-min sessions daily for about 18 months in adolescents.[13] In that study, syncope was re-induced by tilt-testing in a single out of 24 patients (4.2%) after one month of tilt training, in contrast, to 18 out of 23 control patients (73.9%). In addition, over a mean follow-up of 18.2 ± 5.3 months, none of the 24 tilt-trained patients (0%) versus 13 of 23 control patients (56.5%) had spontaneous recurrences of syncope. These differences in recurrences of both tilt-induced and spontaneous syncope between the two study groups were statistically highly significant (both $p < 0.0001$). We reported a case of malignant neurocardiogenic syncope successfully treated with a tilt-training program consisting of 1 session of 30 min daily for one year.[14]

We examined the efficacy of home orthostatic self-training in the long-term prevention of neurocardiogenic syncope in patients randomly assigned to twice daily, versus once daily, versus once every other day training programs.[32] Over follow-ups of over 6 months, no spontaneous episode of syncope was observed among the patients assigned to the twice or once daily training programs. Likewise, no spontaneous episode of syncope occurred in the once every other day training group as long as the patients continued training. However, approximately 50% of the patients in that group quit the training, and syncope and presyncope recurred. Therefore, we recommend that home orthostatic self-training be performed once daily. The mechanisms behind the efficacy of this training therapy for neurally mediated syncope have not been entirely clarified.[33] In addition, no randomized, placebo-controlled study of training therapy for the prevention of neurally mediated syncope has been performed.

References

1) Colman N, Nahm K, Ganzeboom KS, et al: Epidemiology of reflex syncope. Clin Auton Res 2004; 14 Suppl 1: 9–17
2) Ganzeboom KS, Colman N, Teitsma JB, Shen WK, Wieling W: Prevalence and trigger of syncope in medical students. Am J Cardiol 2003; 91: 1006–1008
3) Sheldon RS, Sheldon AG, Conolly SJ, et al: Age of first faint in patients with vasovagal syncope. J Cardiovasc Electrophysiol 2006; 17: 1–6
4) Almquist A, Goldenberg IF, Milstein S, Chen MY, Chen XC, Hansen R, Gornick CC, Benditt DS: Provocation of bradycardia and hypotension by isoproterenol and upright posture in patients with unexplained syncope. N Engl J Med 1989; 320: 346–351
5) Abboud FM: Neurocardiogenic syncope. N Engl J Med 1993; 328: 1117–1120
6) Abe H, Kobayashi Y, Nakashima Y, Izumi F, Kuroiwa A: Effect of beta-adrenergic blockade on vasodepressor reaction in patients with vasodepressor syncope. Am Heart J 1994; 128: 911–918
7) Morillo CA, Leitch JW, Yee R, Klein GJ: A placebo-controlled trial of intravenous and oral disopyramide for prevention of neurally mediated syncope induced by head-up tilt. J Am Coll Cardiol 1993; 22: 1843–1848
8) Abe H, Iwami Y, Nagatomo T, Miura Y, Nakashima Y: Treatment of malignant neurocardiogenic vasovagal syncope with a rate drop algorithm in dual chamber cardiac pacing. Pacing Clin Electrophysiol 1998; 21: 1473–1475
9) Brignole M, Alboni P, Benditt D, et al: Task Force on Syncope, European Society of Cardiology. Guidelines on management (diagnosis and treatment) of syncope. Eur Heart J 2001; 22: 1256–1306
10) Brignole M, Alboni P, Benditt D, et al: Guidelines on management (diagnosis and treatment) of syncope-update 2004. Europace 2004; 6: 467–537
11) Claydon VE, Hainsworth R: Salt supplementation improves orthostatic cerebral and peripheral vascular control in patients with syncope. Hypertension 2004; 43: 809–813
12) Ector H, Reybrouck T, Heidbuchel H, et al: Tilt training: a new treatment for recurrent neurocardiogenic syncope and severe orthostatic intolerance. Pacing Clin Electrophysiol 1998; 21: 193–196
13) Di Girolamo E, Di Iorio C, Leonzio L, et al: Usefulness

of a tilt-training program for the prevention of refractory neurocardiogenic syncope in adolescents: a control study. Circulation 1999; 100: 1798–1801
14) Numata T, Abe H, Nagatomo T, Sonoda S, Kohshi K, Nakashima Y: Successful treatment of malignant neurocardiogenic syncope with repeated tilt-training program. Jpn Circ J 2000; 64: 406–409
15) Reybrouck T, Heidbuche H, Van de Werf F, Ector H: Tilt training. A treatment for malignant and recurrent neurocardiogenic syncope. Pacing Clin Electrophysiol 2000; 23: 493–498
16) Abe H, Kondo S, Kohshi K, Nakashima Y: Usefulness of orthostatic self-training for the prevention of neurocardiogenic syncope. Pacing Clin Electrophysiol 2002; 25: 1454–1458
17) Abe H, Kohshi K, Nakashima Y: Efficacy of orthostatic self-training in medically refractory neurocardiogenic syncope. Clin Exp Hypertens 2003; 25: 487–493
18) Grubb BP, Karas B: Clinical disorders of the autonomic nervous system associated with orthostatic intolerance: an overview of classification, clinical evaluation, and management. Pacing Clin Electrophysiol 1999; 22: 798–810
19) Morillo CA, Eckberg DL, Ellenbogen KA, Beightol LA, Hoag JB, Tahvanainen KU, Kuusel TA, Diedrich AM: Vagal and sympathetic mechanisms in patients with orthostatic vasovagal syncope. Circulation 1997; 96: 2509–2513
20) Madrid AH, Ortega J, Rebollo JG, Manzano JG, Segovia JG, Sanchez A, Pena G, Moro C: Lack of efficacy of atenolol for the prevention of neurally mediated syncope in a highly symptomatic population. A prospective, double-blind, randomized and placebo-controlled study. J Am Coll Cardiol 2001; 37: 554–559
21) Abe H, Sumiyoshi M, Kohshi K, Nakashima Y: Effects of orthostatic self-training on head-up tilt testing for the prevention of tilt-induced neurocardiogenic syncope: comparison of pharmacological therapy. Clin Exp Hypertens 2003; 25: 191–198
22) Sheldon R, Connolly S, Rose S, Klingenheben T, Krahn A, Morillo C, Talajic M, Ku T, Fouad-Tarazi F, Ritchie D, Koshman ML: POST Investigators. Prevention of Syncope Trial (POST): a randomized, placebo-controlled study of metoprolol in the prevention of vasovagal syncope. Circulation 2006; 113: 1164–1170
23) Van Dijk N, Quartieri F, Blanc JJ, Garcia-Civera R, Brignole M, Moya A, Wieling W: PC-Trial Investigators. Effectiveness of physical counterpressure maneuvers in preventing vasovagal syncope: the Physical Counterpressure Manoeuvres Trial (PC-Trial). J Am Coll Cardiol 2006; 48: 1652–1657
24) Sra JS, Jazayeri MR, Avitall B, et al: Comparison of cardiac pacing with drug therapy in the treatment of neurocardiogenic (vasovagal) syncope with bradycardia or asystole. N Engl J Med 1993; 328: 1085–1090
25) Abe H, Kuroiwa A: Demonstration of syncope in patients after pacemaker implantation: role of head-up tilt test to distinguish neurocardiogenic syncope from pacemaker syndrome. Pacing Clin Electrophysiol 19: 293–296, 1996
26) Abe H, Numata T, Hanada H, Kohshi K, Nakashima Y: Successful treatment of severe orthostatic hypotension with cardiac tachypacing in dual chamber pacemakers. Pacing Clin Electrophysiol 2000; 23: 137–139
27) Connolly SJ, Sheldon R, Roberts RS, Gent M: The North American Vasovagal Pacemaker Study (VPS). A randomized trial of permanent cardiac pacing for the prevention of vasovagal syncope. J Am Coll Cardiol 1999; 33: 16–20
28) Sutton R, Brignole M, Menozzi C, Raviele A, Alboni P, Giani P, Moya A: Dual-chamber pacing in the treatment of neurally mediated tilt-positive cardioinhibitory syncope: pacemaker versus no therapy: a multicenter randomized study. The Vasovagal Syncope International Study (VASIS) Investigators. Circulation 2000; 102: 294–299
29) Ammirati F, Colivicchi F, Santini M: Syncope Diagnosis and Treatment Study Investigators: Permanent cardiac pacing versus medical treatment for the prevention of recurrent vasovagal syncope: a multicenter, randomized, controlled trial. Circulation 2001; 104: 52–57
30) Connolly SJ, Sheldon R, Thorpe KE, Roberts RS, Ellenbogen KA, Wilkoff BL, Morillo C, Gent M: VPS II Investigators: Pacemaker therapy for prevention of syncope in patients with recurrent severe vasovagal syncope: Second Vasovagal Pacemaker Study (VPS II): a randomized trial. JAMA 2003; 289: 2224–2229
31) Raviele A, Giada F, Menozzi C, Speca G, Orazi S, Gasparini G, Sutton R, Brignole M: Vasovagal Syncope and Pacing Trial Investigators: A randomized, double-blind, placebo-controlled study of permanent cardiac pacing for the treatment of recurrent tilt-induced vasovagal syncope. The vasovagal syncope and pacing trial (SYNPACE). Eur Heart J 2004; 25: 1741–1748
32) Abe H, Kohshi K, Nakashima Y: Home orthostatic self-training in neurocardiogenic syncope. Pacing Clin Electrophysiol 2005; 28: S246–S248
33) Abe H, Kohshi K, Nakashima Y: Effects of orthostatic self-training on head-up tilt testing and autonomic balance in patients with neurocardiogenic syncope. J Cardiovasc Pharmacol 2003; 41: S73–S76