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Review

Role of permanent cardiac pacing for vasovagal syncope

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ABSTRACT

The role of pacemaker therapy for vasovagal syncope (VVS) is still controversial. The ISSUE 3 study led to reappraisal of pacing therapy (using DDD pacing with the rate-drop response algorithm) for reducing syncope recurrence in a highly selected patient group (age, ≥40 years) with asystolic VVS clinically documented by implantable loop recorder. However, the role of pacemaker treatment for young (age, <40 years) VVS patients remains to be established. Psychological sequelae and the burden of the long-term implanted device should be considered. DDD pacing with closed-loop stimulation seems to be a promising algorithm; however, we need more data to determine the best pacing algorithm. Multicenter, prospective mega trials with a randomized and controlled design are needed to resolve these issues.

Contents

1. Introduction

Vasovagal syncope (VVS) is the most common cause of syncope. VVS is designated as one of the types of reflex syncope (neurally-mediated syncope) in both the Japanese and European guidelines regarding syncope [1,2]. The phenomenon of VVS consists of hypotension and bradycardia or asystole. Therefore, implantation of a permanent pacemaker is thought to be a reasonable treatment. In carotid sinus syncope, pacing therapy is regarded as one of the first-line treatments in patients with recurrent syncope and cardioinhibitory response during carotid sinus massage [1,2]. Although a dominant cardioinhibitory component has been observed in most patients with carotid sinus syncope [3], the vasodepressor factor seems to be the main cause of fainting in most VVS patients. The efficacy of pacing therapy for VVS has been controversial so far. The purpose of this review is to assess the historical background and the efficacy of cardiac pacing in patients with VVS.

2. Clinical experience with pacemaker treatment for vasovagal syncope before the randomized clinical trial (RCT) era

The data in the 1990s concerning the outcomes of permanent cardiac pacemaker use in patients with VVS were conflicting. The usual pacemaker therapy, even DDD pacing, could not prevent VVS during head-up tilt (HUT) testing owing to insufficient efficacy of the vasodepressor factor [4,5]. Sra et al. [4] found that cardiac

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pacing for VVS was less effective than drug therapy. Conventional pacing treatment (i.e., DDD pacing for patients with sinus rhythm or VVI pacing for patients with atrial fibrillation) did not prevent hypotension and syncope or presyncope during HUT testing in VVS patients with asystole or bradycardia [4]. The lack of efficacy of pacing in these patients suggested that even in patients with a cardioinhibitory response, hypotension is predominantly due to vasodepression, whereas vagally mediated bradycardia may play only a secondary part in the pathogenesis of VVS [4,6]. However, it was argued that permanent pacemaker therapy may be useful in preventing syncope in patients with so-called "malignant vasovagal cardioinhibitory response," in which the onset of syncope is thought to be abrupt [6]. In addition, Sra et al. [4] showed that a potential benefit of pacing therapy was that cardiac pacing could diminish the magnitude of hypotension in some VVS patients. This suggested the idea that early intervention with cardiac pacing might prevent or at least alleviate hypotension and syncope.

Petersen et al. [7] reported a possible role for permanent pacing in selected patients with cardioinhibitory malignant VVS in a retrospective, uncontrolled 1994 study. Cardiac pacemakers were implanted in 37 patients. Most of these were programmed to DDI mode with rate hysteresis. During the follow-up period of 50.2 ± 23.9 months, symptomatic improvement occurred in 89% of the patients, with 62% remaining free of syncope and 27% being completely symptom free. In 1997, Benditt et al. [8] reported the results of pacemaker treatment with the rate-drop response (RDR) algorithm in 28 patients with tilt-positive VVS and induced bradycardia. During an average follow-up of 6 months, 78% of patients did not faint at all and an overall 67% reduction in syncope frequency was observed. In 1998, Sheldon et al. [9] also reported efficacy of pacemaker therapy. They implanted a dual-chamber pacemaker with automatic rate smoothing in 12 patients with frequent syncope (median: 3 episodes per month). After implantation, the frequency of syncope decreased by 93% and quality of life improved markedly.

Although these studies demonstrated the efficacy of pacemaker treatment for preventing or reducing VVS, all 3 trials were retrospective and uncontrolled [10]. Therefore, RCTs of cardiac pacing in VVS were proposed in the late 1990s.

3. The era of RCTs: is pacemaker efficacy due to a placebo effect?

Since 1999, several RCTs of pacing therapy for refractory VVS have been conducted (Table 1).

Flammang et al. [11] reported the efficacy of pacemaker treatment for VVS with a severe cardioinhibitory response identified by the adenosine triphosphate test. Twenty patients were randomized to 2 groups: DDD pacemaker implantation (10 patients) and usual medical care (10 patients). During a mean follow-up of 52 months, syncope recurred in 60% of the usual-care patients but in none of the paced patients ($P < 0.02$). In the North American Vasovagal Pacemaker Study (VPS) [12], 54 patients were randomly divided into 2 groups: DDD pacemaker with RDR or no pacemaker. The results of VPS showed a marked reduction in the risk of syncope recurrence with pacemaker implantation (relative risk reduction, 85.4%). In the Vasovagal Syncope International Study (VASIS) [13], 42 patients were randomized to receive a DDI pacemaker with rate hysteresis or no pacemaker. Inclusion criteria were ≥ 3 syncope episodes over the preceding 2 years and a positive cardioinhibitory response to HUT testing. During the follow-up period of 3.7 ± 2.2 years, there was significantly less recurrence of syncope in the pacemaker arm than in the non-pacemaker arm (5% vs. 61%, $P = 0.0006$). In the Syncope Diagnosis and Treatment (SYDIT) Study [14], 93 patients were randomized to receive either a DDD pacemaker with RDR function or the beta-blocker atenolol. Inclusion criteria were age > 35 years, ≥ 3 syncope episodes in the preceding 2 years, and positive response to HUT testing with relative bradycardia. During the mean follow-up of 17.3 months, the recurrence of syncope was significantly lower in the pacemaker group than in the pharmaceutical treatment group (4.3% vs. 25.5%, $P = 0.004$). On the basis of the results of these 3 RCTs, pacing therapy appears to be effective for the prevention of recurrent syncope in patients with VVS. However, double-blind randomized trials showed different outcomes. In the Second Vasovagal Pacemaker Study (VPS II) [15], 100 patients were assigned to receive DDD pacing with RDR or to have only sensing without pacing (ODO). Inclusion criteria were history of typical VVS with ≥ 6 overall episodes of syncope or ≥ 3 episodes of syncope in the preceding 2 years and a positive HUT test. The cumulative risk of syncope at 6 months was not different between the DDD and ODO groups (31% vs. 40%). In the vasovagal SYNcope and PACing (SYNPACE) [16] trial, 29 patients with severe recurrent tilt-induced VVS underwent DDD-RDR pacemaker implantation and were randomized to pacemaker ON or pacemaker OFF. During the follow-up of 23.8 months, the recurrence of syncope showed no significant difference (50% in pacemaker ON and 38% in pacemaker OFF). The median time to first syncope recurrence was also not significantly different.

After these 2 double-blind RCTs failed to prove the superiority of cardiac pacing over placebo in patients affected by VVS, the widely accepted opinion was that cardiac pacing therapy is not very effective and that a strong placebo effect exists [17]. The results of VPS II and SYNPACE were disappointing. However, these 2 trials included patients with VVS of not only the cardioinhibitory type but also the vasodepressor and mixed types. Therefore, the question arises whether pacing therapy could be effective for the cardioinhibitory type of VVS, specifically that with a prolonged asystole [18].

4. Reappraisal of pacing therapy for vasovagal syncope: ISSUE 3

The implantable loop recorder (ILR) has advanced the diagnosis of syncope of uncertain etiology. ILR can record a real-time ECG at

Table 1
Randomized controlled clinical trials of pacemaker treatments for vasovagal syncope.

Trial	Reference	Year	Study design	PM system	*N*	FU (months)	PM effect	Recurrent syncope	*P* value
Flammang	11	1999	PM vs. usual care	DDD	20	52	Yes	0% vs. 60%	< 0.02
VPS	12	1999	PM vs. usual care	DDD-RDR	54	16	Yes[a]	22% vs. 70%	
VASIS	13	2000	PM vs. no	DDI-RH	42	44	Yes	5% vs. 61%	0.0006
SYDIT	14	2001	PM vs. atenolol	DDD-RDR	93	17.3	Yes	4.3% vs. 25.5%	0.004
VASIS 2	15	2002	PM-on vs. PM-off	DDD-RDR	100	6	No	31% vs. 40%	–
SYNPACE	16	2004	PM-on vs. PM-off	DDD-RDR	29	23.8	No	50% vs. 38%	–
ISSUE 3	22	2012	PM-on vs. PM-off	DDD-RDR	77	24	Yes	25% vs. 57%	0.039

PM = pacemaker; FU = follow-up duration; RDR = rate-drop response; and RH = rate hysteresis.

[a] Significant reduction in the post-randomization risk of syncope in pacemaker patients.