Introduction

Neurocardiogenic syncope represents a complex syndrome in which a specific treatment rarely is warranted owing to the sporadic nature of the disorder. However, in a small percentage of patients vasovagal episodes present as a chronic recurring disorder with a disturbing impact on the quality of life. Moreover, in certain circumstances syncope may be life-threatening or cause severe injuries. Therefore a thorough clinical assessment and proper selection of treatment is necessary in some cases of recurrent syncope. Since patients with recurrent neurocardiogenic syncope often are resistant to medical treatment, permanent cardiac pacing has been repeatedly proposed as long-term therapy.1-4 When significant bradycardia is noted during tilt-induced syncopal spells, cardiac pacing may represent a valuable therapeutic option. Several studies have tested the effectiveness of pacing in ameliorating symptoms of vasovagal syncope in the laboratory5-7 and in clinical settings.8,9 Cumulative data suggest that cardiac pacing may significantly reduce symptoms, although the optimal pacing mode has not been clearly defined. In particular, single chamber VVI pacing is unlikely to be effective,5-7 while dual chamber DDI pacing with rate hysteresis (RH) is more promising.8 DDD pacing with a new rate drop function (RDR) recently
has become available in clinical practice.\textsuperscript{9,10} The aim of this open clinical trial was to test the effectiveness of this new pacing modality (DDD-RDR) compared to the best known pacing therapy (DDI with RH) in patients with recurrent cardioinhibitory vasovagal syncope.

**Study Population and Methods**

The study population included 20 patients (12 males and 8 females; mean age 61.1 years, range 27 to 81 years) with recurrent unexplained syncope despite a complete diagnostic evaluation (mean number of syncopal events before tilt testing = 6.8; range 5 to 11). Nine (45\%) patients had suffered severe trauma from one or more episodes. In addition, 5 male patients were engaged in potentially dangerous occupations (2 bus drivers, 2 lorry drivers, 1 taxi driver). To be eligible for inclusion in the study all patients had to fulfill the following criteria: (1) a positive cardioinhibitory response (VASIS type 2B)\textsuperscript{11} to a first head-up tilt test performed according to the Westminster protocol\textsuperscript{12}; (2) a positive cardioinhibitory response to a second head-up tilt test performed within 1 month of the first test using pharmacological treatment with either etilephrine (50 mg/day; 7 patients) or atenolol (100 mg/day; 13 patients). After the second positive head-up tilt test, the patients were randomized to receive one of two types of permanent pacemaker. Twelve patients received a DDD pacemaker with RDR function (Medtronic Thera-I model 7960, Medtronic, Inc. Minneapolis, MN, USA) and eight patients received a DDI pacemaker with RH programmed at 40/80 beats/min (Biotronik Physios TC 01, Biotronik, Lake Oswego, OR, USA). One month after pacemaker implantation all patients underwent a third head-up tilt test and were followed thereafter.

**Pacemaker Programming**

Constant cardiac pacing is not necessary in patients with recurrent isolated vasovagal syncope, while a proper pacing intervention should be delivered for incipient syncopal episodes. Consequently, to avoid inappropriate pacing both pacemakers were programmed with a lower rate at 40 beats/min and an AV delay of 300 ms, thereby favoring spontaneous cardiac rhythm.

**The RDR Algorithm**

The RDR algorithm offers the following programmable parameters: (1) top rate (the heart rate from which the pacemaker recognizes the onset of drop in heart rate); (2) bottom rate (the heart rate at which the pacemaker recognizes that heart rate has fallen sufficiently to warrant pacing intervention); (3) width beats (if the heart rate falls between top and bottom rates in fewer than this number of beats pacing is triggered); (4) confirmation beats (the beats below the bottom rate necessary before the need for pacing is confirmed); (5) intervention rate (pacing rate following confirmation); (6) intervention duration (the duration of pacing before gradual return to intrinsic heart rate).

**RDR Programming**

Because of the complexity of each pacemaker parameter, careful individual programming is necessary. We believe that a critical assessment of the individual response to head-up tilt testing is required to optimize the pacing intervention during an episode. Therefore, the RDR parameters were programmed on the basis of the heart rate behavior during head-up tilt testing in all patients as follows: (1) the heart rate just before the onset of symptoms was used as the top rate; (2) the bottom rate was set at 20 beats/min above the heart rate at which the patient lost consciousness, (3) the width beats were programmed as the number of beats occurring between top rate and bottom rate during the vasovagal reflex induced by head-up tilt testing, (4) to avoid inappropriate pacemaker interventions two confirmation beats were programmed; (5) the intervention rate was programmed at 10 to 20 beats/min above the top rate (at least 110–120 beats/min); (6) intervention duration was programmed according to the duration of recovery from symptoms after tilt table lowering.

**Statistical Analysis**

Data are expressed as mean ± SD and have been analyzed with Fisher’s exact test.

**Results**

**Head-up Tilt Testing after Implantation**

Three of the 12 patients (25\%) paced in DDD-RDR mode and 5 of the 8 patients (62.5\%) paced in DDI-RH mode had syncope during the third
head-up tilt test performed after pacemaker implantation. Five DDD-RDR paced patients (41.6%) had a negative response to head-up tilt due to an appropriate pacemaker intervention during the test, while four (33.4%) did not develop a vasovagal reaction during the diagnostic procedure. Two of the DDI-RH paced patients (25%) had a negative response to head-up tilt from appropriate pacemaker intervention, while one patient (12.5%) had no vasovagal reaction. Two of the three DDD-RDR paced patients with positive response to head-up tilt test underwent pacemaker reprogramming and had a negative fourth head-up tilt test, in one case from appropriate pacemaker intervention and in the other because of absence of a vasovagal reaction. The third patient refused to undergo further head-up tilt testing.

Follow-up

The mean duration of follow-up was 17.7 ± 7.4 months. During follow-up no DDD-RDR paced patients had syncope, while three of the eight patients (37.5%) with DDI-RH pacemaker had a syncopal episode (P < 0.05).

Discussion

Most clinicians agree that benign forms of neurocardiogenic vasovagal syncope do not need any specific therapeutic intervention. However, recurrent, un heralded, traumatic forms occurring in older patients are considered malignant and require a careful clinical assessment and a personalized therapeutic approach. Several studies have evaluated the effects of cardiac pacing in the prevention of vasovagal episodes in the laboratory and in clinical settings, although limited prospective data have been gathered. Several studies have tested the effectiveness of temporary pacing during tilt induced vasovagal syncope. In a study by Fitzpatrick et al., temporary pacing with simulated hysteresis did not prevent hypotension and all patients remained symptomatic. However, it prevented syncope in 85.7% (6/7 patients) of the cases. In a subsequent paper, Samoil et al. compared two different pacing strategies in tilt induced vasovagal syncope. DVI pacing prevented syncope in 50% (3/6 patients) of the cases, while prolonging symptoms to syncope in 33.3% (2/6 patients) of the cases. However, VVI pacing was ineffective, although a trend toward a longer prodromal phase was noted in all cases. In the study by Sra et al., 22 patients underwent two consecutive tilt tests, the first without pacing and the second with demand pacing available (AV sequential tilt tests, the first without pacing and the second with demand pacing available (AV sequential tilt tests, the first without pacing and the second with demand pacing available (AV sequential tilt tests, the first without pacing and the second with demand pacing available (AV sequential tilt tests, the first without pacing and the second with demand pacing available (AV sequential tilt tests, the first without pacing and the second with demand pacing available (AV sequential tilt tests). Syncope was noted in 5 patients (5/22, 22.7%) during paced tilt compared with 18 (18/22, 81.8%) during the unpaced tilt test. Cumulative evidence from tilt-based studies cannot be considered conclusive as too few patients were enrolled and because tilt induced vasovagal hypotension is unlikely to be prevented by the pacing modalities used in the preliminary experiences. With respect to clinical studies, the outcome of 37 patients paced for cardioinhibitory vasovagal syncope was retrospectively evaluated by Petersen et al. Dual chamber pacemakers with rate hysteresis were implanted in 84% of the cases, and patients were followed for a mean period of 50.2 months. A significant symptom reduction was noted in 89% of patients, and 62% remained syncpe-free during follow-up. On the basis of these results, DDI pacing with RH presently is considered the most effective pacing option for cardioinhibitory forms of vasovagal syncope. However, even if cardiac pacing may improve the clinical outcome of patients with recurrent cardioinhibitory vasovagal syncope, the correct pacing mode remains controversial. Recently, Benditt et al. reported a multicenter clinical experience with DDD-RDR pacing in 39 patients with recurrent vasovagal syncope. Twenty-three (58.9%) remained asymptomatic during a mean follow-up of 204 days, while 6 (15.3%) had recurrences, and 10 (25.6%) had presyncope. These encouraging data add support to the role of cardiac pacing in severe recurrent forms of vasovagal syncope. A critical appraisal of the incomplete effectiveness of previously tested pacing modalities in preventing tilt induced vasovagal syncope reveals that most of the pacing failures may be related to delayed pacemaker intervention during the episode. Patients with vasovagal syncope do not need continuous pacing, but require physiological pacing at the very moment of the vasovagal reaction. Pacemaker intervention should always consider the temporal relation between the development of hypotension and bradycardia. To prevent syncope, the ideal device should sense the initial heart rate drop and
pace early in the episode at a relatively high rate. Such relative tachycardia is expected to provide a sufficient cardiac output to overcome the effects of vasodepression. Therefore, the new RDR function included in a DDD pacemaker may represent a significant improvement in pacing therapy for vasovagal syncope. In this clinical study this new pacing modality was compared with the best-known pacing mode (DDI with RH) in a strictly selected population of patients with a high recurrence rate of cardioinhibitory vasovagal syncope resistant to medical treatment and with a high incidence of trauma. Approximately 60% of such patients are expected to have another syncopal spell within 1 year of head-up tilt testing and need particular clinical attention. In such defined patients, pacing therapy is probably a promising therapeutic option to reduce the incidence of potentially dangerous syncopal episodes. In our series, DDD-RDR pacing was fully effective in preventing recurrences over the intermediate term (17.7 months).

Moreover, it proved to be superior to DDI-RH pacing (P < 0.05), previously considered the best pacing mode for these patients. Another point of interest in this study was the absence of a significant difference between the two tested pacing options in the assessment of effectiveness during head-up tilt testing. This finding suggests that, although tilt testing was necessary for the proper programming of RDR function, its role in correctly predicting the effectiveness of any form of therapy may be overemphasized. The only measure of the impact of a specific therapy in recurrent vasovagal syncope hinges on a sufficiently long clinical follow-up. This experience in carefully selected patients with cardioinhibitory vasovagal syncope represents a preliminary step before studies in which the enrollment of subjects with various forms of the syndrome (mixed and vasodepressor), and a longer follow-up, should be considered.

References

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