

Role of Pacing in the Management of Neurocardiogenic Syncope

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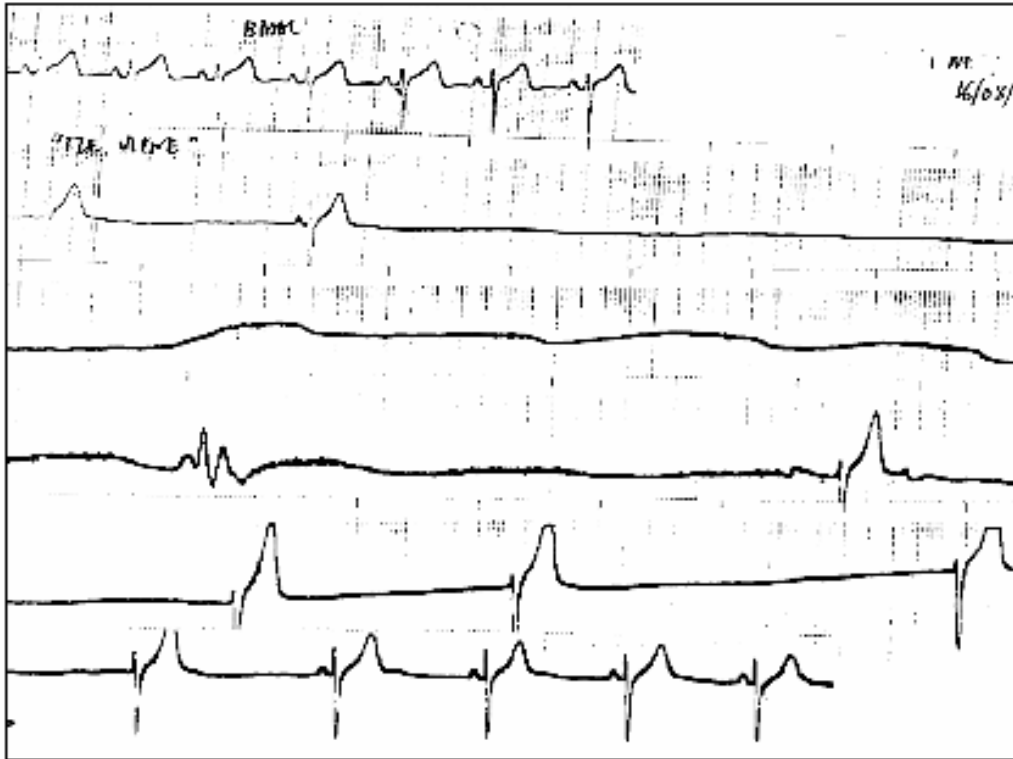
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INTRODUCTION

Vasovagal syncope or the common faint is also called neurally-mediated syncope or neurocardiogenic syncope, is a relatively common entity. It commonly occurs in young individuals with structurally normal hearts and is usually preceded by premonitory symptoms of nausea, diaphoresis and lightheadedness (1-4). When there are known triggers such as the sight of blood or sharp pain or with consistent warning symptoms, it can be easily managed by avoidance or lying down. On occasion, individuals experience repeated syncopal spells with insufficient warning to protect themselves and without a clearly identified trigger such as pain. This has been called malignant vasovagal syncope and although the spells may be infrequent, definitive therapy is indicated. The first line of therapy is pharmacologic based on the current understanding of the pathophysiologic mechanism. If this proves ineffective and there is a significant bradycardic component, then pacing may be a valuable adjunctive therapy for these patients.

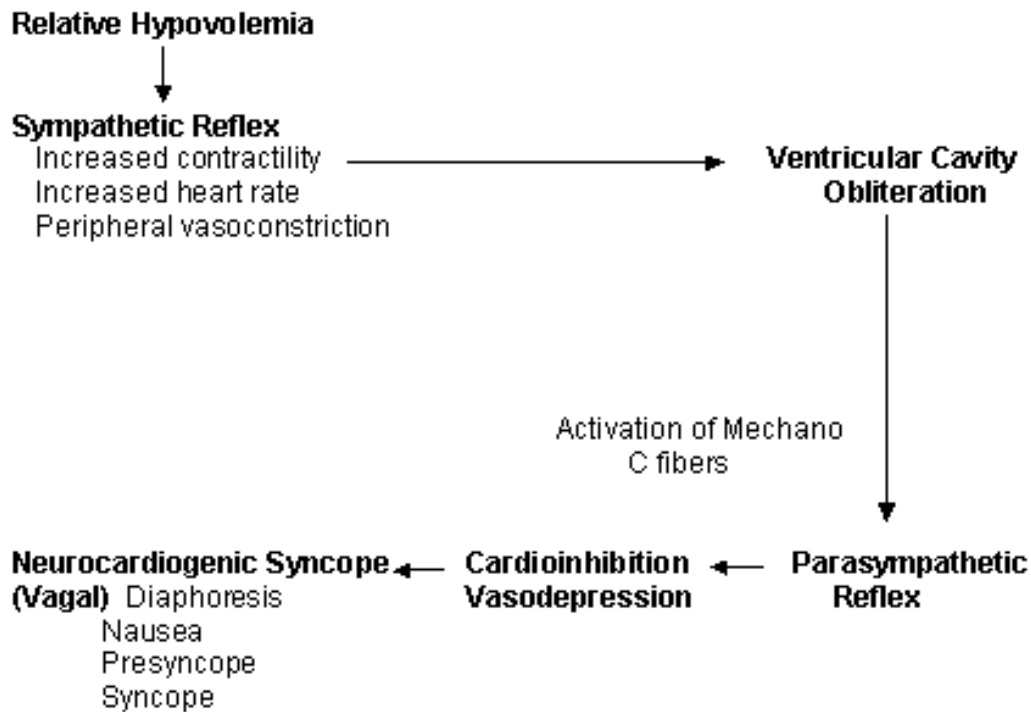
Neurocardiogenic syncope has been divided into three types (5,6). Type 1 is mixed characterized by a combination of both vasodepression and cardioinhibition. In this group, the hypotension develops prior to the bradycardia and the bradycardia is generally not severe. The heart rate either does not fall below 40 bpm or remains below 40 bpm for less than 10 seconds. Type 2 is cardioinhibitory with a major period of asystole and is subdivided into (a) and (b). In type 2a, the hypotension precedes the bradycardia but the bradycardia is marked with sustained periods of asystole ([Figure 1](#)). On tilt table testing, the asystole is > 3 seconds. In Type 2b, the bradycardia either precedes or coincides with the development of hypotension. Again, the bradycardia is severe. Type 3 is pure vasodepression where there is minimal to no decrease in the heart rate associated with the hypotension. In each case, there is usually a transient initial increase in heart rate either coincident or following the onset of the hypotension.

Figure 1: Continuous ECG recording during Tilt Table test in a young woman with recurrent syncope, a normal physical examination and normal non-invasive cardiac tests. Tracing courtesy of Dr. José Rodríguez de Freitas, Uruguay



MECHANISM

The proposed mechanism is an exaggerated normal physiologic reflex (7-9). It starts with the patient becoming relatively hypovolemic as may occur when standing quietly for a protracted period of time. The resultant hypotension triggers a sympathetic reflex with an increase in heart rate, myocardial contractility and peripheral vasoconstriction all of which are intended to compensate for the hypotension in an effort to maintain cerebral perfusion. Given the initial hypovolemic status, the increased contractility in an otherwise normal heart results in ventricular cavity obliteration. The contact between the ventricular walls generates a pressure wave detected by the intramyocardial baroreceptors, mechanoc fibers, as a massively elevated pressure. This, in turns, triggers a vagal or parasympathetic reflex resulting in peripheral vasodilation (vasodepression) and slowing of both the sinus rate and AV nodal conduction (cardioinhibition). ([Figure 2](#))

Figure 2: Schematic diagram of hemodynamic cascade:

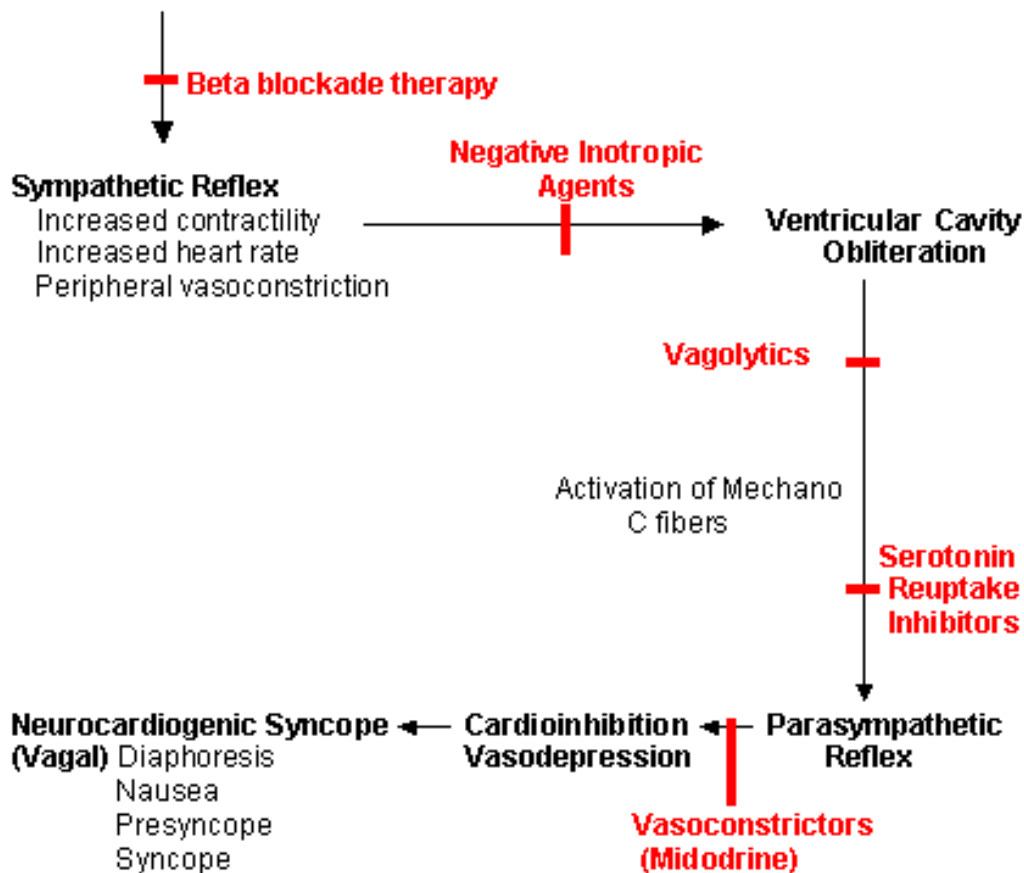
PHARMACOLOGIC THERAPY

The primary pharmacologic approaches to the management of neurocardiogenic syncope are directed towards interrupting the reflex cascade (10-12). First line of therapy is maintaining adequate intravascular volume with sufficient fluid and salt intake. If this is not sufficient, then the addition of a mineralocorticoid may be helpful. Of the specific drugs that have been used, beta adrenergic blocking drugs have had the best results although not all studies have demonstrated a positive response. Primary negative inotropic and vagolytic agents such as disopyramide phosphate (Norpace) have proven disappointing and due to a significant incidence of side effects, are not generally used. In recent years, midodrine (13,14), developed for the treatment of primary orthostatic hypotension, has been used with some success by causing peripheral vasoconstriction. The limitation is that the frequency of dosing resulting in a significant incidence of noncompliance. When these agents fail, there are some anecdotal reports utilizing the serotonin reuptake inhibitors (15,16) as serotonin is the mediator of the vagal reflex within the central nervous system. The proposed sites of action of the various pharmacologic options are shown in [Figure 3](#). The relative infrequency of the spells combined with side-effects and costs of the medications result in a significant number of patients discontinuing pharmacologic therapy.

Figure 3: Pharmacologic interventions

Increase volume – salt, fluids, mineralocorticoids

Relative Hypovolemia



PACING THERAPY

When the cardioinhibitory component of vasovagal syncope was first recognized, pacing appeared to be an obvious therapeutic modality for patients with this condition. Between their spells, the rhythm is normal and pacing would not be required. Except for the pure cardioinhibitory subset, the least frequent of the three types, patients commonly continued to have symptoms despite pacing support (17-19). In recent years, the recommendation for pacing has been restricted to those patients with (a) recurrent syncope despite maximum tolerated pharmacologic therapy combined with (b) a marked cardioinhibitory component. Pure vasodepression (Type 3) will not respond to pacing therapy. The mixed form (Type 1) is likely to continue to have significant symptoms despite the support of the pacing rate although pacing may either markedly reduce the incidence of syncope or delay its onset providing an opportunity for the patients to protect themselves.

One of the first studies that performed a formal evaluation of the role of pacing was performed by Sra and associates (20). This was an acute study using tilt table testing involving 22 patients with marked cardioinhibition although all also had a significant vasodepressive component. All patients received a temporary dual chamber pacing system after the baseline positive tilt-table test. Although the authors

concluded that pacing was ineffective, the results were similar to that with pharmacologic therapy. While syncope continued to occur in 5 patients, it was prevented in 17 although other premonitory symptoms including presyncope continued. In this same group of patients, beta blockade therapy prevented all symptoms in only 10 of 22 patients (40%). Theophylline was effective in only 3 of 12 patients in whom this drug was tested and in 6 of 9 patients who were tried on disopyramide phosphate.

The first "large" study specifically focused on the role of pacing was a retrospective study involving a total of 37 patients with recurrent syncope (21). All patients had a tilt table test with a positive cardioinhibitory component. The majority received dual chamber pacing systems with most of those programmed to the DDI (nontracking) mode at a relatively high base rate combined with a lower escape rate (hysteresis). In that the only time that these patients experience heart block is during the spell when there is also sinus node slowing, these patients do not require a tracking mode between their spells. DDI provides for AV sequential pacing during the episode. The mean follow-up was 50 months and during this time, the group averaged 11 syncopal episodes per year compared to an anticipated 136 episodes if the incidence of syncope based on the pre-implant frequency had not been impacted by the pacing therapy. Eighty-nine percent of the patients had a reduction in their symptoms while 10 (27%) had a total elimination of all symptoms.

The prospective randomized trial was the North American Vasovagal Pacing (NAVPAC) (22) study. The study was terminated after the pilot portion of the study given a dramatic benefit associated with pacing. A total of 56 patients had been enrolled and randomized to either conventional therapy (which was pharmacologic but in actuality, virtually no medications were utilized) to pacing. The specific pacing modality was Medtronic's Rate Drop Response algorithm as implemented in their Thera[®] family of pacemakers. The primary endpoint was time to first recurrence of syncope and this was markedly delayed in the pacing group compared to the control group ($p < 0.0007$). This led to a recommendation to terminate the study as the investigators felt that it would be unethical to continue. Both group continued to have a significant incidence of presyncope and other premonitory symptoms without a statistically significant difference between the two groups. The major limitation of the NAVPAC trial is the lack of long term follow-up (23). As the end point was the time to first recurrence of syncope, the trial ended for that patient once syncope occurred.

In a multicenter trial sponsored by St. Jude Medical, the VASIS trial (24) took a different tack. In a group of patients refractory to pharmacologic therapy with a marked cardioinhibitory response to tilt-table testing, patients were randomized to pacing or no therapy with long term follow-up evaluating the syncope burden (number of syncopal episodes). The number of patients was small ($n = 42$ of which 19 received a pacemaker and 23 did not receive a pacemaker) but the patients were followed for a mean of 3.7 years (range 1 to 6.7 years). The implanted devices were St. Jude Medical Paragon[®] III and Trilogy[®] DC programmed to the DDI mode with rate hysteresis. The base rate was 80 ppm with a hysteresis

escape rate of 45 ppm. The difference between the two groups was significant ($p = 0.0004$) with only a single syncopal episode occurring in the paced group and 14 syncopal spells occurring in the control group.

At this time, there is good evidence that pacing therapy is effective in patients with recurrent syncope which is, in part, due to a major cardioinhibitory component and in whom pharmacologic therapy has not been totally effective, not tolerated or when the patient is noncompliant. Pacing is not considered a first line therapy for this entity as most patients respond to pharmacologic therapy and for reasons that have not been fully elucidated, this seems to be a self-limited condition in many individuals and will spontaneously resolve. Where pharmacologic therapy has not been totally effectively or has been associated with some side effects, continuing a lower dose in conjunction with pacing may give the best results.

GUIDELINES TO PACEMAKER PROGRAMMING

If pacing is to be utilized for the management of neurocardiogenic syncope, a standard VVI or even DDD pacemaker programmed to the usual rates will not be adequate. Although these patients do not require pacing support between their episodes, during the episodes they require all the capabilities of the modern pacemaker. The patient's are relatively hypovolemic. As such, they require atrial pacing to maintain the atrial contribution to ventricular filling which would not be available with a VVI pacemaker although this will support the heart rate. The increased in vagal tone which is the final common pathway for the precipitation of syncope results in both sinus arrest and AV block. As such, single chamber atrial pacing is not recommended for this would not support the ventricle. If pacing is to be utilized, a dual chamber pacing system is required.

In view of the peripheral vasodilation and hypotension that is a major component of the syndrome, pacing at standard rates has been inadequate. Rates of 90 to 110 ppm is commonly required. If the pacemaker were programmed to this base rate, it may well protect the patient against these spells but it would also result in relatively rapid pacing when the patient did not require pacing support. Pacing rates which are physiologically inappropriate, most commonly experienced with rate modulated pacing, may result in bothersome palpitations and long-term pacing would not be tolerated. Thus, there needs to be mechanism which allows the native rhythm at normal rates to inhibit the pacemaker. This is either rate hysteresis choosing a very low escape rate and/or an algorithm such as the rate drop response where high rate pacing will only occur when the rates falls by a preselected number of beats/min within a predefined period of time. Both approaches have proven to be very effective. There is one study (25) which compared both the dual chamber (DDI) rate hysteresis to the rate drop response algorithm reporting a benefit in favor of the rate drop response algorithm but the pacing rate in RDR was 20 to 30 bpm higher than in the DDI mode. As such, this was not a valid comparison.

The pacing mode should be either DDD or DDI. There are subtle differences between these two modes that may favor the selection of one mode over the other for individual patients. In the current devices, the DDD mode utilizes atrial-based timing. This means that following the delivery of an atrial output pulse at the escape rate, the rate will increase to the programmed base rate with atrial pacing whether or not there is concomitant AV block. As such, one may experience either functional single chamber atrial pacing (AR) or dual chamber pacing (AV) at the higher base rate.

The DDI mode utilizes ventricular based timing. To achieve pacing at the higher base rate, a ventricular output at the escape rate must occur. Assuming that the rate slows on a physiologic basis such that AV nodal conduction remains intact resulting in an atrial paced ventricular sensed (AR) complex, the sensed R wave will re-initiate the hysteresis escape interval resulting in functional single chamber atrial pacing at the programmed escape rate. However, if the AV interval is programmed to too short an interval such that a ventricular output is delivered even though there is intact AV nodal conduction (ventricular fusion or pseudofusion), the rate will still increase. Hence, it is essential to also program the AV delay appropriately. There are multiple benefits of the DDI mode. These patients do not require tracking between spells. It also allows for effective management of neurocardiogenic syncope and sinus node dysfunction in the same patient.

Although standard DDI with hysteresis has proven to be very effective, these earlier algorithms required the occurrence of a native R wave to occur in order to reset the hysteresis escape interval. As such, sustained high rate pacing may occur continuing long after the episode has resolved. To address this behavior, a search function has been added to the current algorithms. After a preset or programmable time or number of intervals, the rate either abruptly or progressively slows allowing for the native rhythm to resume control and inhibit the pacemaker.

While selecting the "optimal AV delay" is not as important for the DDD mode, it is important but it becomes critically important for the DDI mode. In the DDD mode, if the AV delay is too short, there will be repeated fusion even though AV nodal conduction is intact. This will result in an increased battery current drain and shortened device longevity. Hence, one wants to program the AV delay in the DDD mode so that the sensed AV delay is slightly longer than the A sense V sense (PV) interval so effect ventricular output inhibition when conduction is normal. In addition, one should not enable Rate Responsive AV Delay shortening as this will also force P sense V pacing at the higher rates. In the DDD mode, one also needs to evaluate the patient for retrograde conduction and either program a sufficiently long PVARP to prevent a pacemaker mediated tachycardia or enable a PMT detection and termination algorithm.

Programming the AV delay becomes critical when the programmed mode is DDI. If the AV delay is too long, it will keep the system functioning at the escape rate when a higher rate is actually required. If the AV delay is too short such that fusion or pseudofusion occurs at the escape rate, the pacing rate will

promptly increase to the programmed base rate even when the sinus node slowing occurred on a physiologic basis. To select the AV delay, it is recommended that the pacemaker be first programmed to the desired base rate (e.g. 90 ppm) with a very long AV delay. In the clinical stable setting without a concomitant vasovagal spell, this should result in atrial pacing with intact AV nodal conduction. In those systems which have electronic calipers where the A paced V sensed (AR) interval is automatically measured and reported, read this measurement off of the programmer screen. In those devices which provide for telemetered markers but without the interval measurements, progressively shorten the AV delay until the markers go from A pace V sense to A pace V pace. Note the shortest AV delay which results in A pace V sense. Then, in both systems, program the base rate to the lowest rate that will still allow for atrial pacing. This may be a higher rate than the final hysteresis escape rate. Again, measure the shortest A pace V sense interval. If this is significantly shorter than the A pace V sense interval at the desired base rate, program the AV delay to the longest interval that results in A pace V pace at that higher rate. This way, when the atrial rate slows, there will be intact AV nodal conduction supporting atrial pacing at the escape rate without allowing a rate increase. If the A pace V pace interval is the same at the desired escape rate or lowest atrial paced rate that can be tested as the A pace V pace interval at the desired higher base rate, it will be necessary to program a slightly longer AV delay. This allows A pace V sense to occur at the escape rate in the absence of a vasovagal spell relying on the increase in vagal tone to sufficiently slow conduction through the AV node during the spell to force a ventricular output and trigger pacing at the programmed base rate.

A limitation of the standard hysteresis and rate drop response algorithms is the slight increase in vagal tone that occurs during sleep resulting in very low physiologic rates. This physiologic rate slowing can trigger high rate pacing. The algorithmic rate increase can be prevented by enabling the Rest Rate algorithm available in some pacemakers. As Rest Rate (26,27) is guided by the sensor and not a preset clock, the device will know when the patient is truly at rest and effectively disable the rate hysteresis feature resulting in atrial pacing at the Rest Rate allowing the pacemaker to continue to appropriate support the patient.

Another challenge to these algorithms is ventricular ectopy. Ventricular ectopic beats or ventricular premature beats (VPB) are commonly associated with a pause following the VPB. Depending on the programmed rates or rate drop zone, this may be sufficient to trigger high rate pacing. Refinements to the original algorithm allow a number of cycles at the escape rate or below the rate drop window to be programmed before high rate pacing will occur.

ASSESSMENT OF ALGORITHM BEHAVIOR

The primary measure of effectiveness will be the level of symptoms with a desirable endpoint being a significant reduction in symptoms. If syncope still occurs, a delay in its onset giving the patient the opportunity to initiate protective actions such as sitting or lying down before overt syncope occurs.

A simple counter reporting the number of times that the algorithm was enabled provides some information but will not allow the physician to determine whether or not the multiple algorithms were appropriate.

The event counter capability in some of the newer pacemakers may allow the physician to assess the degree to which pacing is being actually utilized. The Event Histogram counter in St. Jude Medical pacemakers will provide both an overview as well as detailed information as to the degree of pacing. In addition, to reporting on the total percentage of atrial and ventricular pacing, it will report the relative distribution of pacing states. Those of primary interest will be AR and AV. The vast majority of the complexes should be atrial sense ventricular sense (PR). Further details can be assessed using the detailed event count table which reports the absolute number of complexes in each of the pacing states and further, the absolute number of complexes in each rate bin within each pacing state. Hence, for the DDI mode, a large number (percentage) of AR (A pace V sense) complexes at the escape or rest rates would suggest sinus node dysfunction with intact AV nodal conduction. The number of AV pacing complexes at the programmed base rate would provide an insight into the degree to which pacing was really required.

If the patient complains of recurrent palpitations and there are large numbers of AV paced complexes at the programmed base rate, it is likely that the pacemaker parameters had not been adjusted appropriately.

SUMMARY

Neurocardiogenic syncope is a relatively common entity. In the vast majority of people, there are well defined triggers that can be either avoided or appropriate action taken when avoidance is not feasible. In a smaller number of individuals, there are recurrent syncopal spells without a clear trigger. The basic treatment is pharmacologic therapy, most commonly with beta blocking agents, midodrine and/or serotonin reuptake inhibitors. When the primary mechanism is vasodepression, the only option is pharmacologic therapy. Should drugs prove to be ineffective and there is a major cardioinhibitory component to each episode, then pacing therapy may provide a valuable adjunct to the management of these patients. There are two key capabilities required for such a system. These include the ability to provide a relatively high rate of pacing during the spell and some means for recognizing that the spell has occurred (by either a relative drop in rate or a drop to an absolute low rate) before high rate pacing will result. The addition of Rest Rate and a programmable number of escape cycles will allow the individual device response to be refined but these are not absolutely essential. Being able to program the escape rate to a very low escape rate will prevent triggering high rate pacing by normal physiologic heart rate slowing or by the compensatory pause following a VPB.

Pacing therapy, as good as it might be for a selected patient, is not a guaranteed cure. A beneficial result would be a reduction in the number or severity of the spells. The combination of pharmacologic therapy at a dose level that is not associated with side effects and pacing has been suggested in some papers (28) but not been formally evaluated. This approach offers some promise if pacing is not able to totally eliminate all symptoms.

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