

# Closed Loop Stimulation: Therapy for Malignant Neurocardiogenic Syncope

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## Summary

*Vasovagal syncope (VVS) is often preceded by fluctuations in sympathetic activity and is frequently accompanied by sudden-onset bradycardia. Pacemaker therapy can compensate for the bradycardia and thus prevent loss of consciousness and related subsequent injury to the patient. Pacemakers with Closed Loop Stimulation (CLS) may be particularly effective because they adapt the pacing rate to the contraction dynamics of the right ventricle and can therefore intervene directly in the generation mechanism of the VVS. In this study, we examined 22 patients with malignant VVS (16 female, age  $55.5 \pm 17.3$  years, range 17 – 77 years). Inos<sup>2+</sup> CLS pacemakers were implanted in 17 patients (nine female, age  $63.0 \pm 9.7$  years) who were resistant to conventional  $\beta$ -blocker therapy. A head-up tilt test prior to implantation was used to classify the VVS as either syncope of the cardioinhibitory type IIa ( $n = 13$ ) or IIb ( $n = 1$ ), or as syncope of the vasodepressor type III ( $n = 3$ ). Another tilt-table test was performed following a recovery period of at least one week after the pacemaker implantation. The patients' further disease progress in daily life regarding syncope events was followed for a period of 4 – 48 months after the pacemaker implantation. The results from the tilt-table examinations and daily life after pacemaker implantation suggest that type IIa and IIb syncope were prevented successfully by CLS pacing. In patients with VVS of type III, the symptoms could be alleviated and the prodromal phase extended; however, VVS could not be completely suppressed. None of the 17 patients reported VVS in daily life after the pacemaker implantation, and the quality of life improved for all patients.*

## Key Words

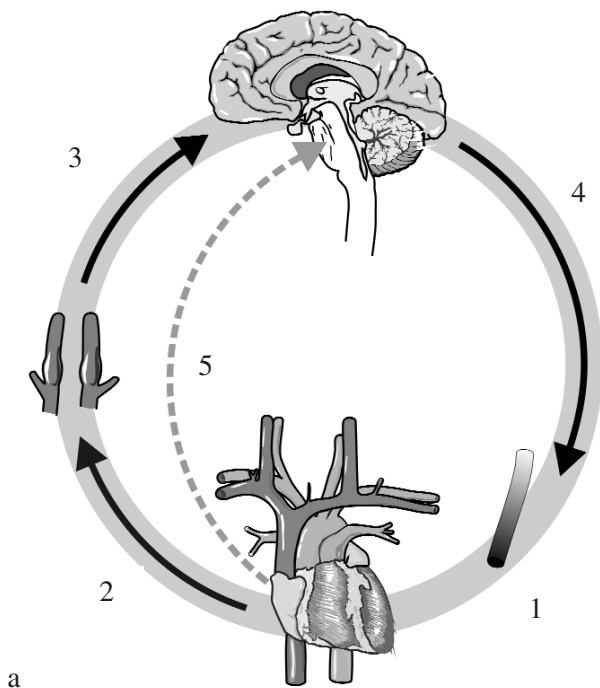
Vasovagal syncope, Closed Loop Stimulation (CLS)

## Introduction

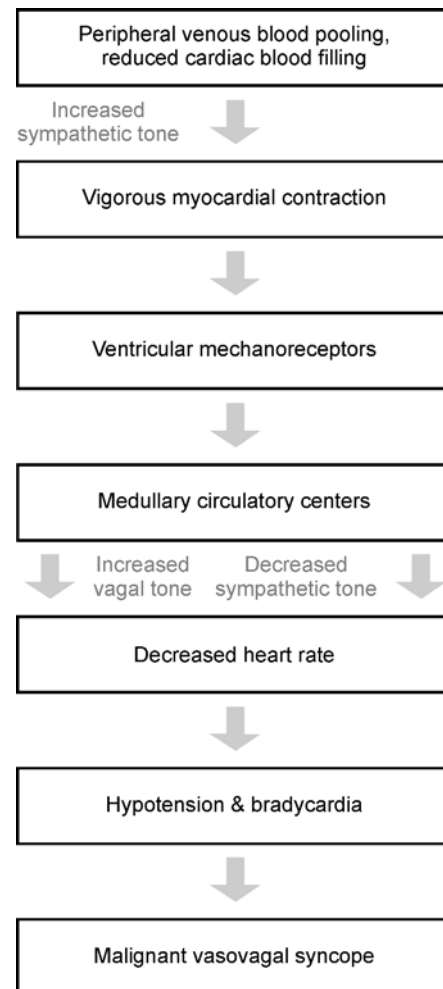
Vasovagal syncope (VVS) often leads to severe injuries, because the repeated loss of consciousness catches the patients by surprise in most cases, without any previous warning. The Bezold-Jarisch reflex model describes the generation mechanism of VVS (Figure 1). Syncope is often triggered during walking or standing when the blood gets pooled in the peripheral veins. The decreased backflow to the heart generates a decrease in stroke volume and cardiac output due to the reduced preload. To counter these effects, the sympathetic nervous system is activated, and the vagal system is inhibited. Heart rate and inotropism are increased as a reaction to the increased sympathetic activity. Due to an excessive release of catechol-

amines and an increased reduction of left ventricular filling ("pumping until empty"), the mechanoreceptors of the left ventricle are activated. This stimulus is conducted to centers in the medulla oblongata via afferent fibers. In these centers, the sympathetic system is inhibited, and the vagal system is more strongly excited. The consequences are inadequate vasodilatation and a drop in blood pressure, often accompanied by bradycardia.

Depending on whether the drop in blood pressure or the bradycardia is dominant, cardioinhibitory and vasodepressor syncope are distinguished. The syncope is characterized by head-up tilt-table examinations, during which syncope is induced by changes in position, often



**Figure 1.** Generation mechanism of vasovagal syncope (Bezold-Jarisch reflex). Panel a) A decreased backflow to the heart due to peripheral venous blood pooling (1) generates a decrease in cardiac output and mean arterial blood pressure (2). To counter these effects, the sympathetic nervous system is activated by the baroreceptor reflex (3) to increase heart rate and inotropism. In vasovagal syncope, the mechanoreceptors of the left ventricle are activated by vigorous myocardial contraction, inhibiting the sympathetic system and exciting the vagal system (5) and, thus, causing a vasodilation and a drop in blood pressure (4).



b

in conjunction with drug provocation [1]. Heart rate and blood pressure are monitored during the tilt tests. By means of these examinations, tilt-induced syncope can be differentiated into the following types according to Sutton [2-5]:

- Type I, also called mixed type, characterizes syncope due to falling blood pressure while the heart rate drops below 40 beats/min (bpm) for less than 10 s.
- The cardioinhibitory type is subdivided into the types IIa and IIb. In type IIa, the blood pressure drops before the heart rate falls below 40 bpm for more than 10 s or before an asystole of more than 3 s occurs. In type IIb, the blood pressure also drops, but after the heart rate falls below 40 bpm for more than 10 s or an asystole of more than 3 s occurs.

- The vasodepressor type III shows a marked drop in blood pressure at constant heart rate or a decrease in the heart rate by up to 10% of its original value.

Aside from general prophylactic measures, such as avoiding dehydration, long periods of standing, or large meals, a variety of drugs are available to treat VVS [6-9]. Serotonin uptake inhibitors and  $\alpha_1$ -agonist such as midodrine are useful in some forms of neurally mediated syncope, but fludrocortison and  $\beta$ -blockers are probably the most favored drugs, and have relatively few side effects.

If the drug therapy is ineffective, AV-sequential pacemakers with special algorithms are indicated for VVS of the cardioinhibitory type [10-12]. Algorithms, such as rate hysteresis [13,14] or reaction to rate drop [13-

18], attempt to detect the precipitating syncope based on the rate drop and to prevent loss of consciousness with an increased rate. Since the heart rate drops by less than 10% in the vasodepressor type, these algorithms cannot be effective for this type. But type IIa syncope is also problematic for these pacemaker algorithms because the heart rate falls only after the drop in blood pressure, and the pacemaker can only react belatedly. Frequently, syncope cannot be prevented by reacting to the decrease in the heart rate. An algorithm to prevent the syncope would have to detect pre-syncope mechanisms and react early with a rate increase.

## Materials and Methods

### Pacemaker

The Inos<sup>2+</sup>CLS pacemaker (Biotronik, Germany) uses a unipolar intracardiac impedance measurement as a sensor signal, which reflects the contraction sequence of the heart [19,20]. Therefore, changes in the contraction dynamics can be detected, e.g., as harbingers of a beginning syncope by a change in the impedance curve. The pacemaker reacts to such changes in the impedance curve with a proportional increase of the pacing rate in the range between the basic rate and the maximum sensor rate. As a therapy for chronotropically incompetent patients, the current algorithm (K software) includes a safety feature to avoid high pacing rates during rest. Nevertheless, as a therapy for VVS, the full dynamic pacing range is needed during rest too. Thus, we used the previous algorithm (H software), which can interfere with the Bezold-Jarisch reflex in any situation as soon as the sympathetic system is activated (Figure 2) and can prevent an inadequate drop in the heart rate by accelerating the pacing rate [21,22].

### Tilt-Table Test

We combined the CLS concept with  $\beta$ -blocker therapy (metoprolol) to form a three-step therapy concept. Each step consists of a tilt-table test. In the applied abbreviated tilt-table protocol, the patient lies in the supine position for 10 min. Before the patient is tilted at an angle of 60° into a more upright position and remains there for 15 min, he or she receives two or three jets of nitrolingual spray. If no syncope has occurred after the 15 min have passed, a provocation with 0.5 mg orciprenaline follows. The type of VVS was diagnosed during the first tilt-table examination. The efficiency of  $\beta$ -blocker therapy was tested in a sec-

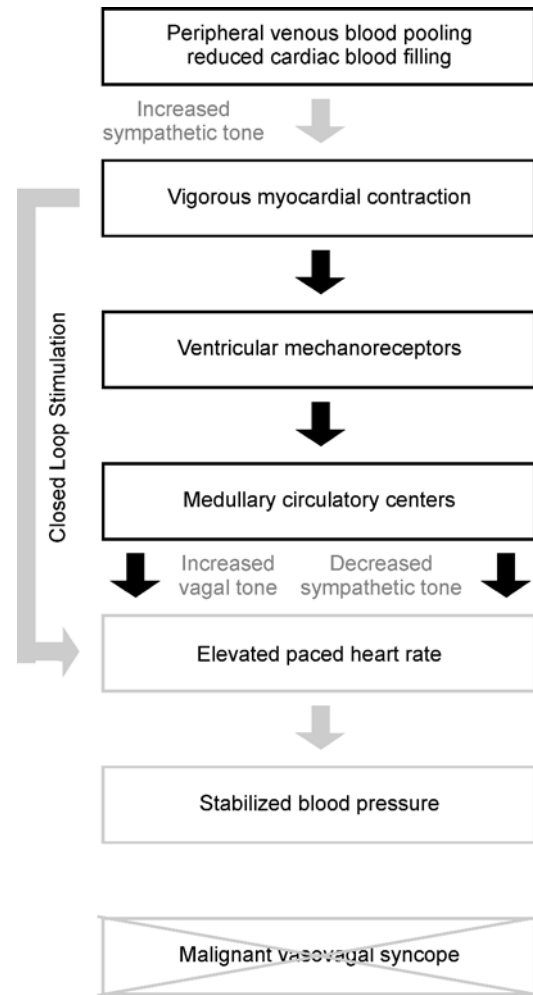


Figure 2. Influence of Closed Loop Stimulation (CLS, Biotronik, Germany) on the generation of vasovagal syncope.

ond tilt-table examination under medication with metoprolol. If the drug therapy was ineffective, the patient was implanted with an Inos<sup>2+</sup> CLS pacemaker. The success of the pacemaker therapy in combination with metoprolol medication was verified in a third tilt-table test.

### Patients

This therapy concept was applied to 22 patients who had suffered injuries, such as fractures and craniocerebral trauma, due to recurring type II or III (pre-)syncope. Among the patients, there were 16 (73%) women and six (27%) men with a mean age of  $55.5 \pm 17.3$  years (17 to 77 years). The patients had a history of repeated syncope with a mean number of

Patient ID	Sex	Age (years)	History of sync.	1. HUTT		2. HUTT + medication		3. HUTT + medication + pacemaker		
				Type	Time to syncope (min)	Type	Time to sync. (min)	Type	Maximum pacing rate (bpm)	Begin pacing (bpm)
1	f	24	5	Ila	4	No VVS				
2	m	24	2	Ila	10	No VVS				
3	m	45	2	Ila	7	No VVS				
4	f	40	> 5	Ila	10	No VVS				
5	f	17	4	Ila	5	No VVS				
6	f	59	2	Ila	4	Ila	4	No syncope	No data	4
7	f	53	2	Ila	9	Ila	9	No syncope	80	2
8	f	57	3	Ila	12	Ila	7	No syncope	87	1
9	m	57	4	Ila	9	Ila	10	No syncope	79	13
10	f	71	1	Ila	7	Ila	6	Pre-syncope III	112	3
11	f	72	3	Ila	5	Ila	11	No syncope	114	2
12	m	47	1	Ila	7	Ila	7	No syncope	106	4
13	f	58	0	Ila	8	Ila	7	Pre-syncope III	109	5
14	m	77	10	Ila	7	Ila	7	No syncope	83	1
15	f	66	3	Ila	13	Ila	13	No syncope	114	2
16	m	53	3	Ila	11	Ila	7	No syncope	88	2
17	f	77	8	Ila	8	*		No syncope	No data	5
18	f	62	4	Ila	5	*		Pre-syncope III	110	4
19	f	52	10	Ilb	15	*		No syncope	118	10
20	f	77	1	III	16	**		Pre-syncope III	No data	
21	f	72	2	III	16	**		Pre-syncope III	No data	
22	f	61	2	III	16	**		Pre-syncope III	No data	

Table 1. Results of the three head-up tilt-table (HUTT) tests. \* = In patients revived during the first test, there was no further tilt-table testing before pacemaker implantation, \*\* = In patients with sino-atrial block, there was no further tilt-table test before pacemaker implantation.

3.6 ± 2.7 episodes. Detailed information on the individual patients can be found in Table 1.

## Results

All 22 patients underwent an initial tilt-table test to diagnose the type of syncope. Nineteen patients exhibited syncope of the cardioinhibitory type, with type IIa occurring in 18 patients, and type IIb in one patient. The syncope of the remaining three patients was characterized as vasodepressor (type III). In the three patients with vasodepressor syncope, an additional sino-atrial block was diagnosed. Three of the 19 patients with cardioinhibitory syncope had to be resus-

citated during the tilt-table examination. These six patients with sino-atrial block and resuscitation during the tilt tests were implanted with Inos<sup>2+</sup> CLS pacemakers after the initial tilt-table examination. In the 16 patients who had not yet been implanted with a pacemaker, first the efficiency of metoprolol ( $\beta$ -blocker) in preventing tilt-induced syncope was tested during a second tilt-table examination. This second tilt-test was negative for five patients, while the remaining 11 patients developed tilt-induced type IIa syncope despite metoprolol therapy. Consequently, these 11 patients were also implanted with Inos<sup>2+</sup> CLS pacemakers. A concluding third tilt-table examination tested whether the CLS algorithm is capable of preventing

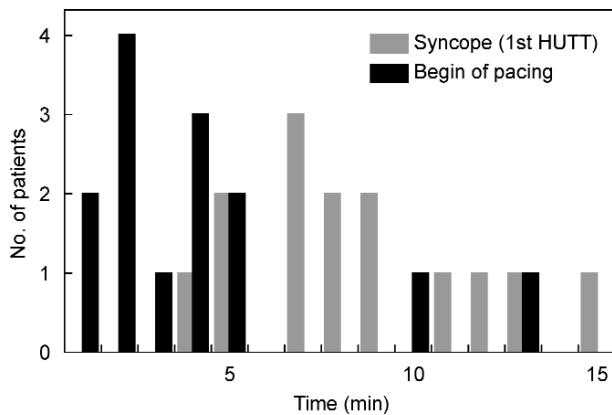


Figure 3. Histogram to compare the reaction times of the pacemaker (Inos<sup>2+</sup> CLS, Biotronik, Germany) with the times until triggering of tilt-induced syncope without therapy.

tilt-induced syncope in patients with implanted Inos<sup>2+</sup> CLS pacemakers. The six patients who had been implanted with a pacemaker after the first tilt-table test because of resuscitation or sino-atrial block as well as the 11 patients who had been implanted with a pacemaker after the second tilt-table test because of drug resistance participated in this third tilt-table examination under  $\beta$ -blocker medication and with pacemaker therapy. Of these 17 patients, none developed syncope during the third tilt-table test. Six patients became pre-syncope, and 11 patients were free of any symptoms (see Table 1).

During the follow-up period, which lasted on average  $12.1 \pm 28.9$  months (4 to 48 months), none of the patients exhibited a recurrence of syncope or pre-syncope in daily life. During the initial tilt-table tests, the syncope occurred on average after  $8.6 \pm 3.2$  min. The Inos<sup>2+</sup> CLS pacemaker reacted on average after a period of  $4.1 \pm 3.4$  min (transition from intrinsic rhythm to pacing), i.e., in a statistically significant manner ( $p = 0.0064$ , Wilcoxon test), before the syncope caused by a drop in blood pressure or heart rate would become manifest (Figure 3). Figure 4 shows an example of a heart rate trend during a tilt-table test. As a control, the percentage of paced heartbeats is displayed in parallel. A drop in the sinus rate shortly after the start of the tilt test (1 min and 5 min) is stabilized by the pacemaker, protecting the patient against a possible further drop in heart rate.

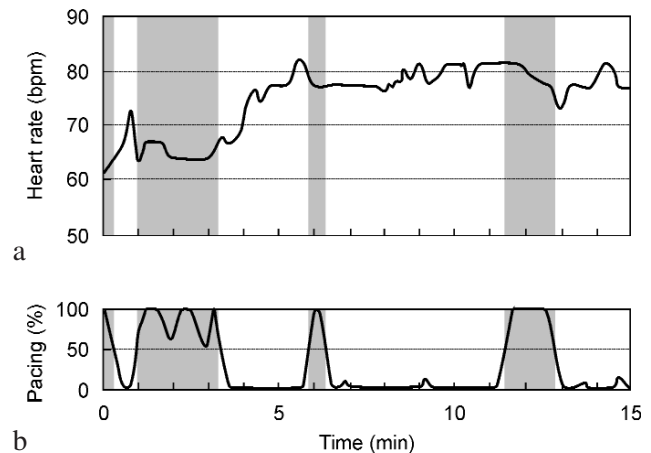


Figure 4. Example of a heart rate trend (panel a) and the percentage of paced heartbeats (panel b). The time intervals during which more than 50% of the heartbeats were paced are marked in grey.

## Discussion

Controversy exists about how informative tilt-table tests are in regard to the occurrence of syncope in daily life [15]. Thus, the VASIS study (Vasovagal Syncope International Study) [14] was able to show that syncope reoccurred in daily life in only 5% of the studied pacemaker patients when rate hysteresis was used. In comparison, syncope recurred in 70% of the patients in the control group without pacemakers. However, during tilt-table tests, 59% of the pacemaker patients presented with syncope, compared to 60% of the patients in the control group. Sra et al. [9] showed that pacemaker therapy was not able to prevent the occurrence of syncope during tilt-table tests. On the one hand, it can be concluded that the results of tilt-table tests must be verified over the long term in daily life. On the other hand, tilt-induced syncope seems to place particularly high demands on pacemaker therapy.

With CLS reacting to the change in the contraction dynamics in the early generation phase of the syncope, the algorithm is equally effective in cardioinhibitory syncope of types IIa and IIb. In type III vasodepressor syncope, CLS can at best alleviate the symptoms, even if the syncope is detected correctly, by counteracting the drop in blood pressure with an acceleration of the heart rate. However, the dominant influence of the hypotonia cannot completely be compensated by an increased heart rate in most cases.



## Conclusion

A common pacemaker therapy for preventing vasovagal syncope (VVS) is based on the measurement of a subsequent rate drop and on a hysteresis. Another concept is provided by Closed Loop Stimulation (CLS), which is sensitive to changes in myocardial contraction dynamics. We showed that in patients with type IIa/b cardioinhibitory, the Inos<sup>2+</sup> CLS pacemaker has a reaction time that is sufficiently short to prevent the occurrence of syncope. Patients with type III vasodepressor VVS still show pre-syncope even after CLS system implantation, but they are free of syncope. After the implantation of a CLS pacemaker, no patient who initially presented with VVS experienced a recurrence.

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