Treatment of persistent sinus bradycardia with intermittent symptoms: are guidelines clear?

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There is uncertainty in the aetiology of syncope in subjects with persistent sinus bradycardia (SB) (sick sinus syndrome). The results of pathophysiological studies suggest a reflex origin of syncope in the vast majority of subjects with SB. From a nosological point of view, ‘syndrome’ is defined as the association of signs and symptoms that have a pathophysiological correlation. Since in most cases the causal relationship between syncope and persistent SB appears very weak, ‘reflex syncope with associated SB’ appears to be the most appropriate diagnosis.

Keywords
- Carotid sinus massage
- Sick sinus syndrome
- Sinus bradycardia
- Syncope
- Tilt testing

The sick sinus syndrome is a descriptive term that refers to a constellation of signs and symptoms defining sinus node dysfunction in a clinical setting. The most frequent electrocardiographic (ECG) sign is persistent sinus bradycardia (SB), (sinus rate < 50 bpm). Although persistent clinical manifestations of bradycardia (due to the consequent reduction in cerebral and peripheral perfusion) such as subtle symptoms of fatigue, irritability, lassitude, inability to concentrate, lack of interest, forgetfulness, and dizziness can be expected, it is more difficult to explain intermittent symptoms (syncope and pre-syncope), which are present in about a half of the patients affected by sinus node dysfunction requiring hospital assistance.1,2 Although persistent symptomatic bradycardia clearly defines sick sinus syndrome, the meaning of intermittent severe SB or sinus arrest is less clear. Indeed, the same event (i.e. intermittent symptomatic sinus arrest) may be diagnosed by one physician as sick sinus syndrome and by another as cardio-inhibitory reflex syndrome. On the other hand, the same syncope may be diagnosed as reflex if not documented, whereas it may be diagnosed as sick sinus syndrome if there is fortuitous documentation of a pause.

This uncertainty of the aetiology of syncope in subjects with SB is also reflected in the recommendations for pacing therapy of the European3 and American guidelines.4 Indeed, in the European guidelines, ‘Recurrent severe vasovagal syncope in patients who show prolonged asystole during ECG recording’ is a class Ila indication, and in the American guidelines, ‘Significantly symptomatic neurocardiogenic syncope associated with bradycardia documented spontaneously’ is a class Iib indication.

Pathophysiology of syncope in subjects with sinus bradycardia

The possible role of autonomic factors in the genesis of signs and symptoms characterizing sick sinus syndrome has been suggested for a long time. Two studies5,6 have specifically evaluated the relationship between syncope and abnormal reflexes in patients with SB. Brignole et al.5 performed head-up tilt testing (HUT) and carotid sinus massage (CSM) with the method of symptoms in 35 patients with SB and syncope and compared the results with those obtained in 35 patients with normal sinus rate who were affected by syncope of uncertain origin. The percentage of positive HUT in the subjects with SB was high (54%): higher than that recorded in the subjects with syncope of uncertain origin (26%). The percentage of positive CSM in the subjects with SB was also high (60%) and similar to that observed in patients with syncope of uncertain origin (63%). Thus, an abnormal neural reflex played a major role in causing syncope in subjects with SB. In order to evaluate...
whether a sinus node dysfunction could enhance the cardio-inhibitory efferent reflex response, and therefore predispose patients to positivity in these tests, Alboni et al.3 studied two groups of subjects with SB, one with history of syncope and one without. The clinical characteristics, Holter monitoring data, and basal and intrinsic corrected sinus node recovery time (CSNRT) were similar in the two groups. The patients with SB and syncope had a higher prevalence of positive response to HUT (60 vs. 12%, \( P = 0.001 \)) and CSM (44 vs. 22%, not significant) than those without syncope; overall, 76% of the patients with syncope had at least one positive test vs. 36% of those without syncope (\( P = 0.01 \)). Moreover, positivity to these tests was independent of the presence of intrinsic sinus node dysfunction and the severity of SB. The results of these two studies suggest that, in subjects with SB, syncope is mainly related to an abnormal neural reflex and that the diseased sinus node may play a marginal facilitating role in the development of a cardio-inhibitory reflex, with the possible exception of the minority of patients with a very prolonged CSNRT suggestive of a major depression of sinus node automaticity.7 In other words, these results suggest that when in the general population an asymptomatic subject with SB experiences a neurally mediated syncope, he/she becomes a sick sinus syndrome patient.

A reflex mechanism of syncope fits well with the unpredictable natural history of syncopal recurrences (only 46% recurrence rate in non-treated patients during 4-year follow-up)3–7 and can explain why neurological symptoms have no prognostic relevance in subjects with sinus node dysfunction.8 However, another possible mechanism of syncope must be considered, that is, a prolonged asystole secondary to a diseased sinus node (cause–effect relationship). In brady–tachy syndrome, the depression of the sinus node is likely to be effective in reflex syncopes when a prolonged asystolic reflex is documented during a spontaneous syncope.9 Therefore, also in patients with reflex syncope with associated SB, without other symptoms attributable to prolonged asystole, pacemaker implantation appears indicated. If the CSNRT is not prolonged and the HUT is positive, we should consider that the mechanism of reflex syncope is heterogeneous, with more cardiac pacing could be effective when an asystole is documented at the time of syncope, there is no rationale for the use of pacing in patients with dominant vasodepressor syncope. Likely for this reason, controlled trials of tilt-guided therapy have often failed to show a benefit, and evidence of the efficacy of empirical therapy for reflex syncope is weak.10,11

The recognition of an important vasodepressor reflex makes pacing therapy questionable. On the other hand, cardiac pacing is likely to be effective in reflex syncopes when a prolonged asystolic reflex is documented during a spontaneous syncope.9 Therefore, also in patients with reflex syncope with associated SB, without other symptoms attributable to prolonged asystole, an attempt to document a spontaneous event should be made before embarking upon permanent cardiac pacing. In any case, it must be underlined that the decision to implant a pacemaker needs to be kept in the clinical context of a benign condition,8 the intention being to avoid intermittent symptoms and not to treat an otherwise asymptomatic SB.

### Practical implications

Distinguishing sick sinus syndrome from reflex syncope with associated SB has a practical value in the selection of candidates for cardiac pacing. While cardiac pacing is an effective therapy in sick sinus syndrome,6 its value is more questionable in the latter cases.

From a practical point of view, subjects with SB and syncope, without other symptoms attributable to sinus node dysfunction, should undergo autonomic tests (HUT potentiated with nitroglycerin and CSM with the method of symptoms) and electrophysiological study in order to assess, as far as possible, the mechanism of syncope. In the presence of depressed sinus node automaticity (CSNRT > 800 ms), pacemaker implantation appears indicated. If the CSNRT is not prolonged and the HUT is positive, we should consider that the mechanism of reflex syncope is heterogeneous, with severe bradycardia or asystole accounting for only about half of the syncopal events, while a dominant vasodepressor reflex is the likely mechanism in the other cases.9 While cardiac pacing could be effective when an asystole is documented at the time of syncope, there is no rationale for the use of pacing in patients with dominant vasodepressor syncope. Likely for this reason, controlled trials of tilt-guided therapy have often failed to show a benefit, and evidence of the efficacy of empirical therapy for reflex syncope is weak.10,11

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### Making guidelines more clear

In the present guidelines, the clinical situation of persistent SB with intermittent symptoms is discussed both in the sick sinus syndrome section and in the vasovagal syncope section, but the terminology and the recommendations are different. Therefore, they should be unified in the section reflex syncope with associated SB. In the clinical setting, defining a correlation between intermittent symptoms and heart rhythm is warranted. On the basis of the present knowledge, in subjects with asymptomatic SB and syncope, indication to pacemaker implantation should be confined to patients with prolonged CSNRT or with documentation of spontaneous asystole.

### Syncope and sinus bradycardia: what is the diagnosis?

From a nosological point of view, ‘syndrome’ is defined as the association of signs and symptoms that have a pathophysiological correlation. Both signs and symptoms are necessary to define a syndrome. Thus, ‘sick sinus syndrome’ should be defined only when symptoms are clearly correlated with a severe bradycardia/asystole secondary to a diseased sinus node (cause–effect relationship). In brady–tachy syndrome in whom syncope is the only symptom, a diagnosis of sick sinus syndrome can be made in a minority of patients who show: (i) ECG documentation of prolonged pause/s following the termination of a tachycardia or (ii) prolonged CSNRT (>800 ms).3,7 In the other cases, the causal relationship between syncope and persistent SB is very weak, and bradycardia might be an unrelated comorbidity accompanying a reflex syncope. In these cases, especially if HUT and CSM are abnormal, the most appropriate diagnosis appears to be ‘reflex syncope with associated SB’.

### References

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