

## Asymptomatic Arrhythmias in Patients with Unexplained Syncope: Do They Have Any Diagnostic Value?

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**S**yncope is a common clinical entity that occurs in up to 40% of the general population during a lifetime. According to statistics, nearly 1% of referrals to the emergency department are for syncope, while 40% of those patients are hospitalised.<sup>1</sup> Interestingly, initial evaluation is able to define the cause of syncope in only 23-50% of patients, while even after full conventional work up, 10% to 26% of patients will remain undiagnosed.<sup>1,2</sup>

The most unequivocal proof of diagnosis is the documentation of haemodynamic and electrocardiographic behaviour during a spontaneous syncopal episode. However, even in this case the actual cause of syncope may vary. For instance, an ECG recording of complete heart block may be attributable to a neurally mediated syndrome but also to structural abnormalities of the conduction system.

Until now, the patient had to wait for a newly documented syncopal episode before the diagnosis of syncope could be made. However, given the sporadic nature of the symptom, which recurs unpredictably over months or even years, this cannot be considered as the optimum therapeutic strategy. This so-called “watch and wait” strategy is associated with certain unfavourable consequences, such as the risk of physical injury or sudden cardiac death, increased overall mortality, impact on quality of life,

as well as the economic burden for health care systems.<sup>3-7</sup>

### Asymptomatic arrhythmias and pre-syncopal episodes

According to ECGs from Holter and implantable loop recorder (ILR) monitoring, asymptomatic arrhythmias are frequently recorded in the elderly presenting with syncope.<sup>8,9</sup> If these arrhythmias cannot be attributed to reversible causes, such as hyperkalaemia or sleep apnoea syndrome, is it reasonable to assume that they have any diagnostic value?

Patients with syncope of arrhythmic origin may also experience arrhythmic episodes that do not result in loss of consciousness. These episodes, defined as non-syncopal, are much more common than syncope itself and are often misinterpreted as “imminent” syncope. However, is it justifiable to base decision-making for syncope diagnosis and treatment on these asymptomatic arrhythmias?

Undoubtedly, a good correlation between the nature of non-syncopal documented arrhythmic events (either pre-syncopal or asymptomatic) and those recorded during a spontaneous syncopal episode would not only allow the use of these former arrhythmias as surrogate endpoints, predictive of the mechanism of syncope, but

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would also enable the anticipation of treatment without waiting for documentation of a syncopal episode.

### **Impact of non-syncopal arrhythmic events on the diagnosis and treatment of syncope**

Many studies have sought to evaluate a potential predictive value of documented non-syncopal episodes. In a study that included 85 patients with recurrent undiagnosed syncope, after loop recorder implantation and a mean follow up of  $10.5 \pm 4$  months, 58 patients (68%) experienced recurrent events and 50 of them managed to activate the device properly to achieve symptom-rhythm correlation.<sup>10</sup> Thirteen of them experienced only recurrence of syncope (with an arrhythmia evident in 69%), while 27 experienced only pre-syncope (with an arrhythmia evident in 24%). In 10 patients recurrence of both syncope and pre-syncope occurred and, surprisingly, when an arrhythmia was documented during pre-syncope, the same arrhythmia was also detected during syncope (in 3 out of 4 patients). The remaining 6 patients had sinus rhythm (SR) during pre-syncope; nevertheless, in half of them an arrhythmia was documented during syncope. It is therefore clear that pre-syncope was much more common than syncope, although it was much less likely for an arrhythmia to be recorded during pre-syncope compared with syncope (24% versus 69%,  $p=0.0005$ ). Interestingly, patients who experienced an arrhythmia during pre-syncope were highly likely to experience the same arrhythmia during a spontaneous syncopal episode, in contrast to patients with SR during pre-syncope, in who an arrhythmic cause during syncope could not be excluded.

A subsequent study<sup>11</sup> by the same investigators confirmed the above findings. After a follow-up period of 1 year, 73% of the 85 participants experienced recurrence of syncope or pre-syncope. Out of a total of 150 recurrent events, syncope occurred 3 times less frequently than pre-syncope but was more likely to be associated with an arrhythmia (42% vs. 12%). In 16 patients both syncope and pre-syncope occurred, with an arrhythmia during the syncopal episode detected in 9 of them. The same arrhythmia during pre-syncope was detected in only 6 of those 9 patients, while the remaining 3 patients had normal SR during pre-syncope. According to the above, pre-syncope should not always be associated with an ominous arrhythmia, but should be considered as a non-specific symptom, often causally unrelated to syncope. Nonetheless, an arrhythmia documented during pre-syncope has a

strong positive predictive value regarding the mechanism of a spontaneous syncopal episode.

In another study,<sup>12</sup> investigators attempted to define whether asymptomatic arrhythmias could preclude waiting for recurrence of a spontaneous syncopal episode, dictating a treatment decision that would result in the resolution of syncope. Sixty patients with recurrent unexplained syncope underwent ILR implantation and arrhythmic episodes were pre-specified as significant or borderline, according to the likelihood of resulting in a syncopal episode. After 1 year of follow up, 29 participants experienced asymptomatic arrhythmias, which according to the investigators' classification were significant in 9 of them (15%), leading to the decision for pacemaker implantation in 7 out of 9. Twenty other patients (33%) experienced borderline asymptomatic arrhythmias that were not diagnostic and did not lead to any changes in the therapeutic approach. However, during further follow up, 5 of these patients (25%) developed a similar arrhythmia of diagnostic value that led to an appropriate treatment decision. Ultimately, prolonged monitoring revealed frequent asymptomatic arrhythmias (in 48% of patients), resulting in treatment decisions that resolved syncope in 15% of them. Furthermore, borderline arrhythmias (detected in 1/3 of patients) even though not diagnostic, were at least suggestive of a subsequent diagnostic bradycardic episode.

In accordance with the above were the results of a sub-study of ISSUE-2<sup>13</sup> (International Study on Syncope of Uncertain Etiology), which included 41 patients with suspected neurally-mediated syncope. During a follow up of  $\leq 24$  months, 32 patients experienced both syncopal and non-syncopal episodes (14 of them pre-syncope and 18 non-specific symptoms). In 9 of them, ILR recordings revealed an arrhythmia during the non-syncopal episode; interestingly, the same arrhythmia was also documented during the index syncope (i.e. the first documented syncope during which an ECG recording was obtained). However, the findings in the remaining 23 patients, in whom SR was detected during non-syncopal episodes, were conflicting. Although in 16 of them SR was also the underlying rhythm during the index syncope, in the other 7 patients (in 3 during pre-syncope and in 4 during non-specific symptoms), the index syncope was associated with an arrhythmia. Overall, 20 of the 32 patients experienced a non-syncopal episode that preceded the first syncopal episode, by an average of 137 days (1 to 436). Therefore, detection of an arrhythmia during a non-syncopal episode could al-

low a reliable aetiological diagnosis of syncope and, most importantly, without having to wait for a new documented syncopal episode to occur.

Second and third generation ILRs have the ability, not only to be manually activated by the patient or a bystander after a symptomatic episode, but also to be automatically activated in the case of occurrence of predefined arrhythmias, even asymptomatic. The utility of this capability –the auto activation feature– was evaluated in a study conducted in 50 patients with recurrent syncope after second generation ILR implantation.<sup>14</sup> The study found that 90.6% of all the most likely diagnoses (i.e. arrhythmias recorded during episodes that were accompanied by syncope or near syncope) were provided by the auto activation feature, while impressively it also provided 87.1% of all arrhythmia diagnoses (even during asymptomatic episodes). Thus, the automatic activation feature in second generation ILRs has proven more effective than conventional patient-activated recordings for detecting arrhythmias.<sup>15</sup> Not only did it decrease the required mean time between ILR implantation and detection of the first episode of an important arrhythmia, but it also enhanced the likelihood of making a presumptive diagnosis in the absence of overt syncope.

## Conclusions

As asymptomatic arrhythmias are frequently observed in patients with recurrent syncope, implementation of second or third generation ILRs could substantially facilitate decision making, based on the diagnostic value of non-syncopal episodes. In brief, documentation of an asymptomatic arrhythmia or an arrhythmia during pre-syncope can be considered a diagnostic finding, predictive of the ECG pattern observed during spontaneous syncope. Therefore, it may allow therapeutic decisions, without anticipating an actual syncopal episode, minimising the duration between ILR implantation and management decision. In contrast, documentation of SR during a non-syncopal episode does not permit exclusion of the presence of an arrhythmia during syncope; therefore, heart rhythm monitoring should not be discontinued.

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