



# The benefit of pacemaker therapy in patients with neurally mediated syncope and documented asystole: a meta-analysis of implantable loop recorder studies

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## Aim

Although the efficacy of cardiac pacing in patients with neurally mediated syncope (NMS) and documented asystole is established, a more robust point estimate of the benefit, which is not possible with any individual study, is lacking.

## Methods and results

We undertook a meta-analysis of individual participant data from four studies that reported follow-up data on syncope recurrence with cardiac pacing in patients with NMS who had had an electrocardiographic (ECG) documentation of an asystolic event by means of implantable loop recorder (ILR). Of a total of 1046 patients, who had ILR implanted, 383 (36.6%) patients had an ECG documentation of a diagnostic event during mean follow-up of  $13 \pm 10$  months. Of these, 201 (52%) patients, corresponding to 19.2% of the total ILRs, had an asystolic event of  $12.8 \pm 11.0$ s duration documented and met the criteria for pacemaker therapy. Follow-up was available in 121 (60%) of those patients with asystolic events. Syncope recurred after pacing in 18 (14.9%) patients with an actuarial rate of 13% [95% confidence interval (CI)  $\pm 6$ ] at 1 year, 21% (95%CI  $\pm 10$ ) at 2 years, and 24% (95%CI  $\pm 11$ ) at 3 years. On multivariable Cox regression analysis, positive tilt test response was the only significant predictor of syncope recurrence with a hazard ratio (95% CI) of 4.3 (1.4–13). On the contrary, type of asystolic event (sinus arrest or atrioventricular block), prodrome, cardiac abnormalities, number and duration of history of syncope, age, and gender were not predictors of recurrence of syncope.

## Conclusion

A long asystolic pause, suitable for pacemaker therapy, was found in one of five patients with ILR. After pacemaker implantation, most of these patients remained free of syncope recurrence for up to 3 years. The benefit of pacemaker was greater in patients with negative tilt test.

## Keywords

Syncope • Reflex • Neurally mediated • Implantable loop recorder • Sinus arrest • Atrioventricular block • Pacemaker • Cardiac pacing • Meta-analysis

## Introduction

The diagnostic yield of implantable loop recorders (ILR) in patients affected by certain or likely neurally mediated syncope (NMS) is well established from several large studies in the literature performed in

the last two decades. Asystolic events accounted consistently in these studies for about half of the diagnoses.<sup>1,2</sup> Therefore, cardiac pacing was the most frequent therapy prompted by ILR observations. Less known is the outcome after pacemaker implantation due to small number of such patients reported in individual studies. The

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## What's new?

- By means of a meta-analysis of individual patient data from four studies performed in patients with asystolic reflex syncope documented by implantable loop recorder, we had a more robust point estimate of the benefit of cardiac pacing which was not possible with any individual study.
- We estimated that, after pacemaker implantation, 65–87% of these patients will remain free of syncope recurrence for up to 3 years. Further research is very unlikely to change the confidence in the estimate of effect.
- We estimated that patients with negative tilt test will have <6% risk of syncope recurrence within 3 years. This rate is similar to that observed in patients paced for intrinsic atrioventricular block.
- On the contrary, the patients with positive tilt test will have a higher risk of recurrence of syncope with a large confidence range of 13–53% which makes any estimate of the benefit of pacing uncertain. Further research is warranted.

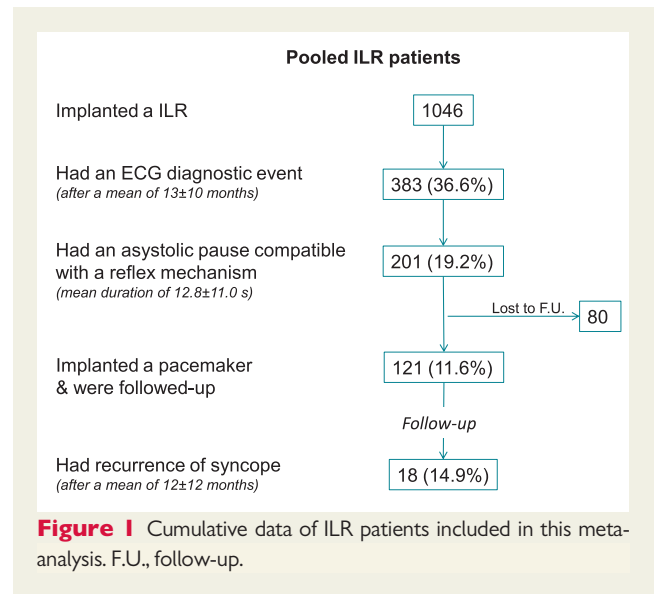
efficacy of cardiac pacing in patients affected by NMS is debated due to the risk of syncope recurrence favoured by hypotensive reflexes (vasodepression) that are virtually always associated.<sup>3</sup>

We aimed to perform a meta-analysis of individual data from four studies<sup>4–7</sup> that recruited patients affected by certain or suspected NMS, implanted (ILR), and reported follow-up data on syncope recurrence after ILR-guided cardiac pacing to have a more robust point estimate which is not possible with any individual study.

## Methods

The four studies<sup>4–7</sup> included in this meta-analysis were of patients aged  $\geq 40$  years affected by severe, recurrent, likely NMS. These studies were performed by the same group utilizing a rather homogeneous method for selection of patients, collection of data, and outcome evaluation, thus allowing pooling of individual data from the original databases of the four studies. This meta-analysis includes the vast majority of patients with reflex syncope who have an available follow-up after cardiac pacing. From a MedLine analysis of the literature, only one other study<sup>8</sup> reported similar data in further 14 patients who had an asystolic event compatible with a reflex mechanism and received a pacemaker. Lacking individual data, these patients could not be included in analysis, but the results of that study are discussed in the Discussion.

In accordance with the guidelines of the European Society of Cardiology (ESC),<sup>1</sup> NMS was considered likely when the clinical features were consistent with a reflex mechanism and competing diagnoses had been excluded. Specifically, exclusion criteria were the following: (i) suspected cardiac arrhythmic syncope [inadequate sinus bradycardia (<50 b.p.m.) or sinoatrial block, second-degree Mobitz I atrioventricular (AV) block, second-degree Mobitz II or third-degree AV block, paroxysmal tachyarrhythmia or ventricular tachycardia, and bundle branch block]; (ii) severe structural heart disease and/or significant electrocardiographic (ECG) abnormalities; (iii) orthostatic



hypotension; and (iv) non-syncopeal causes of transient loss of consciousness. Moreover, patients with (v) reflex syncopes due to reversible causes (e.g. vasoactive drugs, concomitant diseases, etc.) were excluded.

An asystolic syncope >3 s or non-syncopeal asystole >6 s recorded by ILR was considered compatible with a likely reflex mechanism when it was part of a self-terminating short episode characterized by: (i) sinus arrest—progressive sinus bradycardia or initial sinus tachycardia followed by progressive sinus bradycardia until sinus arrest; (ii) sinus bradycardia plus AV block—progressive sinus bradycardia followed by AV block (and ventricular pause/s) with concomitant decrease in sinus rate; (iii) AV block—sudden onset AV block (and ventricular pause/s) with constant P-P cycle implying no rise in sinus rate in response to ventricular arrest or bradycardia. These patients were candidates to receive a dual-chamber pacemaker with rate hysteresis, and those patients with an available follow-up after pacemaker implant were included for analysis (Figure 1).

Conversely, the following findings did not confirm NMS and suggested an intrinsic asystolic event: (i) sinus arrest at the end of paroxysmal atrial fibrillation, i.e. brady-tachy form of sick sinus syndrome and (ii) asystolic events followed by persistent bradycardia or AV block. These patients were not included in the analysis.

## Statistical analysis

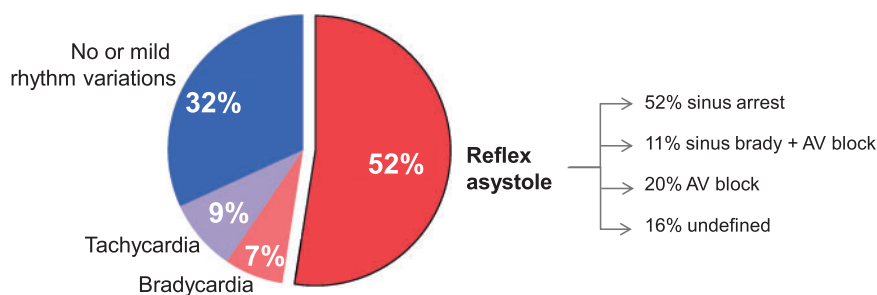
The raw data of individual patients enrolled in four studies<sup>4–7</sup> were pooled in a unique database that was available for this meta-analysis. Continuous data were presented as mean  $\pm$  standard deviation or median (interquartile range), as appropriate, whereas categorical data were presented as absolute and relative frequencies. The Kolmogorov–Smirnov method was used to check the normality of distribution. Continuous variables were compared using the *t*-test or a non-parametric Mann–Whitney test. The Fisher's exact test was used to compare proportions. The time to the first syncope recurrence was analysed by means of the Kaplan–Meier survival curves, which were compared using the log-rank test. The stepwise Cox proportional hazards regression allowed analysing the effect of several

**Table 1** Baseline characteristics of the total population of patients receiving ILR and of patients with asystolic NMS documented by ILR who received an active pacemaker and of those who did not

Characteristics	ILR, all (n = 1046)	ILR, asystole (n = 201)	PM (n = 121)	No PM (n = 80)
Age (years), mean (SD)	66 (13)	66 (13)	66 (14)	66 (13)
Male gender, n (%)	474 (45)	89 (44)	54 (44)	35 (44)
Syncope events				
Total events, median (IQR)	5 (4–10)	6 (4–10)	5 (4–10)	6 (4–10)
Events in the last 2 years, median (IQR)	4 (3–5)	4 (3–5)	4 (3–5)	4 (3–5)
Age at first syncope (years), mean (SD)	53 (21)	53 (21)	55 (21)	50 (21)
Without prodrome, n (%)	635 (61)	132 (66)	80 (66)	52 (66)
Any ECG or structural cardiac abnormality, n (%)	132 (13)	19 (9)	10 (8)	9 (11)
Tilt test, performed, n (%)				
Any positive response	438 (47)	81 (49)	45 (46)	36 (53)
Asystolic response $\geq 3$ s	100 (11)*	30 (18)*	16 (16)	14 (21)
ILR findings				
Mean duration of follow-up (months), mean (SD)	13 (10)	–	14 (9)	–
Asystole classification, n (%)				
Sinus arrest	–	105 (52)	58 (48)	47 (59)
Sinus brady + AV block	–	23 (11)	12 (10)	11 (14)
AV block	–	41 (20)	26 (21)	15 (19)
Undefined	–	32 (16)	26 (21)	6 (8)
Asystole duration (s), mean (SD), s	–	12 (10)	11 (8)	12 (11)

AV, atrioventricular; ECG, electrocardiogram; ILR, implantable loop recorder; IQR, interquartile range; PM, pacemaker; SD, standard deviation.  
\*P = 0.001.

### ECG diagnoses



**Figure 2** Overall ECG diagnoses during ILR observations. An asystolic pause compatible with a reflex mechanism accounted for 52% of diagnoses.

risk factors on syncope recurrence. Analyses were performed using the MedCalc version 15.8 (Med Calc Software, Mariakerke, Belgium).

## Results

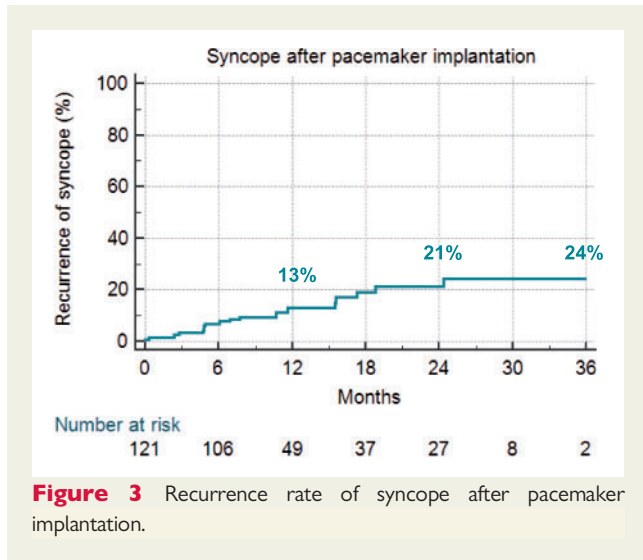
The baseline characteristics of the patients and their ILR findings are presented in *Table 1*.

Of a total of 1046 patients who had ILR implantation, 383 (36.6%) patients had an ECG documentation of a diagnostic event during a mean follow-up of  $13 \pm 10$  months with an actuarial estimate of 52% [95% confidence interval (CI) 46–58] at 36 months. Of these, 201

(52%) patients, corresponding to 19.2% of total ILRs, had a documentation of an asystolic event of  $12.8 \pm 11.0$  s duration (symptomatic in 184 patients and asymptomatic in 17 patients) compatible with a reflex mechanism and met the criteria for pacemaker therapy (*Figures 1 and 2*). Follow-up after pacing was available in 121 (60%) of these patients with asystolic events. In the other 80 patients, follow-up data were unavailable ( $n = 41$ ) or they did not receive an active pacemaker because they were randomized to pacemaker off arm ( $n = 39$ ).

### Outcome after cardiac pacing

Syncope recurred after pacing in 18 of 121 (14.9%) patients with an actuarial rate of 13% (95% CI  $\pm 6$ ) at 1 year, 21% (95% CI  $\pm 10$ ) at



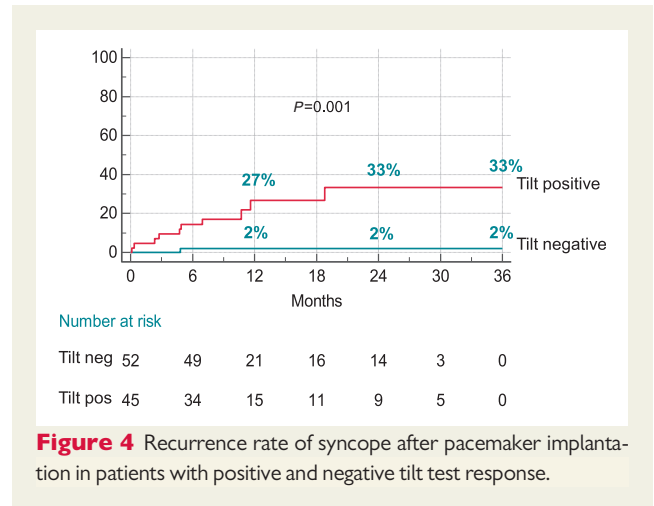
**Figure 3** Recurrence rate of syncope after pacemaker implantation.

2 years, and 24% (95%CI ±11) at 3 years (Figure 3). On multivariable Cox regression analysis, positive tilt test response was the only significant predictor of syncopal recurrence with a hazard ratio of 4.3 (95% CI 1.4–13); on the contrary, type of asystolic event (sinus arrest or AV block), prodrome, cardiac abnormalities, number and duration of history of syncope, age, and gender were not predictors of recurrence of syncope. No heterogeneity between studies was present. At 3 years, syncope recurred in 1 (2%) tilt-negative patient (95%CI ±4%) and in 10 (33%) tilt-positive patients (95%CI ±20%) (Figure 4): 7 of these patients had had a mixed/vasodepressor response and 3 patients a cardioinhibitory response during the index tilt test. The clinical characteristics of tilt-positive and tilt-negative patients were similar (Table 2). When tilt testing was removed from the model, the total number of syncope episodes during life was predictive of syncope recurrence after cardiac pacing [hazard ratio 1.04 (95% CI 1.01–1.07)].

## Discussion

A long asystolic pause of likely reflex origin suitable for pacemaker therapy was found in 19.2% of patients who had received an ILR. This rate is slightly higher than the rate of 16% found by Farwell *et al.*<sup>9</sup> and 15% found by Edvardsson *et al.*<sup>10</sup> in patients with unexplained syncope after initial workup (cardiac syncope unlikely). After pacemaker implantation, 76% (95% CI 65–87%) of these patients remained free of syncope recurrence for up to 3 years. This meta-analysis provides a more robust point estimate, which was not possible with any individual previous study. Further research is very unlikely to change our confidence in the estimate of effect.

Despite NMS is a common disease, this relatively small meta-analysis included most of the studies available in literature concerning paced patients for ILR-documented asystolic NMS. Sud *et al.*,<sup>8</sup> among a heterogeneous population of 122 patients who had received an ILR, found further 14 patients who had an asystolic event compatible with a reflex mechanism (sinus arrest or sinus arrest plus AV block) and received a pacemaker; of these, 6 (42%) patients had syncope



**Figure 4** Recurrence rate of syncope after pacemaker implantation in patients with positive and negative tilt test response.

**Table 2** Comparison between paced patients who had a positive or a negative response during tilt test

Characteristics	Tilt positive (n = 45)	Tilt negative (n = 52)	P-value
Age (years), mean (SD)	64 (10)	65 (13)	0.8
Male gender, n (%)	19 (42)	27 (52)	0.4
Syncope events			
Total events, median (IQR)	6 (4–10)	4.5 (4–6)	0.5
Events in the last 2 years, median (IQR)	3 (3–5)	4 (3–5)	0.8
Age at first syncope (years), mean (SD)	50 (22)	56 (20)	0.2
Without prodrome, n (%)	26 (58)	35 (67)	0.4
Any ECG or structural cardiac abnormality, n (%)	4 (9)	2 (4)	0.4
ILR findings: asystole classification, n (%)			
Sinus arrest	17 (38)	30 (58)	0.7
Sinus brady + AV block	5 (11)	5 (10)	1.0
AV block	10 (22)	9 (17)	0.6
Undefined	13 (29)	8 (15)	0.14

AV, atrioventricular; ECG, electrocardiogram; ILR, implantable loop recorder; IQR, interquartile range; PM, pacemaker; SD, standard deviation.

recurrence after a median of 4.7 years, but syncope burden was very low and decreased from 2.17 per year before to 0.45 per year after pacing. In the Syncope Unit Project 2 (SUP 2) study,<sup>11</sup> we also observed a similar decrease of the syncope burden from 1.9 in the year before to 0.13 in the year after pacemaker implantation.

The benefit of a pacemaker was greater in patients with negative tilt test. The observed 2% recurrence rate at 36 months with pacing and its tight upper confidence interval of 6% show a benefit similar to that observed in patients paced for intrinsic AV block.<sup>12,13</sup> Thus, pacemaker therapy can be offered to these patients with the same confidence as it can in patients with intrinsic cardiac AV block. Further research is very unlikely to change our confidence in the estimate of this effect.

On the contrary, the benefit was less in patients with a positive tilt test. One-third of these patients will have a recurrence of syncope during the following 3 years although some benefit may still accrue in terms of reduced syncope burden. Due to the large confidence interval with an estimate of recurrence at 3 years ranging from 13% to 53%, no definite conclusion can be made regarding the effect of cardiac pacing in this subgroup of patients. Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the present estimate. No other factor, except positive tilt testing, was able to predict the recurrence of syncope. Patients with positive and negative tests had similar baseline characteristics and similar ECG patterns when an episode was documented by ILR, which make them indistinguishable from each other. This finding supports the hypothesis that tilt testing is a useful tool for distinguishing patients with an isolated cardioinhibitory reflex from those with an associated hypotensive susceptibility that may play an additive role in causing syncope. Patients should be informed that they might have some recurrence of syncope, despite cardiac pacing. Since, in these patients, the neurally mediated reflex is both vasodilation and bradycardia, antihypotensive measures should be added to cardiac pacing, such as, e.g. discontinuation/reduction of antihypertensive therapy<sup>14</sup> or addition of midodrine<sup>1</sup> or fludrocortisone.<sup>15</sup> However, implementation of methods for a better discrimination of the relative role of cardioinhibition and vasodepression in causing syncope are warranted and will be the objective of future studies.

## Limitations

The diagnosis of NMS was presumptive based on clinical features and exclusion of competing diagnoses, i.e. intrinsic cardiac pauses, according to the current ESC guidelines.<sup>1</sup> We cannot exclude that an undiagnosed intrinsic sinoatrial or AV conduction abnormality might have played a role in causing an asystolic pause in a few tilt-negative patients. We previously showed that this happened in 13% of cases.<sup>16</sup> Such a circumstance seems unlikely in most patients included in this meta-analysis. Indeed, as per protocol, we identified and excluded from analysis the patients with ILR features suggesting an intrinsic conduction abnormality. Moreover, the clinical features of tilt-negative patients were indistinguishable from those of tilt-positive patients who are more likely to be affected by neurally mediated syncope.

## Conclusion

One out of five patients aged  $\geq 40$  years affected by severe, recurrent, likely NMS had the documentation of an asystolic pause by means of ILR. After pacemaker implantation, most of these patients remained free of syncope recurrence for up to 3 years. The benefit of

pacemaker was greater in patients with negative tilt test who had a low recurrence rate as that observed in patients with intrinsic AV block. On the contrary, owing to the large confidence interval, the estimate of benefit was uncertain in patients with positive tilt test.

**Conflict of interest:** R.S. is a consultant to Medtronic Inc. and a member of the speakers' bureau of Abbott Inc. (St. Jude Medical).

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