IJC Heart & Vasculature 24 (2019) 100386

Contents lists available at ScienceDirect

IJC Heart & Vasculature

journal homepage: http://www.journals.elsevier.com/ijc-heart-and-vasculature

Role of baseline 12 lead ECG in predicting syncope caused by arrhythmia in patients investigated using an implantable loop recorder

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ARTICLE INFO

Article history:
Received 12 April 2019
Received in revised form 30 May 2019
Accepted 13 June 2019
Available online 27 June 2019

Keywords:
Syncope
Implantable loop recorder
Arrhythmia
Bifascicular block

ABSTRACT

Aim: To evaluate the role of baseline 12 lead ECG in predicting the syncope mechanism during continuous monitoring using an implantable loop recorder (ILR).
Methods: Consecutive patients with syncope implanted with an ILR were enrolled. Baseline 12 lead ECG were related to ECG diagnosis derived from ILR tracings recorded at the time of syncope recurrence.
Results: In total 300 patients with a mean age of 66 ± 16 years were included, 49% (146/300) received an ILR-guided diagnosis during follow-up. Patients with abnormal baseline ECG more frequently received an ILR-guided diagnosis compared to those with normal baseline ECG 59% vs. 44%, $p = 0.018$. For a diagnosis of arrhythmic syncope, the corresponding frequencies were 45% vs. 26%, $p = 0.001$.
Patients with bifascicular block significantly more common received an ILR-guided diagnosis 76% (25/33) compared to those with normal baseline ECG 44% (90/205), $p \ll 0.001$. In this subgroup, 96% (24/25) were diagnosed with arrhythmic syncope, 23 of which were due to bradyarrhythmia. Bifascicular block occurred almost exclusively among those ≥60 years (31/33). After logistic regression the adjusted OR for arrhythmic syncope was significant for bifascicular block 5.5 (95%CI 2.3–13.2), $p \ll 0.001$. PPV for bifascicular block in predicting arrhythmic syncope was 73% and NPV 73%.
Conclusion: A baseline 12 lead ECG with bifascicular block was a strong predictor for syncope during follow-up, most often due to bradyarrhythmia caused by intermittent complete heart block. No other ECG findings were associated with the ILR outcome. We find it reasonable to consider permanent pacing instead of an ILR for patients with bifascicular block and unexplained syncope.

1. Background

The prevalence and incidence of syncope is high with a lifetime risk of 42% in the general population [1]. The prognosis of syncope is related both to underlying comorbidities and etiology, with cardiac syncope having a significantly higher mortality than syncope of non-cardiac causes [1,2]. Cardiac syncope has, with few exceptions, an arrhythmic mechanism.

Syncope is a diagnostic challenge due to its infrequent and unpredictable nature. An initial diagnostic workup consisting of careful history, physical examination including orthostatic blood pressure measurements and electrocardiogram (ECG) is able to explain the cause of syncope in 23–50% of patients [3,4]. When the cause of syncope remains uncertain after the initial evaluation the next step is risk stratification (for major cardiovascular events or sudden cardiac death). The gold standard is an ECG recording simultaneously to a syncopal event i.e. symptom versus ECG correlation [5]. For this purpose the implantable loop recorder (ILR) represents a useful diagnostic modality [6].

Studies have confirmed the high diagnostic yield of prolonged monitoring with ILR compared to conventional testing (Holter monitoring, tilt test and electrophysiological study) [7,8]. In the European Society of Cardiology (ESC) Syncope guidelines from 2018 an ILR is recommended in the early phase of the evaluation of syncope in non-high-

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https://doi.org/10.1016/j.ijcha.2019.100386

risk patients and after comprehensive workup in high-risk patients [6]. However, there is a paucity of data on preimplant factors affecting the ILR outcome. Our aim was to investigate the role of the baseline 12 lead ECG in predicting syncope and its mechanism during continuous monitoring with an ILR.

2. Patients and methods

This was an observational cohort study including consecutive patients implanted with an ILR for the indication of syncope/presyncope at two Swedish hospitals between 2007 and 2016 within the same administrative region that serve a population of 300,000 inhabitants. Patients were recruited retrospectively during the period of 2007–2014 ($n = 203$) and prospectively during the 2015–2016 ($n = 97$). Patient consent was obtained through an opt-out procedure. One patient declined participation. The ILRs were manufactured by Medtronic (Minneapolis, Minnesota, USA) $n = 298$ (Reveal XT/DX/Linq) or Biotronik (Berlin, Germany) $n = 2$ (BioMonitor). The manufacturers did not sponsor or influence the study.

Medical records and device interrogations were reviewed for baseline characteristics, 12 lead ECG, ILR guided diagnoses and resulting intervention. The ILR was programmed by a specialist nurse or biomedical technician to automatically record the following events: pauses due to sinus arrest or atrioventricular block ≫3 s, bradycardia ≪30 bpm and ≫4 beats and tachycardia ≫176 bpm and ≫16 beats. If algorithm for atrial fibrillation was available, it was activated.

Three cardiologists (ES, JE, NE) adjudicated and classified the baseline 12 lead ECGs. The diagnoses were grouped according to ESC 2018 recommendations of ECG findings suggestive of arrhythmic syncope [6]. In bifascicular block left bundle branch block (LBBB), right bundle branch block (RBBB) plus left anterior hemiblock (LAH) or left posterior hemiblock (LPH) were included. Atrioventricular (AV) block I was defined as PR interval ≥200 ms. An ECG recording during syncope recurrence was considered diagnostic and providing an ILR-guided diagnosis and was compared with the baseline ECG. Presyncope was considered non-diagnostic. In addition, asymptomatic arrhythmias were considered potentially diagnostic if periods of Mobitz II or AV block III, ventricular pauses ≫3 s or rapid prolonged episodes with paroxysmal supraventricular or ventricular tachycardia were detected during ECG monitoring [6]. ECG diagnoses for those with arrhythmic syncope were also classified according to the ISSUE classification [9]. All patients with ECG findings suggestive of neurally mediated syncope e.g. progressive sinus bradycardia followed by sinus arrest or progressive sinus tachycardia followed by progressive bradycardia and sinus arrest were classified in ISSUE class 3.

Follow-up time was from implantation to ILR-guided diagnosis, explantation or until data collection for the present study after at least 12 months follow-up. The study was approved by the Regional Ethical Review Board of Lund (Dnr 2014/653) and was conducted in accordance with the principles in the Declaration of Helsinki.

2.1. Statistical analysis

Data was subjected to descriptive statistical analysis. Continuous variables are presented as means and standard deviations (SD) or medians and range and categorical variables as frequencies and percentages. Univariate analysis of the continuous variables was performed using the Student's *t*-test or in the case of not normally distributed data the non-parametric Mann-Whitney *U* test was used. To illustrate time to diagnosis a Kaplan-Meier curve was used and the non-parametric Logrank test was used for statistical comparison. For categorical variables Fisher's exact test or chi-square test were used. Logistic regression was used to calculate unadjusted and adjusted odds ratios for risk factors for arrhythmic syncope. Risk factors included in the regression analysis were bifascicular block, AV block I and age ≥60 years. A multivariate analysis was performed in the entire population to calculate adjusted odds ratios for ECG findings predicting syncope due to bradyarrhythmia, including all abnormal ECG findings listed in Table 1. Enter method was used and variables with probability value ≪0.1 was included in the final model (bifascicular block and QRS duration ≫120 ms). Collinearity diagnostics was performed with VIF (variance inflation factor). Two-tailed tests were applied. A probability value of ≪0.05 was regarded as statistically significant. Data processing and analyses were carried out using IBM SPSS version 24.

3. Results

3.1. Patient population

A total of 301 patients received an ILR but one declined participation. Mean age was 66 ± 16 years and 49% ($n = 147$) were women. Two hundred fifteen (71%) patients were over 60 years. For 288 patients the indication was syncope, and for 12 patients it was presyncope. The follow-up time lasted from inclusion to ILR guided diagnosis in 49% ($n = 146$), explantation in 37% ($n = 111$) and until data collection 14% ($n = 43$) for the present study.

3.2. Baseline 12 lead ECG

All 300 patients had a baseline 12 lead ECG recorded which was adjudicated by three cardiologists for findings associated with arrhythmic syncope. For five ECGs a second assessment was required for consensus (long QT ($n = 3$), early repolarization ($n = 1$) and normal ECG ($n = 1$)). The baseline ECG findings for those with confirmed arrhythmic or non-arrhythmic syncope compared to those without an ILR guided diagnosis (no syncope recurrence) during follow-up are reported in Table 1. Bifascicular block, wide QRS and AV block I were the most frequent abnormal ECG findings. Among those with bifascicular block 24 had LBBB, eight had RBBB + LAH and one had RBBB + LPH.

3.3. Arrhythmia diagnoses during ILR monitoring

One hundred forty-six patients (49%) had a syncope recurrence during continuous ECG recording. These ECGs were classified according to the ISSUE classification, see Table 2. In 27 of 29 patients with sinus arrest the median duration was 9 (4–40) seconds. Among 38 patients with bradycardia due to AV block all had intermittent AV block III except for two who had AV block II type II. In the eight patients with supraventricular arrhythmia, five were diagnosed with atrioventricular nodal reentrant tachycardia, one with focal atrial tachycardia and for two the arrhythmia mechanism was unknown. Among patients with ventricular tachycardia (VT) one had polymorphic VT and one high burden of

Table 1
Baseline 12 lead ECG findings.

	Arrhythmic $n = 97$	Non-arrhythmic $n = 49$	No diagnosis $n = 154$
Bifascicular block	24	1	8
QRS ≫120 ms	7	1	5
Sinus bradycardia ≪50 bpm	4	1	3
Sinus tachycardia	0	0	0
Ventricular tachycardia	0	0	1
Preexcitation	0	0	0
Long QT	0	2	1
Q-waves	3	1	6
Early repolarization	0	4	1
AV block I	21	5	22
None of above ECG findings	54	36	115

ECG = electrocardiography. AV block = atrioventricular block. Reported values are *n*. Twenty-six patients had more than one ECG abnormality: 12 bifascicular block + AV block I, 4 QRS ≫ 120 ms + AV block I, 2 bifascicular block + AV block I + long QT, 2 AV block I + Q-waves, 2 sinus bradycardia + early repolarisation, 1 bifascicular block + AV block I + sinus bradycardia, 1 bifascicular block + sinus bradycardia, 1 AV block I + sinus bradycardia and 1 AV block I + long QT.

Table 2
Diagnoses separately per ISSUE class.

	Diagnoses ($n = 146$)
Type 1, Asystole RR pause ≥3 s	67 (46)
Type 1A, Sinus arrest	29 (20)
Type 1B, Sinus bradycardia plus AV block	1 (0.7)
Type 1C, AV block	37 (25)
Type 2, Bradycardia. Decrease of HR ≫30% or ≪40 bpm for 10 s	7 (4.8)
Type 3, No or slight rhythm variations	49 (34)
Type 4, Tachycardia. Increase of HR ≫30% and HR ≫120 bpm	23 (16)
Type 4A, Sinus tachycardia	2 (1.4)
Type 4B, Atrial fibrillation	8 (5.5)
Type 4C, Supraventricular tachycardia (except sinus)	8 (5.5)
Type 4D, Ventricular tachycardia	5 (3.4)

AV block = atrioventricular block. HR = heart rate. Reported values are *n* (%).

premature ventricular complexes while the other three had monomorphic VT. Asymptomatic arrhythmias were recorded in another 20 patients (13 of these patients had normal baseline ECG) with the following ECG findings: atrial fibrillation ($n = 5$), atrial fibrillation with asystole ≪5 s ($n = 4$), supraventricular tachycardia ($n = 5$), non-sustained ventricular tachycardia ($n = 2$), AV block II ($n = 2$) and sinus arrest ($n = 2$). Thus, 134 patients had neither syncope nor ILR-recorded arrhythmias during follow-up.

3.4. Role of 12 lead ECG in predicting the mechanism during recurrent syncope

Patients with abnormal baseline ECG more frequently received an ILR guided diagnosis as compared to those with normal baseline ECG, 59% vs 44%, $p = 0.018$. For a diagnosis of arrhythmic syncope, the corresponding frequencies were 45% vs 26%, $p = 0.001$.

In total 33 patients had bifascicular block at baseline ECG and this group had the highest incidence of ILR-guided diagnosis 76% (25/33) compared to those with normal baseline ECG 44% (90/205), $p \ll 0.001$. Of those with an ILR-guided diagnosis, 96% (24/25) were diagnosed with arrhythmic syncope due to bradyarrhythmia, $n = 23$ (22 asystole, 1 bradycardia) and tachyarrhythmia, $n = 1$ (atrioventricular nodal reentrant tachycardia). One patient had no arrhythmia at the time of syncope recurrence and was accordingly diagnosed with syncope of non-arrhythmic origin. Among the 23 patients with bradyarrhythmia, 19 were due to intermittent complete heart block, three had sinus pauses and one sinus bradycardia.

Bifascicular block was found almost exclusively among those above 60 years (31 of 33 patients). After logistic regression the adjusted odds ratio for arrhythmic syncope for bifascicular block was 5.5 (2.3–13.2, $p \ll 0.001$), but age was no longer an independent risk factor. The positive predictive value for bifascicular block in predicting arrhythmic syncope was 73% (24/33) while the negative predictive value was also 73% (195/267). Multivariate analysis in the entire population resulted in an adjusted odds ratio for bifascicular block in predicting syncope due to bradyarrhythmia of 11.4 (95% CI 5.0–26.2), $p \ll 0.001$. No other baseline ECG findings were associated with the outcome of the ILR registration.

In the total population 32% (97/300) were diagnosed with arrhythmic syncope and in 76% (74/97) of these patients, the cause was bradyarrhythmia. For those with arrhythmic syncope due to tachyarrhythmia, 24% (23/97), only five had abnormal baseline ECG.

3.5. Time to ILR guided diagnosis in relation to baseline 12 lead ECG

For all included patients the mean follow-up time was 21 ± 15.4 (range 0.25–60) months, separately for those who have not yet received an ILR-guided diagnosis (154/300) 30 ± 12.9 months. One hundred forty-six patients received an ILR-guided diagnosis after a mean of 11 ± 10.8 (median 7, range 0.25–42) months. For time to ILR-guided diagnosis separately for those with bifascicular block, AV block I and normal baseline ECG see Fig. 1.

4. Discussion

A bifascicular block in the baseline 12 lead ECG was a strong predictor of receiving an ILR-guided diagnosis, most often due to bradyarrhythmia caused by intermittent complete heart block, and almost exclusively occurred in those over 60 years of age. No other baseline ECG findings were associated with a subsequent ILR-guided diagnosis.

The patients who received an ILR had already undergone an initial investigation and therefore constituted a study population of unexplained syncope. We do not know how many patients in the initially unselected population with syncope who were hospitalized or had an immediate intervention due to ECG findings. The absence of ECG findings predictive of arrhythmic syncope with the exception of bifascicular block in our patients with unexplained syncope is keeping in line with current guidelines for the management of syncope [6] and cardiac pacing [10]. Notably, syncope due to tachyarrhythmia is rarely linked to baseline ECG findings compared to bradyarrhythmia which is more often is associated with existing conduction disturbances.

4.1. The predictive role of bifascicular block in the baseline ECG

Few studies have investigated the relationship between baseline 12 lead ECG and syncope mechanism. One of our main findings was that a bifascicular block in the baseline 12 lead ECG was associated with the likelihood of receiving an ILR guided diagnosis during follow-up. Bifascicular block was almost exclusively found in patients over 60 years of age and 74% (23/31) of these patients with bifascicular block were diagnosed with arrhythmic syncope after a median of three (range 0.25–30) months. In all but one the mechanism of syncope was bradyarrhythmia and for most of these patients the underlying mechanism of bradyarrhythmia was intermittent complete heart block. Only two patients were younger than 60 years, and one of them was diagnosed with an arrhythmic syncope (bradyarrhythmia) during follow-up. However, after adjustment for bifascicular block age was not an independent risk factor for arrhythmic syncope. The positive predictive value for bifascicular block in predicting syncope due to arrhythmia was 73% and a multivariate analysis in the entire population showed a significant odds ratio of 11.4 for bifascicular block in predicting syncope due to bradyarrhythmia. Patients with baseline ECG findings with LBBB ($n = 24$), RBBB + LAH ($n = 8$) and RBBB + LPH ($n = 1$) behaved similarly in their risk of having an arrhythmic syncope. Among these patients there were 15 patients with additional AV block I, which further increased the risk for arrhythmic syncope.

Current guidelines support the use of an electrophysiological study in patients with bifascicular block and syncope [10]. However, patients with negative electrophysiological study are not free of risk for high-degree AV block as shown in the ISSUE-1 study [11] in which 42% (22/52) of patients with bundle branch block and a negative electrophysiological study relapsed with syncope within 3–15 months of follow-up, most often due to complete heart block. A study by Kadmon et al. [12] found a positive predictive value of 56.3% (9/16) for conduction abnormalities (including long PR interval and bundle branch block) in predicting the diagnosis of bradyarrhythmia within 11.9 ± 9.5 months of follow-up. The proportion of patients with a diagnosis of bradyarrhythmia was somewhat higher in our study compared to the other two studies which may be explained by the fact that we specifically looked at those with bifascicular block. If a patient has had abrupt episodes of syncope and shows bifascicular block with or without AV block I the annual risk of higher degree of AV block and significant bradyarrhythmia is considerable, and it can therefore be reasonable to consider pacemaker without preceding electrophysiological study. This view is supported in a recent study by Sheldon et al. [13], where a strategy of empiric permanent pacing in patients with

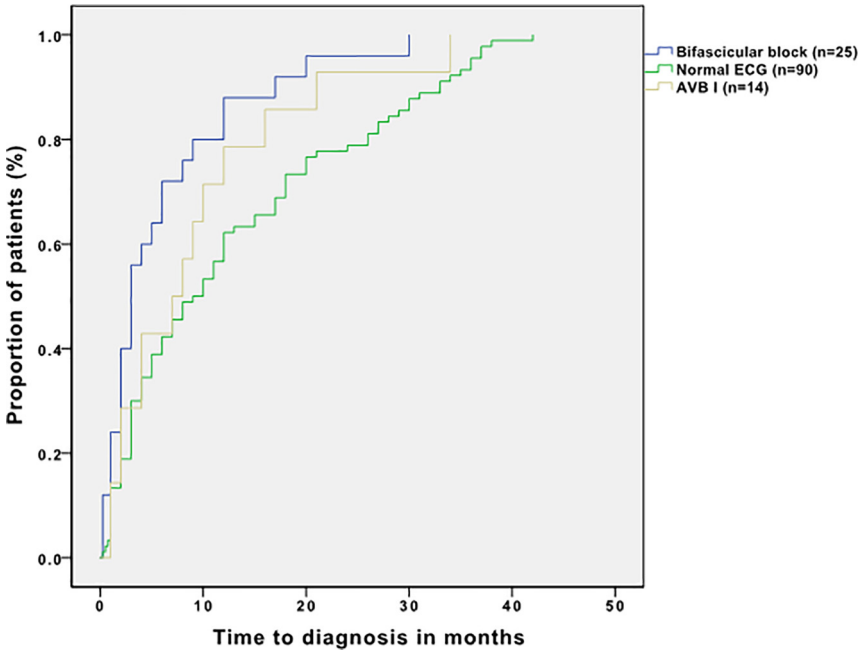

Fig. 1. Kaplan-Meier curve illustrating time to diagnosis separately for those with bifascicular block (median 3 months, range 0.25–30) compared to those with atrioventricular block I (median 7 months, range 1–34) or normal baseline ECG (median 9 months, range 0.25–42). The difference in time to diagnosis is statistically significant, Log Rank (Mantel-Cox) $p = 0.004$.

syncope and bifascicular block effectively reduced major adverse events, but not the proportion of patients with syncope. Their conclusion was that permanent pacing is a preferred strategy in elderly patients with few but recent syncope spells and bifascicular block.

The current ESC 2013 guidelines on Cardiac Pacing and Cardiac Resynchronization Therapy stresses the importance of using available diagnostic tests e.g. external and internal loop recorders to achieve a diagnosis before pacemaker implant [10]. A previous study has reported that a significant proportion (38%) of patients with bundle branch block and unexplained syncope have syncope spells for reasons other than complete heart block [14] and that active cardiac pacing compared to inactive pacing mainly improve symptoms with only a very small proportion (14%) of patients benefit from pacing because of actual bradyarrhythmia [15]. However, the guidelines leave an opening for the physician, to in selected patients, do an individual cost-benefit evaluation, particularly for older patients with recurrent unpredictable syncope episodes without prodromes [10].

In our study we observed a strong association between bifascicular block, including left bundle branch block or right bundle branch block with left posterior or left anterior fascicular block, and the likelihood for an arrhythmic syncope. No such association was found for patients with right bundle branch block or other intraventricular conduction abnormalities (QRS duration ≪120 ms). We find it reasonable to, in consultation with the patient, consider a permanent pacemaker in patients with unexplained syncope and a bifascicular block, especially if there is also an AV block I. This would save healthcare resources and save many patients from traumatic events.

4.2. How helpful was the baseline ECG in finding arrhythmias not associated with a syncopal event but potentially capable of causing syncope?

Of the 300 patients, 154 did not experience a syncope during follow-up, and 39 of these patients had abnormal ECGs at baseline. In some of these patients the ILR disclosed asymptomatic arrhythmias, some of which might hypothetically cause episodes of syncope if the follow-up time was long enough. Atrial fibrillation and especially pauses during spontaneous conversion from AF to sinus rhythm is a potential cause of syncope which may have been identified with longer follow-up.

Finally, 102 patients had a normal baseline ECG and did not show any arrhythmias during follow-up. Whether they were low-risk patients or would have shown arrhythmias and/or a syncopial event during continued follow-up we cannot know.

5. Limitations

This was an observational study in two Swedish hospitals, so our results may not necessarily be representative of those of other hospitals and regions.

Due to the retrospective design no predefined diagnostic criteria for syncope or presyncope were applied, but assessment relied on the treating physician's discretion. In addition, all patients had a clinical indication for an ILR. Furthermore, no causal relationships can be concluded, and the retrospective study design poses a risk for unmeasured confounders and biases. On the other hand, it allows us to report our real-world experience of the use and diagnostic yield of an ILR in a syncope population.

6. Conclusions

A baseline 12 lead ECG with bifascicular block was a strong predictor for syncope during follow-up, most often due to bradyarrhythmia caused by intermittent complete heart block. No other ECG findings were associated with the ILR outcome.

Bifascicular block at baseline was found almost exclusively among those above 60 years of age. We find it reasonable to consider permanent pacing instead of an implantable loop recorder for patients with bifascicular block and unexplained syncope.

Declaration of Competing Interest

ES and NE nothing to declare. CR consultant fees from Medtronic. JE consultant fees from Boehringer Ingelheim, Pfizer, Bayer, AstraZeneca, Sanofi and Medtronic.

Acknowledgement

The authors are grateful to the staff at the pacemaker units at Halland Hospital: Karin Larsson, Martina Pedersen Erdinc, Anette Andersson, Peter Verdin, Jennie Persson and Kristina Davidsson, who run the pacemaker units at the two hospitals and to Emmanouil Charitakis for his help with the statistical analysis.

Funding

The study was supported by Region Halland. Johan Engdahl was supported by the Stockholm County Council (clinical research appointment).

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