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Short communication

Low incidence of arrhythmic syncope and pacemaker implantation in older patients with bifascicular block and implantable cardiac monitor

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ABSTRACT

Background: In patients with unexplained syncope, bifascicular block (BFB) is considered associated with syncope due to either heart block or sinus arrest. Immediate or delayed pacemaker (PM) implantation after ECG documentation of syncopal recurrence by means of implantable cardiac monitors (ICM) is still debated. We aimed to assess the incidence of recurrent syncope and guideline-based PM implantation in patients with syncope and BFB implanted with ICM.

Methods: Consecutive patients with syncope and BFB followed at two tertiary care syncope units and implanted with ICM from 2012 to 2020 were retrospectively reviewed. Only patients with ≥2 clinical visits and ≥ 18 years of age were included. Incidence of a Class I indication for PM implantation was the primary outcome.

Results: Of 635 syncope patients implanted with an ICM, 55 (8.7%) had a BFB and were included. Median age at implantation was 75 [interquartile range, IQR:64–81] years, and 28(49.1%) were women. At 26 [IQR:12–41] months follow-up, 20 (36.3%,16.3%/year) patients experienced syncope: in 6(10.9%) patients syncope was classified 'arrhythmic' with a higher prevalence in older individuals ($p = 0.048$). PM implantation ($N = 14$,25.5%) was more frequent in patients ≥75 years ($p = 0.024$). At survival analysis, patients ≥75 years were at highest risk of arrhythmic syncope and guideline directed PM implantation (Hazard Ratio: 4.5, 95% Confidence Intervals 1.5–13.3).

Conclusions: Most older patients with syncope who received an ICM did not have events during follow-up. One-in-three experienced syncope, and an even smaller number had an arrhythmic syncope with indication for PM implantation. Older age was strongly associated with PM implantation.

1. Introduction

Patients with bifascicular block (BFB) have an increased incidence of syncope [1]. Direct pacemaker (PM) implantation might avoid syncope due to complete heart block [2,3]. However, other causes of syncope could co-exist, leading to reflex or hypotensive syncope recurrence [4–7]. Assessment, management, and prevention of syncope in patients with BFB is challenging. Identification of risk factors and application of preventive strategies could be useful to prevent recurrence. Aging is a well-known risk factor for the development of complete heart block [4,8,9]. However, the real impact of aging on syncope recurrence in patients with BFB is still debated. Therefore, we evaluated the association of age with PM indication in patients with BFB referred for implantable cardiac monitoring (ICM).

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2. Methods

2.1. Patient selection

We reviewed the clinical records of consecutive patients with BFB referred for ICM at Careggi University Hospital, Florence, Italy and Department of Advanced Medical and Surgical Sciences, University of Campania Luigi Vanvitelli, Naples, Italy, from January 2012 to December 2020. Only patients with complete clinical data from ≥2 clinical visits, an ICM monitoring with >1-year follow-up and age ≥ 18 years were included. Patients with left ventricular ejection fraction <35%, indication for PM/ICD implantation, incomplete follow-up and with moderate-to-severe cognitive impairment at baseline, were excluded.

BFB was defined as QRS duration ≥120 ms and left bundle branch block (LBBB), or right bundle branch block (RBBB) and a left fascicular anterior block (LFAB) or left posterior hemiblock (LPB), or any two of three single fascicular blocks documented at different times [4,8,9].

2.2. ICM device and monitoring strategies

Patients received Medtronic (RevealTM-XT, RevealTM-LinQ), Merlin-St Jude Medical (DM3500 series), or Biotronik (Biomonitor-II) devices according to participating center usual policy. Remote monitoring was offered whenever applicable after 2015. All patients were evaluated following standardized protocols with six-month visits or visits at shorter intervals whenever clinically necessary.

The events observed during the follow-up of ICM were classified as:

- *Arrhythmic:* due to sinus arrest or sinoatrial block with asystole, bradycardia, alternating bundle branch block, complete AV block AV block, 2:1 AV block AV block, slow ventricular response atrial fibrillation, ventricular tachycardia
- *Non-arrhythmic:* none of the above - episode were classified as presumed reflex or hypotensive [10].

2.3. Study outcomes

The primary study outcome was the incidence of a Class I indication to PM implantation (spontaneous documented symptomatic asystolic pause >3 s or asymptomatic pause >6 s due to sinus arrest or AVB; symptomatic patients with bradycardia-tachycardia form of sinus node dysfunction; patients with atrial arrhythmia and third- or high-degree AVB) [11].

2.4. Statistical analysis

Patients were divided into two groups according to median age at ICM implantation. Continuous variables are reported as median [Interquartile range, IQR] and compared with non-parametric tests as appropriate. Categorical variables, reported as counts and percentages, were compared across groups with the Chi-Square or Fisher's exact test.

Survival analysis for the primary endpoint was performed with the Kaplan-Meier method and curves compared with the log-rank test. A two-sided p-value<0.05 was considered statistically significant. Analysis was performed using IBM SPSS Statistics for Macintosh, version 27.0 (Armonk, NY: IBM Corp. USA).

3. Results

3.1. Baseline clinical characteristics

A total of 55/635 (8.7%) syncope patients who had implanted an ICM had BFB. These patients were included in the study (Supplementary Fig. 1).

The characteristics of the study population are summarized in

Table 1
Baseline clinical characteristics of patients referred for implantable cardiac monitoring (ICM) and events at follow-up.

	Total group ($N = 55$)	Age subgroups		P
		<75 years ($N = 30$)	≥75 years ($N = 25$)	
Demographic evaluation				
Age, median [IQR], years	75 [64–81]	66 [49–72]	81 [79–85]	<0.001
Women, N (%)	27 (49.1)	14 (46.7)	13 (52.0)	0.789
Number of syncope before ICM implantation, median [IQR]	2 [1–4]	3 [1–4]	2 [1–2]	0.744
Duration of symptoms, median [IQR], years	1 [0–8]	2 [0–24]	0 [0–8]	0.524
Comorbidities, N (%)				
Hypertension	31 (56.4)	12 (40.0)	19 (76.0)	0.007
Atrial Fibrillation	16 (29.1)	6 (20.0)	10 (40.0)	0.104
Cancer (non-active)	13 (23.6)	5 (16.7)	8 (32.0)	0.183
Stroke/Transient Ischemic Attack	11 (20.0)	5 (16.7)	6 (24.0)	0.498
Diabetes Mellitus	8 (14.5)	5 (16.7)	3 (12.0)	0.625
Ischemic Heart Disease	7 (12.7)	2 (6.7)	5 (20.0)	0.373
LVEF<50%	7 (12.7)	3 (10.0)	4 (16.0)	0.678
Dementia	4 (7.3)	0 (0.0)	4 (16.0)	0.023
Pharmacological therapy, N (%)				
ACEi/ARBs	32 (58.2)	12 (40.0)	20 (80.0)	<0.001
Calcium Channel Blockers	6 (10.9)	1 (3.3)	5 (20.0)	0.048
Beta-blockers	12 (21.8)	6 (20.0)	6 (24.0)	0.721
Alpha-1 antagonists	8 (14.5)	5 (16.7)	3 (12.0)	0.625
Diuretics	12 (21.8)	5 (16.7)	7 (28.0)	0.311
Nitrates	1 (1.8)	0 (0.0)	1 (4.0)	0.269
Antiarrhythmic Drugs	5 (9.1)	3 (10.0)	2 (8.0)	0.493
Oral Anticoagulants	5 (9.1)	2 (6.7)	3 (12.0)	0.650
Antiplatelet	29 (52.7)	13 (43.3)	16 (64.0)	0.127
Selective serotonin reuptake inhibitors	10 (18.2)	2 (6.7)	8 (32.0)	0.015
Serotonin and norepinephrine reuptake inhibitors	4 (7.3)	1 (3.3)	3 (12.0)	0.320
Benzodiazepines	8 (14.5)	2 (6.7)	6 (24.0)	0.069
Clinical evaluation upon 1st visit				
Systolic blood pressure, mmHg (median [IQR])	131 [121–150]	134 [122–150]	130 [116–139]	0.157
Diastolic blood pressure, mmHg (median [IQR])	75 [69–82]	79 [75–86]	70 [62–81]	0.211
Orthostatic Hypotension, N (%)	13 (23.6)	4 (13.3)	9 (36.0)	0.049
Right Bundle Branch Block + Left Anterior Hemiblock, N (%)	33 (60.0)	18 (60.0)	15 (60.0)	0.999
Left Bundle Branch Block, N (%)	22 (40.0%)	12 (40.0)	10 (40.0)	
Events at follow up				
Overall follow-up, median [IQR]), months	26 [12–41]	30 [12–47]	25 [7–39]	0.091
Death, N (%)	2 (3.6)	0 (0.0)	2 (8.0)	0.115
Syncope, N (%)	20 (36.4)	10 (33.3)	10 (40.0)	0.690
Associated with an arrhythmic episode N (%)	6 (10.9)	1 (3.3)	5 (20.0)	0.048
Not associated with an arrhythmic episode, N (%)	14 (25.5)	9 (30.0)	5 (20.0)	0.397
Presumed Vasovagal or Reflex Syncope*, N (%)	14 (25.5)	8 (26.7)	6 (24.0)	0.916
Associated with an arrhythmic episode N (%)	3 (5.5)	1 (3.3)	2 (8.0)	
	11 (20.0)	7 (23.3)	4 (16.0)	

(continued on next page)

Table 1 (*continued*)

	Total group ($N = 55$)	Age subgroups		P
		<75 years ($N = 30$)	≥75 years ($N = 25$)	
Not associated with an arrhythmic episode, N (%)	14 (25.5)	4 (13.3)	10 (40.0)	0.024
Pacemaker implantation, N (%)	6 (10.9)	2 (6.7)	4 (16.0)	
Due to arrhythmia associated with syncope, N (%)	8 (14.5)	2 (6.7)	6 (24.0)	
Due to arrhythmia associated with pre-syncope or in asymptomatic patients, N (%)				

ACEi: angiotensin converting enzyme inhibitors; ARBs: angiotensin receptor blockers; LVEF: left ventricular ejection fraction; N: number. *: $p < 0.05$ (as statistically significant) vs. <75 years old.

* According to table 4 of Supplementary Material of reference 3.

Table 1. RBBB + LFAB was present in 33/55 (60.0%) while LBBB in 22/55 (40.0%) patients. No LPB was recorded in patients with RBBB. The median age at ICM implantation was 75 [64–81] years, and 27/55 (49.1%) were women. The number of syncope episodes before ICM implantation or symptom duration were similar in the two age groups. A history of stroke was present in 11/55 (20.0%) patients. Use of Angiotensin-Converting Enzyme inhibitors/Angiotensin Receptor Blockers (ACEi/ARBs), Calcium Channel Blockers, and Selective serotonin reuptake inhibitors increased with age.

3.2. Syncope and PM implantation at follow-up

Patients were followed for 26 [12–41] months. Overall, 20 (36.3%) patients experienced a syncope (incidence rate 16.3%/year), which was associated with a bradyarrhythmia in 6/20 (30%) and not associated in 14/20 (70%) cases. Thus, no patient had syncope associated with a tachyarrhythmia during the monitoring period. The incidence of arrhythmic syncope increased with age ≥ 75 years ($p = 0.048$).

An arrhythmic event was observed in 20 (36.3%) patients; of these, 6 were associated with syncope and while 14 were not (Supplementary Table 1). The most frequent arrhythmic events recorded upon ICM interrogation were sinus arrest and bradycardia ($N = 15$ patients, 27.3%), complete AVB ($N = 5$, 9.1%) and alternating bundle branch block ($N = 4$, 7.3%).

A total of 14 (25.5%) patients were referred for pacemaker implantation: 6 (10.9%) after documentation of an arrhythmic episode associated with syncope and 8 (14.5%) after the documentation of an arrhythmic episode associated with presyncope ($N = 5$) or asymptomatic ($N = 3$).

At survival analysis, the risk of PM implantation and arrhythmic syncope was higher in patients >75 years (Fig. 1A and B).

At binary logistic regression analysis (Supplementary Table 2) age and hypertension were associated with PM implantation: the final model combining both factors explained 26.4% (Nagelkerke R2) of the variance in PM implantation. No association of age with non-arrhythmic syncope was found.

4. Discussion

In our study, 36% of patients with BFB experienced recurrent syncope but only 11% were referred for PM implantation; a further 15% of patients were referred for PM implantation for pre-syncopal or asymptomatic arrhythmic episodes. Of note, 25.5% of patients presented with brady-arrhythmic episodes without any correlation with syncope or pre-syncope.

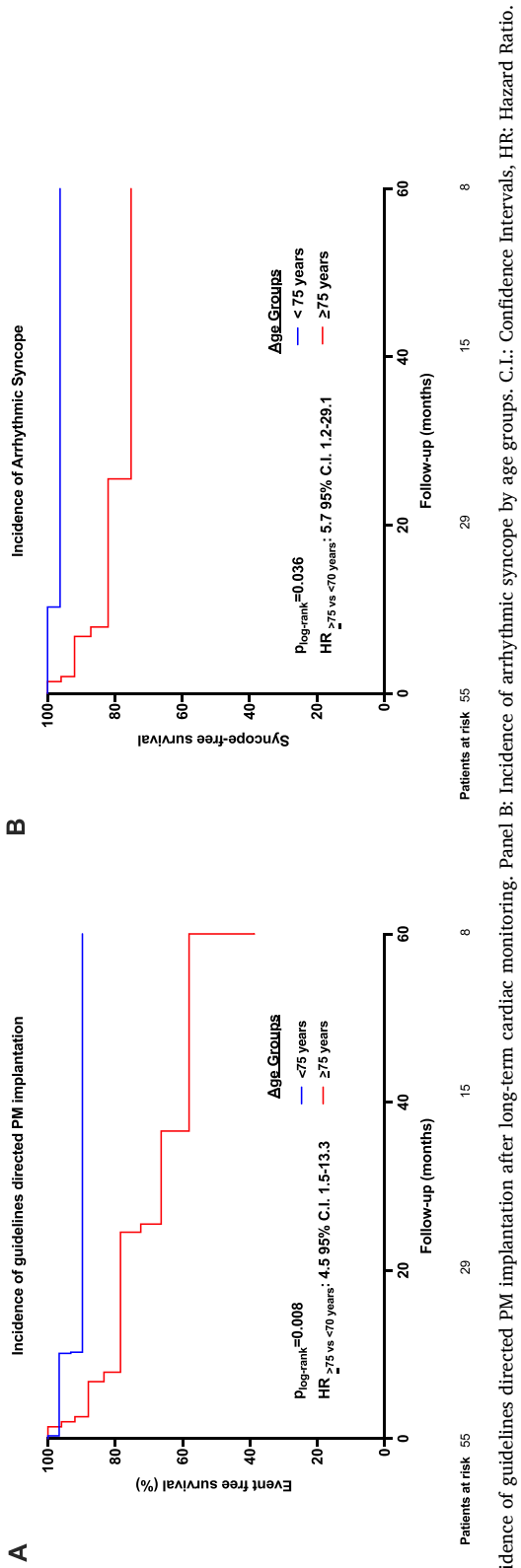

Fig. 1. Panel A: Incidence of guidelines directed PM implantation after long-term cardiac monitoring. Panel B: Incidence of arrhythmic syncope by age groups. C.I.: Confidence Intervals, HR: Hazard Ratio.

Overall, in line with the current literature, age was the strongest risk factor for PM implantation, which was almost 5-times higher in patients ≥75 years. Conversely, age was not associated with non-arrhythmic events, mainly caused by autonomic dysfunction and orthostatic hypotension [12,13]. Recently, the SPRITELY (Syncope: Pacing or Recording in ThE Later Years) study showed that, although the empiric PM reduced the rate of major adverse events in patients with BFB, it did not reduce syncope recurrence as compared to patients receiving an ICM when >50 years old [14]. In their multicenter, randomized trial, the authors hypothesized that failure was due to a significant proportion of events being reflex in nature. The authors also hypothesized that, to reduce failure rate, patients who are unlikely to respond to pacing should be preselected by means of additional diagnostic tests. Overall, these results confirm that in patients with BFB, syncope is heterogeneous in etiology, especially at an advanced age [15]. The diagnosis and treatment of syncope in older individuals with BFB is challenging, and the low diagnostic value of clinical history can influence the clinical management. Notably, in 481 patients stratified by age (≤65 vs. >65 years) the diagnosis of the cause of syncope based on symptoms was 4-times less likely obtained in older patients [16]. Predicting the heart block progression and syncope recurrence in these high-risk patients might be much more difficult. Although the electrophysiological study has been proposed as a mean to address this point, results are conflicting and limited to selected patients [3,17–19].

Two main age-related mechanisms could explain this result: a higher rate of progression from BFB to complete heart block, and the hemodynamic consequences of autonomic dysfunction with loss of protective reflexes counteracting bradyarrhythmias. In older individuals, advanced fibrosis of the conduction system might increase conduction abnormalities, like BFB and LBBB [7,9]. Indeed, the prevalence of LBBB increases up to 17% at 80 years and has been associated with adverse outcome (advanced AVB, syncope, and cardiovascular death) [7,20]. Furthermore, elderly patients with BFB could have higher rate of infra-Hisian vs. supra-Hisian block, predisposing to increased risk of complete heart block and syncope [3]. Notably, age and conduction disease -among other risk factors- have been integrated in models to predict need for PM implantation [21].

No patients were found with LPB and RBBB, a potential worse condition. This finding is, however, in line with the SPRITELY population and with the TRAUMA multicenter registry, where its prevalence ranged from 0.6 to 4.4%. [14,22] Finally, elderly patients could suffer from autonomic system dysfunction and altered blood pressure control: these abnormalities could increase the tendency to reflex syncope in the presence of brady-arrhythmias [5]. Of note, we may not exclude that some of the recurrent episodes may have been iatrogenic since use of beta-blocking agents was not considered an exclusion criterion.

Thus, a pragmatic multiparametric approach led by a multidisciplinary team or syncope specialist aimed at ruling out non-bradyarrhythmic causes of syncope might be warranted for these patients and a long-term monitoring strategy could guide towards the best treatment of syncope [2,19,23].

4.1. Study limitations

This is a retrospective non-randomized cohort study with intrinsic limitations due to the nature of analysis, potential referral bias, potential lack of specialist evaluation aimed at understanding of the patients' symptoms and likelihood of syncope recurrence, limited study cohort, use of beta-blockers, and lack of a control group of patients with BFB implanted with a PM. Moreover, the total number of PM implantation for BFB during the study period was not available and direct comparisons could not be performed. In the last decade the indications for long-term ICM monitoring or pacing may have changed. Ultimately, the decision of whether and how to react to asymptomatic and moderately symptomatic ECG findings from the ICMs was left to the attending physician.

5. Conclusions

The mechanism of syncope in older patients with BFB is heterogeneous, being non-arrhythmic in most of them. Early direct PM implantation, before ECG documentation of the mechanism, should be discouraged because of the high risk of ineffectiveness and, hence, of clinical futility. Our findings support that these patients should be managed through a multiparametric approach, which includes prolonged cardiac monitoring and a careful assessment of non-cardiac causes of syncope.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2022.10.171.

References

[1] M. Santini, et al., Prevention of syncope through permanent cardiac pacing in patients with bifascicular block and syncope of unexplained origin: the PRESS study, Circ. Arrhythm. Electrophysiol. 6 (2013) 101–107.
[2] Z.D. Goldberger, et al., ACC/AHA/HRS versus ESC guidelines for the diagnosis and Management of Syncope: JACC guideline comparison, J. Am. Coll. Cardiol. 74 (2019) 2410–2423.
[3] M. Brignole, et al., 2018 ESC guidelines for the diagnosis and management of syncope, Eur. Heart J. 39 (2018) 1883–1948.
[4] R. Kobza, et al., Twelve-lead electrocardiography in the young: physiologic and pathologic abnormalities, Heart Rhythm. 9 (2012) 2018–2022.
[5] M. Brignole, et al., Low-blood pressure phenotype underpins the tendency to reflex syncope, J. Hypertens. 39 (2021) 1319–1325.
[6] M. Brignole, G. Rivasi, New insights in diagnostics and therapies in syncope: a novel approach to non-cardiac syncope, Heart 107 (2021) 864–873.
[7] A.B. Curtis, R. Karki, A. Hattoum, U.C. Sharma, Arrhythmias in patients ≥80 years of age: pathophysiology, management, and outcomes, J. Am. Coll. Cardiol. 71 (2018) 2041–2057.
[8] R. Shan, et al., Prevalence and risk factors of atrioventricular block among 15 million Chinese health examination participants in 2018: a nation-wide cross-sectional study, BMC Cardiovasc. Disord. 21 (2021) 289.
[9] L.D.J. Ostrander, R.L. Brandt, M.O. Kjelsberg, F.H. Epstein, Electrocardiographic findings among the adult population of a total natural community, Tecumseh, Michigan, Circulation 31 (1965) 888–898.
[10] Task Force for the Diagnosis and Management of Syncope, et al., Guidelines for the diagnosis and management of syncope (version 2009), Eur. Heart J. 30 (2009) 2631–2671.
[11] M. Glikson, et al., 2021 ESC guidelines on cardiac pacing and cardiac resynchronization therapy, Eur. Heart J. 42 (2021) 3427–3520.
[12] P. Torabi, et al., Early and late-onset syncope: insight into mechanisms, Eur. Heart J. ehac017 (2022), https://doi.org/10.1093/eurheartj/ehac017.
[13] C. Sardu, et al., Cardiac syncope recurrence in type 2 diabetes mellitus patients vs. normoglycemics patients: The CARVAS study, Diabetes Res. Clin. Pract. 151 (2019) 152–162.
[14] R. Sheldon, et al., Randomized pragmatic trial of pacemaker versus implantable cardiac monitor in syncope and bifascicular block, JACC Clin. Electrophysiol. 8 (2022) 239–248.
[15] M. Brignole, et al., Mechanism of syncope in patients with bundle branch block and negative electrophysiological test, Circulation 104 (2001) 2045–2050.
[16] A. Del Rosso, P. Alboni, M. Brignole, C. Menozzi, A. Raviele, Relation of clinical presentation of syncope to the age of patients, Am. J. Cardiol. 96 (2005) 1431–1435.
[17] R.S. Sheldon, et al., Electrophysiology studies for predicting atrioventricular block in patients with syncope: a systematic review and meta-analysis, Heart Rhythm. 18 (2021) 1310–1317.
[18] C. Sardu, et al., ELectrophysiological mechanisms underlying the inhibitory CArdiac syncope without asystolic significant pause: therapeutic and prognostic implications. The ELICA randomized trial, Medicine 97 (2018), e11757.
[19] R. Sheldon, et al., Randomized pragmatic trial of pacemaker versus implantable cardiac monitor in syncope and bifascicular block, JACC Clin. Electrophysiol. 8 (2022) 239–248.
[20] P. Eriksson, P.O. Hansson, H. Eriksson, M. Dellborg, Bundle-branch block in a general male population: the study of men born 1913, Circulation 98 (1998) 2494–2500.
[21] X. Xiao, et al., Prediction of pacemaker requirement in patients with unexplained syncope: the DROP score, Heart Lung. Circ. 31 (2022) 999–1005.
[22] P. Palmisano, et al., Management of older patients with unexplained, recurrent, traumatic syncope and bifascicular block: implantable loop recorder versus empiric pacemaker implantation—results of a propensity-matched analysis, Heart Rhythm. (2022), https://doi.org/10.1016/j.hrthm.2022.05.023.
[23] M. Brignole, et al., Early application of an implantable loop recorder allows effective specific therapy in patients with recurrent suspected neurally mediated syncope, Eur. Heart J. 27 (2006) 1085–1092.