Relation of Interatrial Block to Cognitive Impairment in Patients ≥ 70 Years of Age (From the CAMBIAD Case-control Study)

Cristian Herrera, MD[a,b], Vanesa Bruña, MD[a,b], Pedro Abizanda, MD, PhD[c], Pablo Díez-Villanueva, MD, PhD[d], Francesc Formiga, MD, PhD[e], Rosa Torres, MD[f], José Carreras, MD[g], Rocio Ayala, MD, PhD[h], F. Javier Martin-Sánchez, MD, PhD[i], Antoni Bayés-Genis, MD, PhD[j,n], Roberto Elosua, MD, PhD[b,k], Antonio Bayés-de-Luna, MD, PhD[l], and Manuel Martínez-Sellés, MD, PhD[a,b,m,*], on behalf of the CAMBIAD investigators (Appendix)

The association between atrial fibrillation, stroke, and interatrial block (IAB) (P-wave duration ≥120 ms) is well recognized, particularly in the case of advanced IAB. We aimed to assess the association of IAB with mild cognitive impairment. Advanced Characterization of Cognitive Impairment in Elderly with Interatrial Block was a case-control multicenter study, conducted in subjects aged ≥70 years in sinus rhythm without significant structural heart disease. Diagnosis of mild cognitive impairment was performed by an expert geriatrician, internist, or neurologist in the presence of changes in cognitive function (Mini Mental State Examination score 20 to 25) without established dementia. A total of 265 subjects were included. Mean age was 79.6 ± 6.3 years and 174 (65.7%) were women; there were 143 cases with mild cognitive impairment and 122 controls with normal cognitive function. Compared with controls, cases had longer P-wave duration (116.2 ± 13.8 ms vs 112.5 ± 13.3 ms, p = 0.028), higher prevalence of IAB (73 [51.0%] vs 38 [31.1%], p = 0.001), higher prevalence of advanced IAB (28 [19.6%] vs 10 [8.2%], p = 0.002), and higher MVP ECG risk score (2.7 ± 1.4 vs 2.2 ± 1.3, p = 0.004). IAB was independently associated with mild cognitive impairment, both for partial (odds ratio 2.0, 95% CI: 1.1 to 3.9) and advanced IAB (odds ratio 2.8, 95% CI: 1.1 to 6.7). In conclusion, in subjects aged ≥70 years without significant structural heart disease, IAB is independently associated with mild cognitive impairment. This association is stronger in the case of advanced IAB. **(Am J Cardiol 2020;136:94–99)**

The association of atrial fibrillation (AF) with cognitive impairment (CI) and dementia has been previously described.[1,2] The mechanisms that underlie this association are likely multifactorial and not fully understood, but probably result from symptomatic ischemic stroke and silent cerebral infarcts,[3] cerebral hemorrhages, and chronic cerebral hypoperfusion due to hemodynamic alterations that lead to reduced cardiac output and decreased diastolic cerebral arterial flow.[4] In subjects in sinus rhythm, interatrial block (IAB), particularly advanced IAB, is associated with stroke[5,6] and with an increased risk of AF development, an association known as Bayés syndrome.[7] Moreover, as the pathophysiological mechanisms of AF and advanced IAB are similar,[8] it is conceivable that IAB is also associated with CI. Furthermore, other P-wave indexes or characteristics have also been associated with AF, stroke, and CI.[9] Our main objective was to analyze the association between IAB and mild CI in subjects aged 70 years or older. As a secondary objective, we also assessed the association between other P-wave indexes and mild CI.

Methods

The study CAMBIAD (*Caracterización Avanzada en Mayores con Bloqueo InterAuricular del Deterioro cognitivo* - Advanced Characterization of Cognitive Impairment

[a]Servicio de Cardiología, Hospital General Universitario Gregorio Marañón, Madrid, Spain; [b]Centro de Investigacion Biomédica en Red de Enfermedades Cardiovasculares (CIBER-CV), Madrid, Spain; [c]Servicio de Geriatría, Complejo Hospitalario Universitario de Albacete, CIBER de Fragilidad y Envejecimiento Saludable, Instituto de Salud Carlos III, Madrid, Spain; [d]Servicio de Cardiología, Hospital Universitario de la Princesa, Madrid, Spain; [e]Servicio de Medicina Interna, Hospital Universitario de Bellvitge, Idibell, Barcelona, Spain; [f]Servicio de Geriatría, Hospital Universitari de la Santa Creu de Vic, Spain; [g]Servicio de Cardiología, Hospital Universitario de la Santa. Creu i Sant. Pau, Barcelona, Spain; [h]Hospital Universitario de la Cruz Roja, Madrid, Spain; [i]Servicio de Urgencias, Hospital Clínico San Carlos. Instituto de Investigación Sanitaria del Hospital Clínico San Carlos (IdISSC). Universidad Complutense, Madrid, Spain; [j]Institut del Cor, Hospital Universitari Germans Trias i Pujol, Badalona, Spain; [k]Instituto Hospital del Mar de Investigaciones Médicas (IMIM), Barcelona, Facultad de Medicina, Universidad de Vic-Universidad Central de Cataluña, Vic, Spain; [l]Fundación de Investigación Cardiovascular. ICCC-Institute de Investigación, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain; [m]Universidad Europea, Universidad Complutense, Madrid, Spain; and [n]Universidad Autónoma de Barcelona, Barcelona, Spain. Manuscript received July 10, 2020; revised manuscript received and accepted September 8, 2020.

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*Corresponding author: Tel: 34 91 586 82 93; fax: 34 91 586 82 76.
E-mail address: mmselles@secardiologia.es (M. Martínez-Sellés).

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in Elderly with Interatrial Block) is a nationwide, multicenter case-control study conducted in 10 hospitals across Spain. Between June 2019 till March 2020, subjects were enrolled on the basis of the following inclusion criteria: (1) Age ≥ 70 years; (2) Sinus rhythm; (3) Signed informed consent. Exclusion criteria were: (1) Previous diagnosis of AF; (2) Indication of anticoagulation therapy; (3) Implanted cardiac devices; (4) Significant structural heart disease (previous myocardial infarction, coronary or valvular intervention of any kind, history of left ventricular systolic dysfunction, history of severe valve disease); (5) Dementia affecting the activities of daily life in anamnesis or treated with anticholinesterase drugs; (6) Hospital admission.

The study complied with the Declaration of Helsinki, the protocol was approved by the Ethics Committee of the Sant Pau University Hospital and each participant or legal representative signed an informed consent.

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Cases were recruited consecutively if they fulfilled all the following five criteria: (1) Diagnosis of mild CI performed by an expert geriatrician, internist, or neurologist. (2) Changes in cognitive function recognized by an informant or clinician who knows the patient. (3) Mini Mental State Examination (MMSE) score of 20 to 25/30.[10] (4) Preserved functional capacity (self-inflicted and referred by a relative), with a Global Deterioration Scale and Functional Assessment Staging (GDS/FAST) of 3.[11] (5) No evidence of changes in social or occupational functioning.

Controls were defined by the following criteria: (1) Normal cognitive function assessed by an expert physician, and (2) MMSE score ≥ 26/30. Controls were included, if possible, consecutively to cases.

A standard 12-lead surface electrocardiogram (ECG) record was obtained from each patient. The duration of the P-wave and the presence of IAB were measured and evaluated manually in a central laboratory using the GeoGebra 4.2 software after amplifying the original ECG size 20 times. To measure P-wave duration, the interval between earliest and last detection of atrial depolarization in the frontal leads was used, defined as a deviation that deviates from the baseline before the QRS complex. There were two measurements in each ECG and if the P-wave onset and offset were not entirely clear, up to 4 measurements were made. All measurements were performed by an observer blinded to the cognitive status of the subjects, and when in doubt, a second expert observer was consulted.

Subjects were divided into 3 groups: normal P-wave duration (<120 ms), partial IAB (P-wave duration ≥120 ms, positive in inferior leads) and advanced IAB (P-wave duration ≥120 ms with biphasic morphology [±] in inferior leads) (Figure 1).[12]

Morphology−Voltage−P−wave duration (MVP) score was also calculated for all the participants in the study.[13] This score allocates points based on P-wave Morphology in inferior leads (0 to 2), Voltage in lead 1 (0 to 2), and P-wave duration (0 to 2).

Baseline characteristics were registered, including age, education years, body mass index, presence of different cardiovascular risk factors, familial history of dementia,

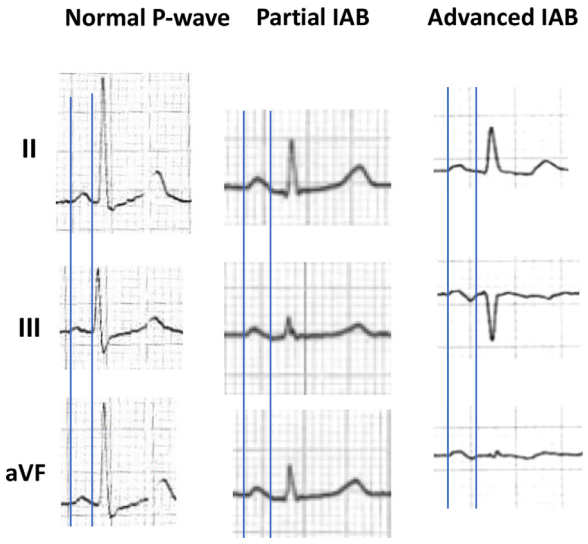

Figure 1. Examples of normal P-wave with duration <120 ms, interatrial block (IAB) with P-wave duration ≥120 ms and a positive (partial IAB) or biphasic (advanced IAB) morphology in inferior leads.

regular exercise practice, and the following indexes: Charlson co-morbidity index,[14,15] CHA_2DS_2-VASc,[16] GDS/FAST, Fatigue-Resistance-Ambulation-Illness-Low weight (FRAIL).[17] Information regarding antiplatelet therapy and statin use was also registered.

Categorical data were expressed as frequencies and percentages. Continuous variables were expressed as mean (standard deviation). We used the Chi-square or Fisher's exact tests for the comparison of categorical variables, and the Student *t* test, ANOVA, or Kruskall-Wallis tests for the comparison of continuous variables in groups. Multivariable analysis by logistic regression modeling was used to determine the independent predictors associated with CI. The modeling process involved forward and backward stepwise methods with a threshold for exit set at P higher than 0.10 and for entry at P lower than 0.05. We also explored the dose-response pattern of relation between P-wave duration with the presence of CI to explore for linear and nonlinear patterns by using a generalized additive model with penalized spline smoothing (pspline function). Statistical analyses were performed using SPSS, version 23.0 (IBM, Armonk, New York) and R, version 3.4.2 (R Foundation for Statistical Computing, Vienna, Austria).

Results

A total of 266 subjects were included from June 2019 till March 2020. One subject had an illegible ECG. The final population of 265 subjects had a mean age of 79.6 ± 6.3 years and 174 (65.7%) were women. We included 143 cases with mild CI and 122 controls with normal cognitive function. Table 1 shows the baseline clinical characteristics and the results of cognitive evaluation in patients with mild CI and controls. Compared with controls, patients with mild CI had a more advanced age, were more frequently women, with less years of education, a higher proportion of never smokers, and a lower proportion with regular physical activity. They also had higher scores in scales evaluating

Table 1
Baseline clinical characteristics and cognitive evaluation results in cases with mild cognitive impairment and controls

Variable	Mild Cognitive Impairment(n = 143)	Control Group(n = 122)	p Value
Age (years, mean ± SD)	80.9 ± 6.4	78.1 ± 5.7	< 0.001
Women	104 (72.7%)	70 (57.4%)	0.009
BMI (Kg/m^2, mean ± SD)	26.9 ± 4.9	26.9 ± 4.1	0.96
Years of education (mean ± SD)	7.1 ± 4.4	10.1 ± 6.0	<0.001
Arterial hypertension	98 (68.5 %)	88 (72.1%)	0.53
Dyslipidemia	89 (62.2 %)	73 (59.8%)	0.69
Smoker			0.003
Current	5 (3.5%)	3 (2.5%)	
Former	26 (18.2%)	44 (36.1%)	
Never	112 (78.3%)	75 (61.5%)	
Diabetes mellitus	31 (22.4%)	20 (16.4%)	0.31
Regular physical activity	61 (42.7%)	69 (56.6%)	0.02
Family history of dementia	30 (21.0%)	26 (21.3%)	0.98
Antiplatelets	40 (32.0%)	32 (30.2%)	0.66
Statins	59 (47.2%)	60 (55.7%)	0.23
Age-adjusted Charlson score (mean ± SD)	4.5 ± 1.3	4.2 ± 1.3	0.09
CHA_2DS_2-VASc score (mean ± SD)	3.7 ± 1.2	3.4 ± 1.2	0.04
MMSE score (mean ± SD)	24.1 ± 2.8	28.4 ± 2.1	<0.001
FRAIL index (mean ± SD)	1.2 ± 1.1	0.8 ± 1.0	0.002
GDS/FAST (mean ± SD)	2.8 ± 0.4	1.2 ± 0.4	<0.001

Abbreviations: BMI = body mass index; FRAIL = Fatigue, Resistance, Ambulation, Illnesses and Loss of weight scale; GDS/FAST = Global Deterioration Scale/Functional Assessment Staging; MMSE = Mini Mental State Examination; SD = standard deviation. Systemic arterial hypertension was defined as blood pressure > 140/90 mm Hg or current use of antihypertensive drugs. Dyslipidemia was defined as either or combination of total cholesterol ≥240 mg/dl, LDL−cholesterol ≥160 mg/dl, HDL− cholesterol <40 mg/dl, triglycerides ≥200 mg/dl, or use of lipid−lowering medication.

frailty (FRAIL), functional capacity (GDS/FAST), and in CHA_2DS_2-VASc, and lower scores in the MMSE scale.

Table 2 shows the ECG evaluation in patients with mild CI and controls. Compared with controls, cases had higher P-wave duration, higher prevalence of IAB (Figure 1), higher prevalence of advanced IAB, and higher MVP score.

The associations between the presence of IAB and mild CI in univariate and multivariate analyses are shown in Table 3. IAB was independently associated with mild CI.

Table 2
ECG evaluation in patients with cognitive impairment and controls

Variable	Mild Cognitive Impairment(n = 143)	Control Group(n = 122)	p Value
P-wave			
P-wave duration (ms)	116.2 ± 13.8	112.5 ± 13.3	0.03
P-wave voltage in I (mV)	0.08 ± 0.04	0.08 ± 0.04	0.86
IAB			0.001
No	70 (49.0 %)	84 (68.9 %)	
Partial	45 (31.5 %)	28 (23.0 %)	
Advanced	28 (19.6 %)	10 (8.2 %)	
MVP score	2.7 ± 1.4	2.2 ± 1.3	0.004
Other ECG data			
PR interval (ms)	175.9 ± 25.1	183.25 ± 38.65	0.07
LBBB			0.63
No	134 (93.7 %)	116 (95.1 %)	
Incomplete	2 (1.4 %)	0	
Complete	7 (4.9 %)	6 (4.9 %)	
RBBB			0.55
No	118 (82.5 %)	104 (85.2 %)	
Incomplete	10 (7.0 %)	8 (6.6 %)	
Complete	15 (10.5 %)	10 (8.2 %)	
QRS width/duration (ms)	91.4 ± 24.2	86.1 ± 21.1	0.06
QT interval (ms)	384.5 ± 34.9	380.4 ± 30.5	0.32
QTc interval (ms)	413.5 ± 24.8	411.3 ± 21.3	0.43

Abbreviations: IAB = interatrial block; LBBB = left bundle branch block; MS = milliseconds; MVP score = Morphology−Voltage−P−wave duration; ; QTc = corrected QT; RBBB = right bundle branch block.

Table 3
Association of interatrial block (IAB), P-wave duration and MVP score, with mild cognitive impairment in univariate and multivariate analyses

	OR (95% CI)	p Value
Univariate		
IAB: Normal P wave	1	
Partial	1.93 (1.09−3.41)	0.024
Advanced	3.36 (1.53−7.39)	0.003
P-wave duration (10 ms)	1.23 (1.02−1.47)	0.030
MVP score (1 point)	1.30 (1.08−1.57)	0.005
Multivariate		
IAB: Normal P wave	1	
Partial	2.03 (1.05−3.93)	0.036
Advanced	2.75 (1.13−6.66)	0.022
P-wave duration (10 ms)	1.24 (1.00−1.52)	0.048
MVP score (1 point)	1.31 (1.06−1.63)	0.014

Abbreviations: CI = confidence interval; OR = odds ratio; MS = milliseconds; MVP = Morphology−Voltage−P−wave duration.

Adjusted for age, gender, years of education and frailty scale (FRAIL - Fatigue, Resistance, Ambulation, Illnesses and Loss of weight).

This association was particularly strong in the case of advanced IAB. Similarly, the association between P-wave duration and mild CI was linear (Figure 2). The univariate and multivariate associations between P-wave duration and MVP score, and mild CI are also shown in Table 3.

Discussion

In this study involving subjects ≥ 70 years without significant structural heart disease, we found an independent association between IAB and mild CI. This association was stronger in the case of advanced IAB. In comparison to controls, patients with mild CI had a higher prevalence of IAB, higher P-wave duration, and higher MVP score. Interestingly, there were no significant differences between cases with mild CI and controls in all the other ECG parameters not related with the P-wave. Our observations suggest that IAB might represent a risk marker for mild CI.

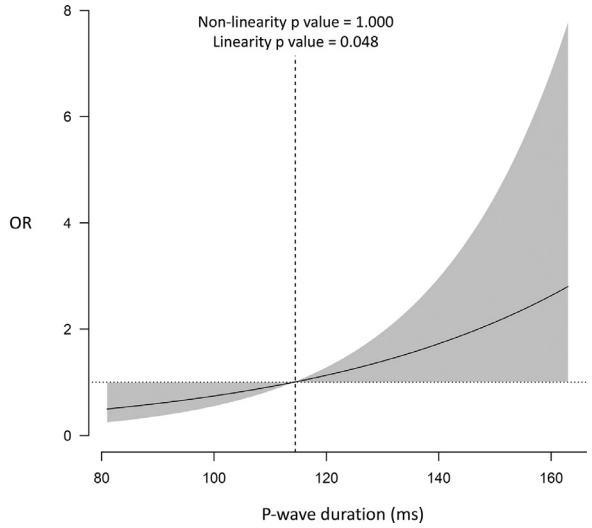

Figure 2. Multivariate adjusted dose-response pattern of the association between P-wave duration with mild cognitive impairment showing the p values for the linear and nonlinear components. The grey colored area represents the 95% confidence interval of the estimated association between P wave duration and cognitive impairment. Adjusted for age, gender, years of education and frailty FRAIL index (Fatigue, Resistance, Ambulation, Illnesses, and Loss of weight). OR = odds ratio.

IAB is the consequence of a delayed conduction of the electrical impulse between the right and left atrium, that produces a P-wave duration >120 ms.[12] This entity, resulting from structural and electrical remodeling of the atria, is related to atrial enlargement, fibrosis, poor contractility, and electromechanical dyssynchrony.[12,18] In partial IAB the electrical impulses are conducted from the right atrium to the left atrium through the normal propagation route (Bachmann bundle in the upper part of the left atrium and upper and middle part of the interatrial septum) but with a delay. Consequently, the duration of the P-wave is prolonged in the surface ECG (> 120 ms) but has a positive morphology in inferior leads. The advanced-IAB is characterized by a full block of the electrical impulse so left atrial activation occurs in a retrograde, caudocranial fashion using muscular connections in the vicinity of coronary sinus and the fossa ovalis, resulting in a bimodal P-wave in inferior leads.[9,12]

Although IAB, particularly advanced IAB, is a strong predictor of AF and ischemic stroke,[5,6] no previous studies have described a link between IAB and CI. Interestingly, in the Cardiac and Clinical Characterization of Centenarians (4C) study,[19] the prevalence of dementia in centenarians progressively increased as the atrial conduction worsened from normal P-wave duration to partial IAB to advanced IAB, reaching the highest rates in the subgroup of patients with AF. In fact, whereas the overall prevalence of advance IAB in median age population is below 1%, it increases to 8% in septuagenarians and 26% in centenarians[9], a progression somewhat similar to CI and dementia rates.

Recently, Gutierrez et al. [20] suggested an association between P-wave duration and dementia in Atherosclerosis Risk In Communities NeuroCognitive Study. However, the study was underpowered to prove an independent association of advanced IAB with dementia, probably because the Atherosclerosis Risk In Communities NeuroCognitive Study cohort was a relatively young population (mean age was 57 years) with a low rate of advanced IAB (< 2%). This small number of patients with advanced IAB might explain the lack of statistical significance. Besides, advanced IAB has, by definition, a P-wave ≥ 120 ms.

CAMBIAD study was specifically design to explore the potential association between mild CI and the presence of atrial conduction disturbances. In addition, the population of subjects was selected starting at an age where mild CI is prevalent. Moreover, we found that this association, recently described in patients with cardiovascular conditions,[21] is also present in the absence of significant structural heart disease. Aging is associated with fibrosis and atrial enlargement, common findings in IAB.[9,22] In fact, CI and dementia share common pathogenic pathways with IAB and AF, including atrial fibrosis, vascular beta-amyloid

deposition, low grade chronic inflammation, and autonomic nervous system dysfunction.[23,24]

The implications of the association between advanced IAB and mild CI are yet to be defined but could be clinically appealing. A systematic cognitive screening might be recommended in patients with IAB, especially in the case of advanced IAB. Conversely, in patients with CI, the presence of IAB could also be ruled out. As anticoagulation seems to have a protective effect for CI and dementia in patients with AF,[25-27] it should be elucidated whether some patients with advanced IAB might also benefit from this therapy. The absence of a temporal relation between episodes of paroxysmal AF with the occurrence of strokes, as several studies in patients with implanted Holter have shown,[28,29] supports the presence of a procoagulant and thrombogenic environment in a dysfunctional left atrium, even in the absence of documented AF.[1,18] Furthermore, the similarity between the pathophysiological mechanisms of advanced IAB and AF could also support the possible beneficial effect of anticoagulation both in preventing thromboembolic events and cognitive decrease in some patients with advanced IAB.[8,9,30]

Our study has some limitations. Diagnoses of mild CI were made by different physicians and although they were all experienced experts that also used validated tools, some heterogeneity cannot be excluded. Additionally, participants did not undergo continuous heart-rhythm monitoring to detect paroxysmal AF, so the possibility that subclinical episodes of AF mediated the association of IAB with cognitive decrease cannot be excluded. Finally, the design of this study is not enough to prove a cause-effect relation. Nevertheless, to our knowledge, this is the first study to evaluate the association of IAB with mild CI in an elderly population without significant structural heart disease. Other strength is the systematic evaluation with validated tools of frailty (FRAIL), functional capacity (GDS/FAST), and CI (MMSE).

In conclusion, the data from our study show that IAB is associated with mild CI in subjects aged ≥70 years without significant structural heart disease. This association is stronger in the case of advanced IAB. Further studies are required to evaluate the underlying mechanisms of this association.

Authors contribution

MMS and ABL formulated the idea. MMS and CHF drafted the protocol, designed the study, collected the data, analyzed the data and drafted the manuscript. VBF and RE analyzed the ECG data. MMS and ABL acquired financial support. All authors participated in recruiting the patients and provided critical review of the protocol, provided resources and facilities for participant recruitment and analysis. MMS and CHF supervised the research activities. All authors critically revised and approved the final version of the manuscript.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relations that could have appeared to influence the work reported in this study.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2020.09.008.

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