Potential Factors That Affect Electrocardiographic Progression of Interatrial Block

Vignendra Ariyaratnam, M.D.,* Mark Kranis, M.D.,† Sirin Apiyasawat, M.D.,‡ and David H. Spodick, M.D., D.Sc.§

From the *Massachusetts Veterans Epidemiology Research and Information Center (MAVERIC), Veterans Affairs Boston Healthcare System, Boston, MA; †Division of Cardiology, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA; ‡Department of Medicine, Saint Vincent Hospital, Worcester, MA; and §Division of Cardiovascular Medicine, Department of Medicine, University of Massachusetts Medical School, Worcester, MA

Introduction: Interatrial block (IAB; P wave ≥ 110 ms) is associated with atrial tachyarrhythmias and left atrial electromechanical dysfunction. This subtle abnormality is highly prevalent and may exist as partial (pIAB) or advanced IAB (aIAB). Indeed, theoretically pIAB could progress to aIAB with worsening interatrial conduction over time. However, this has been poorly investigated. We retrospectively appraised this phenomenon and also evaluated the influence of common clinical factors such as coronary artery disease (CAD), hypertension (HTN), and use of antihypertensive medications.

Methods: Between January 2003 and June 2004, 27 patients who had aIAB on routine 12-lead ECGs were identified. Past serial ECGs of each patient were evaluated for evidence of change in IAB type. Medical records of respective patients were then reviewed for HTN, type of antihypertensive medication used, and other common comorbidities.

Results: Median progression time from pIAB to aIAB was shorter (42 months; mean $\pm$ SD = 39.2 $\pm$ 30.5) compared to that of normal P wave (P-normal) to aIAB (66 months; mean $\pm$ SD = 64.2 $\pm$ 25.6). Use of angiotensin-converting enzyme inhibitors (ACEIs) appeared to significantly delay the progression time in patients who progressed from pIAB to aIAB (50.1 $\pm$ 28.3 vs 10 $\pm$ 10.4 months; $P = 0.04$). Beta-adrenergic blocker use alone did not significantly affect either progression time but when used in conjunction with ACEIs, appeared to slow such progression.

Conclusion: Progression time from pIAB to aIAB is shorter compared to that of P-normal to aIAB. Given the consequences of IAB, awareness of such progression could be important for clinicians in anticipating potential sequelae.

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interatrial block; progression; hypertension; antihypertensive medication; angiotensin-converting enzyme inhibitors; beta-adrenergic blockers

Interatrial delay denotes excessive time for sinus impulses to conduct from the right (RA) to the left atrium (LA).¹ Because on the ECG, time = conduction duration and excessive time or delay = block, such conduction abnormality has been described as interatrial block (IAB). While normal P wave duration has been classified by the World Health Organization/International Society and Federation of Cardiology Task Force as <110 ms, P waves in IAB are prolonged (≥ 110 ms) and commonly notched ($\geq 88\%$, $P = 0.24$; positive predictive value = 94%)²

(Fig. 1). IAB is significant as a predictor of atrial tachyarrhythmias, especially in patients undergoing cardiac surgery.³ IAB is also associated with LA enlargement (LAE),⁴ LA electromechanical dysfunction,⁵ and is a potential risk for embolic strokes.⁶

CLASSIFICATION

Because lesions induced experimentally along the Bachmann Bundle reproduce the foregoing

Address for reprints: David H. Spodick, M.D., D.Sc., Division of Cardiovascular Medicine, Department of Medicine, University Campus, University of Massachusetts Medical School, 55 Lake Avenue North, Worcester, MA 01655. Fax: +508-856-4571; E-mail: spodickd@ummmhc.org

Figure 1. (a) Partial interatrial block (b) Advanced interatrial block.

classic P waves that are synonymous with IAB, this interatrial pathway is thought to be the preferred route for interatrial conduction.^{1,7} Depending on the severity of the conduction delay, IAB may manifest as partial (incomplete) or advanced (complete).¹ Partial IAB (pIAB), the commoner of the two, occurs when sinus impulses from the RA continue to conduct via a "partially blocked" Bachmann Bundle but are delayed in reaching the LA. The resultant lag in LA activation is captured on the ECG as wide, often bifid, P waves (≥ 110 ms)¹ (Fig. 1A). However, when sinus impulses can no longer pass to the LA via the Bachmann Bundle, alternate pathways may be utilized to depolarize the LA and produce its ensuing activation. This is typical of advanced IAB (aIAB) where it is thought that sinus impulses are instead forced to first depolarize the RA with a net vector toward the atrioventricular junction before being reflected caudocranially through the LA to complete the interatrial conduction cycle.¹ Biphasic P waves (+ -) on leads II, III, and aVF depict this type of conduction (Fig. 1B).

While the true significance of aIAB over its partial counterpart is relatively poorly studied apart from its association with increased risk of atrial tachyarrhythmias, we described a previously unreported progression from pIAB to aIAB over the

course of 5 years.⁸ Indeed, such progression may very well be an indication of increasing severity in Bachmann Bundle abnormality. We now retrospectively evaluated what the median times were for progression from normal P wave (P-normal) to aIAB and that of pIAB to aIAB were (P-normal→aIAB vs pIAB→aIAB). We also appraised whether common clinical risk factors of IAB such as, coronary artery disease (CAD), hypertension (HTN), diabetes mellitus, and hyperlipidemia as well as antihypertensive medications such as, angiotensin-converting enzyme inhibitors (ACEIs) and beta-adrenergic blockers (BBs) could have a role in such progression.

METHODS

Between January 2003 and June 2004, we identified 27 consecutive patients at a tertiary care general hospital (Saint Vincent Hospital, Worcester, MA, USA) who had aIAB on routine 12-lead ECGs for this retrospective investigation. Past serial ECGs of each patient were then obtained and evaluated retrospectively for evidence of first noted significant P wave change (pIAB or P-normal) before the development of the currently evaluated aIAB type. Based on such preceding ECG change, patients were subsequently divided into three groups for assessment: (a) P-normal→aIAB, (b) pIAB→aIAB, and (c) no change (preexisting aIAB at baseline). ECGs had been recorded from an electrocardiograph (Marquette 2000; Marquette Electronics Inc., Milwaukee, WI, USA) standardized at 25 mm/s and 10 mm/mV. P waves were measured manually on each ECG lead for the greatest P duration with a calibrated magnifying graticule. Because 1 mm represents 40 ms on ECGs with such standardization, to increase diagnostic specificity we used 120 ms as our criterion for IAB diagnosis (120 ms is also the mode P wave duration in IAB).² The onset of the P wave was defined as the junction between the T-P isoelectric baseline and the beginning of the P deflection while the offset, as the junction between the end of the P deflection and the PR segment. Biphasic (+ -) P waves ≥ 120 ms in leads II, III, and aVF were thus considered aIAB.

Medical records of respective patients were then reviewed for HTN, type of antihypertensive medication used, and other common comorbidities that were preexisting or present at the time of inclusion in the study. Records of ≥ 2 blood pressure readings taken at ≥ 2 clinic or hospital visits after the

initial screening were averaged for the purpose of this study. Based on current recommendations of the Seventh Report of the Joint National Committee of Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VII) for classification of systolic (sBP) and diastolic blood pressures (dBP) in adults ≥ 18 years, we divided our readings as prehypertension (preHTN; sBP 120–139/dBP 80–99 mmHg), Stage 1 HTN (sBP 140–159 or dBP 90–99 mmHg) and Stage 2 HTN (sBP ≥ 160 or dBP ≥ 100 mmHg).^{9,10} All comorbidities and risk factors had been documented in patients' electronic medical records by physicians involved in their care and were consistent with established classifications and guidelines for disease definition and diagnosis outlined by the American College of Cardiology/American Heart Association/American

College of Physicians-American Society of Internal Medicine Task Force on Practice Guidelines. Mean and standard deviation (SD) of population, median duration of progression and P values (<0.05 considered significant) were calculated. Statistical analyses were performed using SPSS Version 10.0 statistical software (SPSS Inc., Chicago, IL, USA).

RESULTS

The median progression time from pIAB→aIAB was expectedly shorter (42 months; mean $\pm$ SD = 39.2 ± 30.5) than that of P-normal→aIAB (66 months; mean $\pm$ SD = 64.2 ± 25.6) among patients in this retrospectively appraised cohort (Table 1). More female study patients progressed from P-normal→aIAB as opposed to pIAB→aIAB while the

Table 1. Comparison of Study Patients Who Had P-Normal→aIAB, pIAB→aIAB, and Preexisting aIAB

Variables	P-normal→ aIAB (n = 9)	pIAB→aIAB (n = 11)	Preexisting aIAB (n = 7)	P value for P-normal→aIAB vs pIAB→aIAB	P Value for Trend
Age upon inclusion in study (mean $\pm$ SD; years)	83.4 $\pm$ 9.2	75.7 $\pm$ 10.6	80.9 $\pm$ 3.1	0.11	0.16
Gender				0.008	0.02
Male	0	6 (54.5%)	4 (57.1%)		
Female	9 (100%)	5 (45.5%)	3 (42.9%)		
PreHTN	0	0	0	N/A	N/A
HTN Stage 1	5 (55.6%)	4 (36.4%)	4 (57.1%)	0.39	0.59
HTN Stage 2	1 (11.1%)	3 (27.3%)	3 (42.9%)	0.37	0.35
HTN (any stage)	6 (66.7%)	7 (63.6%)	7 (100%)	0.88	0.08
ACEI and/or ARB use ^a	3 (33.3%)	9 (81.8%)	5 (71.4%)	0.008	0.03
ACEI only	2 (22.2%)	8 (72.7%)	3 (42.9%)	0.03	0.07
ARB only	1 (11.1%)	1 (9.1%)	2 (28.6%)	0.88	0.48
BB use	5 (55.6%)	8 (72.7%)	4 (57.1%)	0.42	0.68
CAD	5 (55.6%)	8 (72.7%)	4 (57.1%)	0.42	0.68
DM	2 (22.2%)	3 (27.3%)	2 (22.2%)	0.79	0.95
Restrictive CM	0	0	0	N/A	N/A
Dilated CM	1 (11.1%)	4 (36.4%)	2 (28.6%)	0.19	0.43
Hypertrophic CM	0	0	0	N/A	N/A
MS	0	1 (9.1%)	1 (14.3%)	0.35	0.53
MR	1 (11.1%)	2 (18.2%)	1 (14.3%)	0.66	0.91
COPD	2 (22.2%)	3 (27.3%)	2 (28.6%)	0.79	0.95
Hypothyroidism	2 (22.2%)	1 (9.1%)	1 (14.3%)	0.41	0.71
Hyperthyroidism	0	0	1 (14.3%)	N/A	0.23
Hyperlipidemia	2 (22.2%)	2 (18.2%)	4 (57.1%)	0.82	0.17
Mean number of ECGs used	5 (55.6%)	4 (36.4%)	N/A	0.39	N/A
Time to aIAB (months)					0.06
Mean $\pm$ SD	64.2 $\pm$ 25.6	39.2 $\pm$ 30.5			
Median	66 (31–110)	42 (3–101)	N/A	N/A	

No patient was on both types of medication simultaneously.

PreHTN = prehypertension; HTN = hypertension; ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin-receptor blocker; BB = beta-adrenergic blocker; CAD = coronary artery disease; DM = diabetes mellitus; CM = cardiomyopathy; MS = mitral stenosis; MR = mitral regurgitation; COPD = chronic obstructive pulmonary disease; aIAB = advanced interatrial block.

Table 2. Summary of Events that Occurred During the Time of Progression

Events	Total	P-Normal→aIAB	pIAB→aIAB ^a	Preexisting aIAB
CHF	8	4	3	1
MI	1	0	1	1
AF	3	1	0	2
Pulmonary HTN	2	1	1	0
TOTAL	14	6	5	4

^aOne patient had both MI and CHF, and one patient had both CHF and Pulmonary HTN.

opposite was noted among the male patients. CAD and HTN were almost of equal high prevalence in these groups. All the seven patients with preexisting aIAB had HTN while between P-normal→aIAB patients and pIAB→aIAB patients, the prevalence of HTN in any stage was comparable ($P < 0.08$ for trend) (Table 1). None of the study patients had preHTN. Events between P-normal→aIAB patients and pIAB→aIAB patients were fairly similar and comparable (Table 2). Use of ACEIs appeared to significantly delay the progression time in pIAB→aIAB patients but not in P-normal→aIAB patients in this retrospective appraisal (Table 3). BB use alone did not significantly affect either progression time (Table 3) but when used in conjunction with ACEIs, appeared to slow the progression of pIAB→aIAB (Table 3). The linear regression model for use of BBs in addition to ACEIs among patients with CAD and HTN (any stage) also revealed significant correlation with a slowed pIAB→aIAB progression ($P = 0.04$; $r = 0.87$). Data on use of calcium channel blockers and diuretics were omitted for statistical insignificance.

DISCUSSION AND LIMITATIONS

The prevalence of aIAB in the general population is estimated to be $\leq 2\%$ while in geriatric populations, this prevalence rises to approximately 6%.¹¹ As such, aIAB is seemingly greatly overshadowed by its pIAB counterpart that is prevalent at almost pandemic proportions: $>40\%$ in two separate yet comparable general hospital populations.¹ However, IAB, be it partial or advanced, is largely underappreciated in general hospitals and thus being uncommon, aIAB is not only less recognized but also more poorly reported clinically.¹ Needless to say, fewer investigations have been directed toward aIAB. Bayes de Luna et al. reported a much higher incidence of paroxysmal supraventricular tachyarrhythmias among patients with aIAB when

compared to controls who had been matched for echocardiographic LAE (93.7% vs 27.7%, respectively; $P < 0.001$).¹² However, the relationship of aIAB with LAE, LA electromechanical dysfunction, and risk of embolic stroke has been poorly studied. Indeed, as described above, the leading school of thought for such “retrograde” LA conduction that results in (delayed) LA activation in aIAB is thought to principally occur in the region of the atrioventricular node, where a caudocranial (“upward”) deflection of the preceding RA-descending sinus impulses then occurs.^{1,8} However, the exact circuit for such impulse redirection through the LA is poorly understood and few, if any, have conclusively described such LA activation in aIAB.^{1,13} Nevertheless, we had hypothesized that progressive worsening of interatrial conduction via the Bachmann Bundle (or perhaps via any of the other potential transeptal interatrial routes) in pIAB may eventually lead to aIAB.⁸ Our findings confirm our suspicions that while such progression does indeed occur, it probably is a slow process (Table 1). Admittedly, a prospective evaluation would have yielded a better estimate of time-to-progression where matched or at least, comparable follow-up times could perhaps be assessed. Moreover, such an investigation could have allowed for serial ECGs to be appropriately obtained at regular intervals, which was not the case in this necessarily retrospective investigation. The connotation, however, is that if potential contributing factors for such progression are identified, intervention could then be introduced. We had previously described CAD and HTN as possible leading risk factors for IAB.¹⁴ However, although the prevalence of either disease was high between P-normal→aIAB and pIAB→aIAB patient groups in this investigation, we are unable to justify CAD and HTN as significant exposures that could promote progression in either group here. One limitation is clearly that the study sample is small. However, aIAB is most certainly uncommon compared

Table 3. Time to aIAB in Patients with and without Exposure

Group	Time to aIAB <i>with</i> Exposure (months; mean $\pm$ SD)	Time to aIAB <i>without</i> Exposure (months; mean $\pm$ SD)	P Value
Any event (MI,CHF, etc.) and time to aIAB			
P-normal→aIAB (6 of 9 patients)	62.67 $\pm$ 30.7	67.33 $\pm$ 15.5	0.82
pIAB→aIAB (3 of 11 patients)	37.67 $\pm$ 22.3	39.75 $\pm$ 34.5	0.93
Stage 1 HTN and time to aIAB			
P-normal→aIAB (5 of 9 patients)	68.2 $\pm$ 34.1	59.3 $\pm$ 11.5	0.64
pIAB→aIAB (4 of 11 patients)	58.0 $\pm$ 37.4	25.4 $\pm$ 21.9	0.13
Stage 2 HTN and time to aIAB			
P-normal→aIAB (1 of 9 patients)	66	64.0 $\pm$ 27.3	0.95
pIAB→aIAB (3 of 11 patients)	21.0 $\pm$ 19.7	46.0 $\pm$ 32.1	0.25
HTN (any stage) and time to aIAB			
P-normal→aIAB (6 of 9 patients)	67.8 $\pm$ 30.5	57.0 $\pm$ 13.0	0.58
pIAB→aIAB (7 of 11 patients)	42.1 $\pm$ 34.9	34 $\pm$ 24.7	0.69
HTN (any stage) and/or CAD and time to aIAB			
P-normal→aIAB (7 of 9 patients)	65.1 $\pm$ 28.8	61.0 $\pm$ 15.7	0.86
pIAB→aIAB (8 of 11 patients)	42.6 $\pm$ 29.8	5.0	0.26
ACEI and time to aIAB			
P-normal→aIAB (2 of 9 patients)	55.5 $\pm$ 34.6	66.7 $\pm$ 25.3	0.62
pIAB→aIAB (8 of 11 patients)	50.1 $\pm$ 28.3	10 $\pm$ 10.4	0.04
ACEI and/or ARB and time to aIAB			
P-normal→aIAB (3 of 9 patients)	55.5 $\pm$ 34.6	66.7 $\pm$ 25.3	0.62
pIAB→aIAB (9 of 11 patients)	47.0 $\pm$ 28.1	4.0 $\pm$ 1.4	0.07
BB and time to aIAB			
P-normal→aIAB (5 of 9 patients)	63.0 $\pm$ 20.9	65.7 $\pm$ 33.9	0.89
pIAB→aIAB (8 of 11 patients)	40.3 $\pm$ 20.7	36.3 $\pm$ 50.1	0.86
ACEI or BB and time to aIAB			
P-normal→aIAB (6 of 9 patients)	57.7 $\pm$ 22.9	77.3 $\pm$ 30.3	0.31
pIAB→aIAB (9 of 11 patients)	47.0 $\pm$ 28.1	4.0 $\pm$ 1.4	0.07

pIAB = partial interatrial block; CAD = coronary artery disease; aIAB = advanced interatrial block; MS = mitral stenosis; HTN = hypertension; MR = mitral regurgitation; PreHTN = prehypertension; CM = cardiomyopathy; CHF = congestive heart failure; AF = atrial fibrillation; COPD = chronic obstructive pulmonary disease; DM = diabetes mellitus; ACEI = angiotensin-converting enzyme inhibitor; BB = beta-adrenergic blocker; ARB = angiotensin-receptor blocker; MI = myocardial infarction; pIAB→aIAB = progression from pIAB to aIAB; P-normal = normal P wave; P-normal →aIAB = progression from normal P wave to aIAB.

to pIAB and as such, our sample actually serves as an indirect yet large representation of aIAB patients in comparable general hospital populations. Furthermore, because we were investigating patients with aIAB, regardless if they had progressed from P-normal or pIAB, both groups would have had a characteristically high prevalence of CAD and HTN. It is therefore less surprising that neither IAB group showed significance over the other for these diseases in terms of progression.

Several investigations have demonstrated the potential merit of modulating the renin-angiotensin-aldosterone system in efforts of controlling atrial fibrillation (AF).¹⁵⁻¹⁷ In a 1-year, prospective follow-up investigation of patients with persistent AF undergoing electrical cardioversion, Zaman et al.¹⁶ showed that the number of defibrillation attempts required to restore sinus rhythm and the

incidence rate ratio of readmissions for AF were significantly lower in those treated with ACEIs. Most interestingly, they also showed that ACEI use significantly reduced (signal-averaged) P wave duration in those patients (135 ± 3 ms vs 150 ± 2 ms; $P = 0.002$). In the randomized prospective investigation by Madrid et al.¹⁷ which compared an angiotensin-receptor blocker (ARB) plus amiodarone with amiodarone treatment alone among patients with persistent AF, fewer patients receiving ARB had recurrence of AF (84.79% vs 63.16%, $P = 0.008$). Their analysis of time to first recurrence also showed that those patients had a greater probability of remaining free of AF (79.52% vs 55.91%, $P = 0.007$). These findings further fuel our hypothesis that ACEI use could slow the progression of IAB and raise questions whether ACEIs (or ARBs, although its usage was limited in our cohort) may

have a direct effect on the Bachmann Bundle by either altering its refractoriness, possibly via suppression of atrial fibrosis by cytokine modulation and cardiac remodeling or through unloading of a pressure- and stretch-overloaded atria.^{7,18} It is possible that either medication has properties that may play a multifaceted role in exerting a double-pronged effect of not only addressing the potential cause, HTN^{10,14,18} but also in ameliorating the underlying mechanism, IAB, that leads to the potential sequela, AF.^{7,16,17} However, our sample size is small and only an appropriately designed prospective investigation using a larger cohort can yield answers on the true effects of pharmacotherapy. Moreover, it can also always be argued that CAD and HTN may pose as confounding elements since either medication can be an important part of the armamentarium in their clinical management. However, all groups were patients with aIAB and thus, the extent of affliction with such risk factors could possibly have been similar (Table 1). As such, ACEI and/or ARB usage/exposure should somewhat proportionately reflect the prevalence of CAD or HTN particularly and remain statistically insignificant but this was not the case (Tables 1 and 3). Our limited sample leaves little room for determination of both, confounding mechanisms and possible etiologies that may be better addressed in a structured, prospective assessment. It was therefore difficult to exactly quantify the extent of pharmacotherapy use in our retrospective investigation where we could only provide a clinical baseline of medication usage based on current medical records from the time aIAB was present on corresponding ECGs.

CONCLUSION

Progression time from pIAB→aIAB is shorter compared to that of P-normal→aIAB. Due to the sequelae of pIAB, such as LAE, LA electromechanical dysfunction and particularly, AF, recognition of pIAB and the risk of its progression to aIAB could be important for physicians in appropriately anticipating atrial tachyarrhythmias. However, prospective evaluation using a larger cohort is much needed to conclusively ascertain contributing factors that could affect such progression.

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