Original Article

Prevalence and characterization of coronary artery disease in patients with symptomatic bradyarrhythmias requiring pacemaker implantation

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A B S T R A C T

Background: This study was conducted to assess the prevalence and characterization of CAD in high risk patients requiring pacemaker implantation for symptomatic bradyarrhythmias.
Methods: This study included 100 patients with symptomatic sinus node dysfunction or atrioventricular block, who were at high risk of CAD or had previously documented atherosclerotic vascular disease (ASCVD). Coronary angiography was performed before pacemaker implantation. CAD was defined as the presence of any degree of narrowing in at least one major coronary artery or its first order branch. Obstructive CAD was defined as $\geq$50% diameter stenosis. CAD was categorized as single vessel disease (SVD), double vessel disease (DVD), or triple vessel disease (TVD); and obstructive CAD in the arteries supplying the conduction system was sub-classified according to Mosseri's classification.
Results: Out of 100 patients (mean age 64.6 ± 10.7 years), 45 (45%) had CAD. 29% patients had obstructive CAD while 16% had non-obstructive CAD. 53.3% patients had SVD, 15.6% had DVD and 31.1% had TVD. Among patients with obstructive CAD; Type I, II, III and IV coronary anatomies were present in 6.9%, 34.5%, 10.3% and 48.3% patients respectively. Presence of CAD significantly correlated with dyslipidemia (p = 0.047), history of smoking (p = 0.025), and family history of CAD (p = 0.002).
Conclusion: Angiographic CAD is observed in a substantial proportion of patients with symptomatic bradyarrhythmias and risk factors for CAD. It could be argued that such patients should undergo a coronary work-up before pacemaker implantation. Treatment of concomitant CAD is likely to improve the long term prognosis of these patients.

1. Introduction

Bradyarrhythmias, defined as heart rate below 60 beats per minute, are a common clinical occurrence and comprise of a variety of rhythm disorders including sinus node dysfunction (SND) and atrioventricular (AV) conduction disturbances or blocks.[1,2] These disorders can result from various intrinsic and extrinsic conditions causing damage to the conduction system. Furthermore, bradycardia can be a normal physiologic response under certain circumstances (during sleep, healthy athletes). Clinical presentation of bradyarrhythmias ranges from asymptomatic electrocardiographic (ECG) findings to a broad array of symptoms which may be typical (syncope, near syncope) or atypical (dyspnea, angina, dizziness, fatigue, lethargy).[2] Symptoms can be either permanent or intermittent and unpredictable. Many individuals with conduction system disorder are asymptomatic and never seek medical attention.[3,4] As far as etiology of bradyarrhythmias is concerned, it is difficult to ascribe conduction system disease to a specific cause, in a substantial proportion of

patients. Although it is true that many of these patients have heart disease, usually ischemic, a cause-and-effect relationship is difficult to document. In fact, unless the conduction defect occurred in the setting of acute myocardial infarction, histologic examination of the conduction system in most of these individuals shows nonspecific scarring and fatty infiltration regardless of the presence or absence of underlying ischemic heart disease.[5] Previous studies have suggested that histologic changes in the conduction system are insufficient to explain the disorder, leading to the assumption that associated disease conditions like coronary atherosclerosis, hypertensive cardiovascular disease, congenital heart disease or myocardial disease, may have an important role in the pathogenesis of these disorders.[5,6]

The prevalence of coronary artery disease (CAD) in chronic conduction disorders has been reported to be 15–70%, depending on patients characteristics and the diagnostic modality used to detect CAD.[7–10] Although dobutamine stress echocardiography (sensitivity – 88%, specificity – 92%) and exercise thallium-201 myocardial SPECT (sensitivity – 94%, specificity – 31%) have been used to diagnose CAD in patients with transvenous pacemakers, coronary angiography remains the 'gold standard' for confirming diagnosis.[10] Beyond its possible causative role, the presence of CAD makes the prognosis of conduction disorder worse.[11,12] Moreover, since patients with symptomatic complete heart block or sick sinus syndrome may not develop angina owing to their low heart rate, the underlying CAD may remain undiagnosed or underdiagnosed, which in turn may have serious implications on their clinical outcomes despite treatment of bradycardia with permanent pacemaker implantation. This study was conducted with an aim of assessing the prevalence and characterization of CAD in high risk patients requiring permanent pacemaker implantation for symptomatic bradyarrhythmias. To the best of our knowledge, there is very limited data of such nature available among Indian population. We believe that it is important and useful to have such data for formulating appropriate method of care in such patients.

2. Patients and methods

2.1. Study design

This single-center hospital based prospective observational study, was conducted in the Department of Cardiology, Sher-i-Kashmir Institute of Medical Sciences, Srinagar, Jammu and Kashmir, between 2012 and 2015.

2.2. Study population

We enrolled consecutive patients requiring permanent pacemaker implantation for symptomatic sinus node dysfunction or atrioventricular blocks who fulfilled the eligibility criteria as described below.

2.2.1. Inclusion criteria

i. Patients above the age of 40 years with symptomatic sick sinus syndrome or conduction disorders, who fulfilled the ACCF/AHA/HRS criteria for permanent pacemaker implantation.[13]
ii. Patients deemed to be at high risk for CAD or previously documented ASCVD (fulfilling one or more of following criteria).
   a. High Framingham risk score (10 year CHD risk ≥ 20%).[14]
   b. Two or more than two conventional risk factors including hypertension (defined as patient taking any anti-hypertensive drugs at the time of presentation or if blood pressure recorded was ≥140 mmHg systolic and/or ≥90 mmHg diastolic, on at

least two separate occasions); type-2 diabetes mellitus (diagnosed on the basis of fasting plasma glucose of ≥126 mg/dL or Hemoglobin A_1C greater than 6.5% or symptoms of diabetes plus random blood glucose concentration ≥200 mg/dL or patient on anti-diabetic medications); obesity (body mass index > 30 kg/m² body surface area); history of angina; smoking (defined as if the patient smoked >1 cigarette per day regularly for more than 6 months or had quit smoking for less than 2 years); dyslipidemia (defined as total cholesterol ≥200 mg/dL, or LDL cholesterol ≥130 mg/dL, or triglycerides ≥150 mg/dL, or HDL cholesterol ≤40 mg/dL or any combination of these criteria); age (male ≥ 45 years and females ≥ 55 years); and positive family history of CAD.
   c. Previous history of ASCVD, including CAD (documented on angiography), stroke, transient ischemic attack (TIA), peripheral vascular disease (PVD), abdominal aortic aneurysm, chronic kidney disease (CKD), percutaneous coronary intervention (PCI), coronary artery bypass grafting (CABG) or familial hypercholesterolemia.
iii. Patients who gave consent for the study.

2.2.2. Exclusion criteria

i. Acute illness including acute coronary syndrome (ACS), myocarditis, infective endocarditis or sepsis.
ii. History of chronic diseases known to cause conduction disturbances like connective tissue disorders, infiltrative disorders, muscle dystrophies or systemic malignancies.
iii. Intake of drugs known to cause bradyarrhythmias like digoxin, beta blockers, calcium channel blockers or anti-arrhythmic medications.
iv. Presence of severe anemia, coagulopathy, end stage renal disease (ESRD) or dyselectrolemia.
v. Patients with congenital heart disease (including congenital heart block), valvular heart disease or cardiomyopathy.
vi. History of allergy to contrast agents.
vii. Patients who refused to give consent for the study.

2.3. Methods

A detailed history including presenting symptoms, past history, family history of CAD or conduction disorders, history of atherosclerotic risk factors and drug history was taken from all patients. Complete physical examination including cardiovascular examination was then performed. Base line investigations including electrocardiogram (ECG), complete blood count, kidney function tests, liver function tests, arterial blood gas analysis, serum electrolytes, lipid profile, serum uric acid, fasting blood sugar, thyroid profile, coagulation profile were obtained. Echocardiography to rule out significant structural heart disease or cardiomyopathies and to assess left ventricular function was also done in all the cases. Risk calculation was done according to the Framingham coronary heart disease risk score and only patients having high risk (10 year CHD risk ≥20%) were included in the study.[14] One day prior to pacemaker implantation, coronary angiography (CAG) was performed via trans-radial or trans-femoral approach using the standard Judkins technique. The angiograms were assessed by two independent interventional cardiologists who were blinded to the clinical details of the patients. Coronary artery disease was defined as the presence of any degree of narrowing in at least one major coronary arteries [left anterior descending (LAD), left circumflex (LCx), right coronary artery (RCA)] or their first order branches. Obstructive CAD was defined as ≥50% diameter

stenosis (visual estimation of lesion diameter compared with the adjacent normal segment) in any of these vessels, while ≤50% diameter stenosis was labeled as non-obstructive CAD. CAD was categorized as single vessel disease (SVD), double vessel disease (DVD), or triple vessel disease (TVD) according to number of major branches with atherosclerotic involvement. Among patients with obstructive CAD, the location of stenosis in the LAD and RCA, as the arteries supplying the conduction system, was classified according to Mosseri et al.'s classification.[11] *Type I.* Anatomy not compromising blood supply to the conduction system, namely, either the absence of significant narrowing in the LAD, RCA, LCx, posterolateral ventricular (PLV), or posterior descending artery (PDA) or the presence of mid-distal LAD lesions beyond the septal branches. *Type II.* Pathological coronary anatomy involving septal branches emerging from the LAD, without significant lesions in the RCA. *Type III.* Pathological coronary anatomy compromising blood supply to the sinoatrial (SA) nodal or AV nodal branches but not compromising blood flow to the septal branches. This subset includes patients with distal LAD lesions after the septal branches. *Type IV.* Combination of Type II and Type III pathological coronary anatomy that compromises blood supply both to the septal branches and SA or AV arteries. We also studied the correlations of various clinical and demographic variables with the presence or absence of CAD in these patients.

2.4. Consent and ethical issues

After explaining the study in detail, an informed consent was taken from each patient. The study protocol was cleared by the Institutional Ethics Committee. As a part of study protocol, the cost of CAG was exempted by the hospital administration.

2.5. Statistical analysis

Statistical analysis was performed by SPSS software package (version 20.0, SPSS Inc, Chicago, Illinois, USA). All continuous variables were expressed as mean ± SD, and categorical variables were reported as frequency and percentages. Group comparisons were performed with Student t-test or crosstabs. The Chi-square test or Fisher exact test was used for categorical variables. A p-value of <0.05 was considered statistically significant.

3. Results

During the study period of 3 years, a total of 100 patients with symptomatic bradyarrhythmias requiring permanent pacemaker implantation and at high risk of CAD or previously documented ASCVD were enrolled in the study.

3.1. Patient characteristics

The mean age of our patients was 64.6 ± 10.7 years, ranging from 40 to 95 years. Out of 100 patients 53 were males and 47 were females. Complete heart block was present in 58 patients, 11 patients had sick sinus syndrome, second degree heart block was seen in 9 patients, trifascicular block was present in 5 patients, and 17 patients had bifascicular block.

3.2. Frequency and distribution of coronary artery disease

Out of 100 patients, 45 were documented to have CAD on coronary angiography while 55 did not have CAD. Out of 45 patients with CAD, 29 had obstructive CAD and 16 had non-obstructive CAD. In terms of the number of vessels involved, 24 patients (53.3%) had single vessel disease (SVD), 7 patients

(15.6%) had double vessel disease (DVD) and 14 patients (31.1%) had triple vessel disease (TVD). When coronary anatomy of the patients with obstructive CAD was categorized according to Mosseri's classification; 2 patients (6.9%) had Type I coronary anatomy, 10 patients (34.5%) had Type II coronary anatomy, 3 patients (10.3%) had Type III coronary anatomy, and 14 patients (48.3%) had Type IV coronary anatomy.

3.3. Clinico-demographic correlates of coronary artery disease

To study the correlation of CAD with various clinical and demographic variables, we divided the patients into two groups; Group I (Patients without CAD) and Group II (Patients with CAD). As described in Table 1, we found that presence of CAD on coronary angiography was significantly correlated with dyslipidemia ($p = 0.047$), history of smoking ($p = 0.025$), and family history of CAD ($p = 0.002$). There was no significant correlation between CAD and age ($p = 0.228$), sex ($p = 0.841$), hypertension ($p = 0.387$), diabetes ($p = 0.562$), obesity ($p = 1.000$), or past history of ASCVD ($p = 0.200$). Presence of CAD was also not correlated with presenting symptoms (Table 2) including syncope ($p = 0.511$), pre-syncope ($p = 0.642$), chest pain ($p = 0.082$), dyspnea ($p = 0.958$), or palpitations ($p = 0.767$). As depicted in Tables 3 and 4, we also did not find any significant correlation between CAD and type of bradyarrhythmia ($p = 0.374$) or number of risk factors present ($p = 0.228$).

Table 1
Correlation of presenting symptoms with presence or absence of CAD.

Presenting complaints	Coronary artery disease (Total = 100)		p value
	Absent ($n = 55$)	Present ($n = 45$)	
Syncope [n (%)]	37 (62.27%)	33 (73.33%)	0.511
Pre syncope [n (%)]	17 (30.90%)	12 (26.67%)	0.642
Chest pain [n (%)]	10 (18.18%)	15 (33.33%)	0.082
Dyspnea [n (%)]	8 (14.54%)	10 (22.22%)	0.320
Palpitations [n (%)]	4 (7.27%)	4 (8.89%)	1.000

CAD – coronary artery disease; n – number; % – percentage.

Table 2
Distribution of risk factors among patients with and without CAD.

Risk factors	Coronary artery disease (Total = 100)		p value
	Absent ($n = 55$)	Present ($n = 45$)	
Hypertension [n (%)]	47 (85.45%)	41 (91.11%)	0.387
Diabetes [n (%)]	15 (27.27%)	10 (22.22%)	0.562
Obesity [n (%)]	3 (5.45%)	3 (6.67%)	1.000
Smoking [n (%)]	16 (29.09%)	23 (51.11%)	0.025
Dyslipidemia [n (%)]	13 (23.64%)	19 (42.22%)	0.047
Family history [n (%)]	7 (12.72%)	20 (44.44%)	0.002

CAD – coronary artery disease; n – number; % – percentage.

Table 3
Correlation between type of bradyarrhythmia and coronary artery disease.

Bradyarrhythmias	Coronary artery disease (Total = 100)		p value
	Absent ($n = 55$)	Present ($n = 45$)	
Complete heart block [n (%)]	29 (52.72%)	29 (64.44%)	0.374
Sinus node dysfunction [n (%)]	7 (12.72%)	4 (8.89%)	
Second degree heart block [n (%)]	4 (7.27%)	5 (11.11%)	
Trifasicular block [n (%)]	2 (3.64%)	3 (6.67%)	
Bifasicular block [n (%)]	13 (23.64%)	4 (8.89%)	

n – number; % – percentage.

Table 4
Correlation between number of risk factors and coronary artery disease.

Number of risk factors	Coronary artery disease (Total = 100)		*p* value
	Absent (*n* = 55)	Present (*n* = 45)	
Two [*n* (%)]	36 (65.45%)	36 (80.00%)	0.228
Three [*n* (%)]	15 (27.27%)	8 (17.78%)	
Four [*n* (%)]	4 (7.27%)	1 (2.22%)	

n – number; % – percentage.

4. Discussion

The main findings of our study were:

i. Angiographic CAD was observed in nearly half (45%) of the patients requiring permanent pacemaker implantation for symptomatic bradyarrhythmias and risk factors for CAD, and nearly one third (29%) had obstructive CAD.
ii. In patients with obstructive CAD, Type IV and Type II coronary anatomies (according to Mosseri et al.'s classification) were most common (48.3% and 34.5% respectively).
iii. Presence of CAD was significantly correlated with dyslipidemia (*p* = 0.047), history of smoking (*p* = 0.025), and family history of CAD (*p* = 0.004).

Bradyarrhythmias and conduction system disorders are prevalent among middle age and elderly population and many of these patients are also at high risk of having CAD. Bradyarrhythmia is often observed in patients with acute myocardial infarction or coronary artery bypass graft, and in patients experiencing transient exercise-induced ischemia.[15–18] Conversely, the prevalence of CAD in chronic conduction disorders has been reported to be 15–70%, depending on patients' characteristics, diagnostic modality and criteria used to define CAD.[7–10] In a necropsy series of 100 patients with chronic heart block, Davies MJ reported that only 15% of the patients had CAD of sufficient severity to account for the heart block.[7] Hsueh et al. performed coronary angiography non selectively in 113 patients with symptomatic bradyarrhythmias and found incident CAD in 20% of these patients.[8] Brueck et al., in an angiographic study of 507 patients requiring pacemaker implantation and at least one atherosclerotic risk factor, found a remarkable 71% incidence of CAD in such patients.[9] Our study revealed an overall 45% incidence of CAD and 29% incidence of significant CAD in these patients. Considering all these data together, we conclude that although chronic CAD is not considered to be a dominant cause of conduction system disturbances in current clinical practice, the incidence of CAD in patients with symptomatic bradyarrhythmias requiring permanent pacemaker implantation and risk factors for CAD is quite high. Although the justification of performing invasive coronary angiography could be debated (considering its cost and risks), we suggest some form of CAD screening in these patients, before pacemaker implantation. The diagnosis of CAD in this patient group has potentially significant clinical implications. First, CAD may have an etiological role in the genesis of these rhythm disturbances. According to the previous studies, one-third of patients with sinus node dysfunction and 15% of patients with chronic atrioventricular block could be attributed to the underlying chronic CAD.[7,19] Having said that, revascularization in patients with coexistent CAD and conduction disorders has been shown to have little or no impact on the reversibility of conduction disturbances in all but one study.[20–23] It is widely believed that the ischemic damage to the conduction system in chronic CAD is permanent and does not reverse with revascularization. However, a study conducted by Zhong et al. in patients with 'symptom-free' bradyarrhythmias and associated significant CAD demonstrated that PCI delayed the demand for pacemaker implantation among these patients when compared to a similar control group who did not undergo revascularization.[23] Given the results of this study and the fact the 29% of our patients had obstructive CAD, it would be worthwhile to perform a randomized case control study among Indian patients who have significant CAD and conduction system disturbances, that do not immediately require pacemaker implantation, to see the effect of revascularization on the same. Second, concomitant CAD has a major prognostic impact on these patients. Although symptoms related to bradycardia improve in most patients after pacemaker implantation, those with coexistent CAD have worse outcomes in the long-term.[12,24,25] Risk factor modification, guideline directed medical therapy and revascularization, when indicated, is likely to reduce CAD related mortality and morbidity in these patients. Finally, after permanent pacing, certain other issues among patients with coexistent CAD deserve attention. The distorted electrocardiography of a pacemaker-dependent patient makes it invalid for the diagnosis of myocardial ischemia or infarction, making it compulsory to use alternative and more expensive modalities for such purposes. Additionally, increased or fixed heart rate, a loss of AV synchrony, and abnormal contraction and relaxation patterns of the left ventricle after cardiac pacing may aggravate underlying myocardial ischemia.[26,27] Hence, in patients with symptomatic bradyarrhythmia demanding permanent pacemaker implantation, early diagnosis of coexistent CAD is important for adequate pacemaker-mode selection and better patient care.

In an attempt to characterize the coronary anatomy in patients on permanent artificial pacemakers, Mosseri et al. devised a classification (described in Section 2.3), keeping in mind the blood supply of the various components of cardiac conduction system.[11] In their initial study, they found that Type II and Type IV pathological coronary anatomies, compromising blood flow to the septal branches of LAD or both septal branches and RCA respectively, were most frequently observed in these patients. This was subsequently confirmed in other studies by Tandogan et al.,[28] Yesil et al.,[29] and Wei et al.[30] Our study revealed that Type IV coronary anatomy was most common (48.3%) followed by Type II anatomy (34.5%), while Type III and Type I were relatively uncommon, accounting for 10.3% and 6.9% cases of obstructive CAD respectively. These findings were consistent with previous studies. We also found that presence of CAD in these patients was significantly correlated with dyslipidemia, history of smoking, and family history of CAD. Hence, the presence of these risk factors should further prompt us to perform coronary work-up in such patients. Also, presence of CAD had no significant correlation with age, presence of diabetes, hypertension, obesity or past history of ASCVD (known to be strongly associated with CAD). Whether this lack of significant association was due to small sample size or ethnic attributes of Kashmiri population needs to be confirmed by larger studies. To conclude, we would like to stress that even though the conduction disturbances may not reverse with revascularization, appropriate management CAD with pharmacological or non-pharmacological therapy is likely to improve the long term outlook of these patients.

5. Conclusion

Angiographic CAD is observed in a substantial proportion of patients with symptomatic bradyarrhythmias and risk factors for CAD. It could be argued that these patients should undergo a coronary work-up before pacemaker implantation. Diagnosis and appropriate management of concomitant CAD is likely to improve

the long term prognosis of these patients, over and above the benefits derived from pacing.

6. Limitations

The present study had some important limitations. First, this was a single center study with a small sample size, and there was no control group. Therefore, extrapolation of these results to general population requires further validation from larger prospective multi-center studies. Second, only patients who were admitted for permanent pacemaker implantation were included in the study. The association of CAD with asymptomatic and less severe conduction disturbances needs to be studied further. Lastly, we did not assess the effect of revascularization on the outcome of these patients. Long term follow up needs to be done to quantify the prognostic benefit derived from revascularization in this patient group.

Conflicts of interest

The authors have none to declare.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.ihj.2016.06.013.

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