Heart, Lung and Circulation (2019) **28,** 272–276
1443-9506/04/$36.00
https://doi.org/10.1016/j.hlc.2017.12.005

ORIGINAL ARTICLE

Outcomes of Heart Block in Myocarditis: A Review of 31,760 Patients

Gbolahan O. Ogunbayo, MD [a*], Samy-Claude Elayi, MD [a], Le Dung Ha, MD [b], Odunayo Olorunfemi, MD [b], Ayman Elbadawi, MD [b], Deola Saheed, MD [c], Vincent L. Sorrell, MD [a]

[a]Gill Heart Institute, University of Kentucky, Lexington, KY, USA
[b]Rochester General Hospital, Rochester, NY, USA
[c]Cooper University Hospital, Camden, NJ, USA

Received 15 April 2017; received in revised form 7 October 2017; accepted 8 December 2017; online published-ahead-of-print 24 December 2017

Background Various electrocardiographic abnormalities, including atrioventricular conduction block, have been reported in patients with myocarditis. We performed an observation study to describe the characteristics and outcomes of inpatients diagnosed with myocarditis complicated by heart block (HB) in a large national cohort.

Methods We identified patients with primary ICD-9 codes for myocarditis HB from the Nationwide Inpatient Sample (NIS) Database from 1998 to 2013. We compared the baseline characteristics and compared clinical outcomes between patients with and without HB, and in patients with/without high degree atrioventricular block (HDAVB).

Results From the NIS database, 31,760 patients had a principal diagnosis of myocarditis and HB was reported in 1.7% of these patients (n = 540). Female gender and Asian race were independently associated with HB. Out of 540 patients, 363 patients had HDAVB (67.2%) and 177 patients had not advanced HB (32.8%). Not advanced HB was not associated with an increased mortality rate compared to patients without HB (0% vs. 2.7%, $p = 0.315$). On the other hand, the incidence of cardiogenic shock, respiratory failure and renal failure were higher in patients with HDAVB (26.2% vs. 5.0%, 33.9% vs. 5.9% and 29.2% vs. 5.5%, $p < 0.001$ respectively). Patients with HDAVB required more procedural support (incidence of intra-aortic balloon pump 17.8% vs. 3.3%). They also had significantly longer lengths of hospital stay (9.4 ± 9.4 vs. 4.3 ± 8.4, $p < 0.001$) and higher mortality (15.5% vs. 2.7%, $p < 0.001$). Compared to myocarditis patients without HB, the odds for mortality in myocarditis patients with HDAVB 1.58 (95% CI = 1.03–2.49, $p = 0.039$).

Conclusions The incidence of HB and HDAVB among patients with acute myocarditis was 1.7% and 1.1% respectively. Female gender and Asian race were both independently associated with significant odds for the occurrence of HB and HDAVB. High degree atrioventricular block was independently associated with increased morbidity and mortality.

Keywords Myocarditis • Heart block • High degree atrioventricular block

*Corresponding author at: Division of Cardiovascular Medicine, University of Kentucky, 326C.T. Wethington Bldg., 900 South Limestone Street, Lexington, KY 40536-0200. Tel.: +773 501 7532; fax: +859 323 6475., Email: gbolahanogunbayo@yahoo.com

Introduction

Various electrocardiographic abnormalities have been reported in patients with myocarditis [1–5]. These include abnormalities in the ST-T wave segment, Q waves, atrioventricular block (AV block) or bundle branch blocks [1,5]. The aim of this study was to describe the clinical characteristics and outcomes of patients with myocarditis complicated by HB in a large national database in the USA.

Methods

Patients 18 years and older with primary ICD-9 codes for myocarditis (422.0, 422.90–422.93, 422.99 and 429.0) were identified and extracted from the NIS database from1998 to 2013. The primary diagnosis was used because this was the diagnosis responsible for hospital admission (after clinical assessment and diagnostic testing). According to the Agency for Health Research and Quality (AHRQ), the primary diagnosis is derived after the record of the patient's admission is reviewed and this primary diagnosis is the established condition chiefly responsible for that hospitalisation [6]. Furthermore, patients with secondary ICD 9-DM codes for HB (First degree AV block, 426.11; Mobitz type II Second degree AV block, 426.12; Other Second degree AV block, 426.13; Complete AV block, 426.0) were identified. National estimates were estimated using the trend weights provided with the database.

We compared the baseline characteristics and outcomes of patients with myocarditis and HB to patients with myocarditis but no HB. We also described outcomes in patients with high degree atrioventricular block (HDAVB), i.e. complete HB and second degree Mobitz type II HB.

Continuous variables were reported as means and standard deviations while dichotomous variables were reported as counts with percentages. The Pearson's chi-square and Analysis of variance (ANOVA) tests were used to determine between-group differences for dichotomous and continuous variables respectively. We applied adjusted logistic regression analysis to describe the relationship between variables that were significant in univariate analysis and in-hospital mortality from HB. We determined statistical significance at $p < 0.05$. We used the SPSS software (IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp Released 2016) for our statistical analyses. The office of research integrity of our institution deemed this study exempt for review as the database does not contain any of the 18 Health Insurance Portability and Accountability Act (HIPAA) patient identifiers.

Results

Patient Population

From the NIS database, we identified 31,760 patients with a primary diagnosis of myocarditis. The average age of these patients was 45.7 ± 17.1 years and 62.3% (n = 19,756) were female. Heart block was reported in 540 (1.7%) of these patients. Not advanced HB was documented in 117 patients with first-degree HB (21.6%) and 60 patients with not-advanced second-degree HB (11.2%). The remaining patients (363 patients, 67.2%) were reported to have HDAVB (Figure 1).

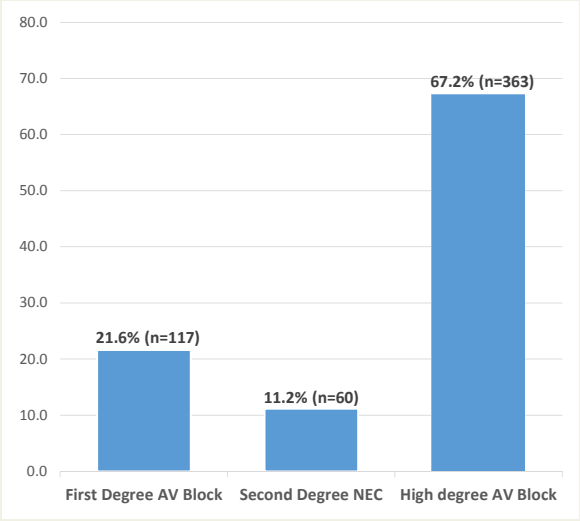

Figure 1 Distribution of types of Heart Block. Abbreviation: NEC, Not elsewhere classified

Myocarditis patients with HB were older (45.7 ± 17.1 years vs. 42.1 ± 17.5 years, $p < 0.001$) and had more females (49.1% vs. 37.5%, $p = 0.012$). A significantly higher proportion of Asians were reported to have HB (9.3% vs. 1.6%, $p < 0.001$) (Table 1). The two subgroups [female gender (OR: 1.32, 95% CI 1.09-1.59, $p = 0.004$), Asian race (OR: 4.69, 95% CI 3.33-6.61; $p < 0.001$)] had significant odds for HB.

Myocarditis Patients With and Without Not-Advanced HB

There was no documented case of in-hospital mortality for myocarditis patients with not-advanced HB. The incidence of cardiogenic shock (8.6% vs. 4.9%, $p = 0.311$), respiratory failure (3% vs. 5.9%, $p = 0.458$), acute renal failure (5.8% vs. 5.5%, $p = 0.924$) and cardiac arrest (0% vs. 1.7%, $p = 0.513$) were comparable between myocarditis patients with and without not advanced HB (Table 2). Compared to patients without HB, patients with not-advanced HB were comparable in terms of requirements for mechanical circulatory support with intra-aortic balloon pump (IABP) (2.9% vs. 3.3%, $p = 0.88$), steroid therapy (0% vs. 0.2%, $p = 0.793$), mechanical ventilation (5.7% vs. 6.0%, $p = 0.943$), as well as acute dialysis (5.8% vs. 5.9%, $p = 0.976$) (Table 2).

Myocarditis Patients With and Without HDAVB

Sixty-seven per cent (n = 363 out of 540) of patients with HB were reported to have HDAVB (1.1% of patients with myocarditis). There were more females (56.3% vs. 37.5%, $p = 0.001$) and Asians (12.5% vs. 1.6%, $p < 0.001$) compared

Table 1 **Baseline Characteristics of patients with Myocarditis with and without HB/HDAVB.**

Variables	Myocarditis						Heart Block		
	HDAVB n = 363 (1.1%)	No HDAVB n = 31,397	P Value	HB n = 540 (1.7%)	No HB n = 31,220 (98.3%)	P Value	HDAVB n = 363 (67.2%)	No HDAVB n = 177 (32.8%)	P Value
Age	45.8 ± 17.3	42.1 ± 17.5	<0.001	45.7 ± 17.3	42.1 ± 17.5	<0.001	45.8 ± 17.3	45.4 ± 16.8	<0.001
18-39	117 (32.3)	15934 (50.8)	0.001	179 (33.2)	15872 (50.8)	<0.001	117 (32.3)	62 (35.1)	0.767
40-64	203 (56.0)	11428 (36.4)	<0.001	291 (54.0)	11339 (36.3)	<0.001	203 (56.0)	88 (49.9)	0.544
>65	43 (11.8)	4035 (12.9)	0.786	70 (12.9)	4008 (12.8)	0.991	43 (11.8)	27 (15.1)	0.627
Female	204 (56.3)	11773 (37.5)	0.001	265 (49.1)	11712 (37.5)	0.012	204 (56.3)	61 (34.4)	0.03
Race									
Caucasian	171 (47.2)	17078 (54.4)	0.212	244 (45.1)	17006 (54.5)	0.049	171 (47.2)	72 (40.9)	0.527
Black	30 (8.3)	2976 (9.5)	0.726	40 (7.5)	2966 (9.5)	0.468	30 (8.3)	10 (5.8)	0.639
Hispanic	16 (4.3)	2644 (8.4)	0.198	30 (5.6)	2630 (8.4)	0.276	16 (4.3)	14 (8.1)	0.407
Asian/Pacific Islander	45 (12.5)	510 (1.6)	<0.001	50 (9.3)	505 (1.6)	<0.001	45 (12.5)	5 (2.9)	0.103
Co-morbidities									
Hypertension	67 (18.4)	8142 (25.9)	0.139	125 (23.2)	8084 (25.9)	0.521	67 (18.4)	58 (33.0)	0.087
Diabetes mellitus	19 (5.2)	2656 (8.5)	0.31	35 (6.5)	2640 (8.5)	0.47	19 (5.2)	17 (9.3)	0.408
Coronary artery disease	34 (9.3)	5034 (16.0)	0.114	65 (12.1)	5003 (16.0)	0.256	34 (9.3)	31 (17.7)	0.205
Congestive heart failure	191 (52.5)	7443 (23.7)	<0.001	256 (47.4)	7377 (23.6)	<0.001	191 (52.5)	65 (36.8)	0.12
Atrial fibrillation/ Atrial flutter	72 (19.8)	2154 (6.9)	<0.001	110 (20.4)	2117 (6.8)	<0.001	72 (19.8)	38 (21.5)	0.658

Abbreviations: HDAVB, High-degree atrioventricular block; HB, heart block.

Table 2 **Inpatient morbidity and mortality and procedure requirement for myocarditis patients with and without not-advanced HB, HDAVB and all types of HB.**

	Not advanced HB (n = 177)			HDAVB (n = 363)		
	Not advanced HB n = 177 (0.6%)	No HB n = 31,220 (98.3%)	P Value	HDAVB n = 363 (1.1%)	No HB n = 31,220 (98.3%)	P Value
Inpatient mortality	0 (0)	834 (2.7)	0.315	56 (15.5)	834 (2.7)	<0.001
Cardiogenic shock	15 (8.6)	1541 (4.9)	0.311	95 (26.2)	1541 (4.9)	<0.001
Cardiac Arrest	0 (0)	523 (1.7)	0.513	63 (17.4)	523 (1.7)	<0.001
Respiratory failure	5 (3)	1841 (5.9)	0.458	123 (33.9)	1841 (5.9)	<0.001
Acute renal failure	10 (5.8)	1706 (5.5)	0.924	106 (29.2)	1706 (5.5)	<0.001
Pericardial effusion	13 (7.6)	1704 (5.5)	0.566	21 (5.7)	1704 (5.5)	0.926
Procedures						
Balloon counterpulsation	5 (2.9)	1032 (3.3)	0.88	65 (17.8)	1032 (3.3)	<0.001
Extracorporeal membrane oxygenation	0 (0)	69 (0.2)	0.776	5 (1.4)	69 (0.2)	0.033
Injection of steroid	0 (0)	58 (0.2)	0.793	10 (2.7)	58 (0.2)	<0.001
Intubation/Mechanical ventilation	10 (5.7)	1870 (6.0)	0.943	128 (35.3)	1870 (6.0)	<0.001
Haemodialysis for acute renal failure	10 (5.8)	1856 (5.9)	0.976	106 (29.2)	1856 (5.9)	<0.001
Temporary pacemaker	0 (0)	97 (0.3)	0.734	155 (42.6)	97 (0.3)	<0.001
Permanent Pacemaker	0 (0)	62 (0.2)	0.786	72 (19.7)	62 (0.2)	<0.001

Abbreviations: HDAVB, High-degree atrioventricular block; HB, heart block.

Table 3 Inpatient morbidity and mortality and procedure requirement for myocarditis with HDAVB vs. not-advanced HB.

	HDAVB n = 363 (67.2%)	Not advanced HB n = 177 (32.8%)	P Value
Inpatient mortality	56 (15.5)	0	0.012
Cardiogenic shock	95 (26.2)	15 (8.6)	0.03
Cardiac Arrest	63 (17.4)	0	<0.001
Respiratory failure	123 (33.9)	5 (3.0)	<0.001
Acute renal failure	106 (29.2)	10 (5.8)	0.005
Pericardial effusion	21 (5.7)	13 (7.6)	0.699
Procedures			
Balloon counterpulsation	65 (17.8)	5 (2.9)	0.027
Extracorporeal membrane oxygenation	5 (1.4)	0	0.471
Injection of steroid	10 (2.7)	0	0.319
Intubation/Mechanical ventilation	128 (35.3)	10 (5.7)	0.001
Haemodialysis for acute renal failure	106 (29.2)	10 (5.8)	0.005
Temporary pacemaker	155 (42.6)	0	<0.001
Permanent Pacemaker	72 (19.7)	0	0.004

Abbreviations: HDAVB, High-degree atrioventricular block; HB, heart block.

to patients without HDAVB. The incidence of cardiogenic shock, respiratory failure and acute renal failure were higher in this subgroup (26.2% vs. 4.9%, 33.9% vs. 5.9% and 29.2% vs. 5.5%, $p < 0.001$ respectively) (Table 2). These patients were also more likely to receive advanced mechanical circulatory support (IABP 17.8% vs. 3.3%, $p < 0.001$), steroid therapy (2.7% vs. 0.2%), mechanical ventilation (35.3% vs. 6.0%, $p < 0.001$) and acute dialysis (29.2% vs 5.9%). These patients also had a mean longer length of hospital stay (9.4 ± 9.4 days vs. 4.3 ± 8.4 days, $p < 0.001$ and higher mortality (15.5% vs. 2.7%, $p < 0.001$).

The group of 540 patients with HB was sicker and had higher mortality (10.4% vs. 2.7%, $p < 0.001$) compared to patients without HB. It should be emphasised that this difference in morbidity and mortality could be attributed to the subgroup of patients with HDAVB. Overall, when adjusted for age, gender and comorbidities (hypertension, diabetes mellitis (DM), congestive heart failure (CHF), coronary artery disease (CAD), chronic kidney disease (CKD), atrial fibrillation/flutter), indicators of disease severity (cardiogenic shock, respiratory failure, acute renal failure, cardiac arrest, acute myocardial infarction, stroke/transient ischaemia attack, acute haemodialysis, use of mechanical circulatory support), the odds for mortality in myocarditis patients with HDAVB compared to patients without HB was significant at 1.58 (95% CI = 1.03-2.49, $p = 0.039$). Also, there was no statistical difference in mortality in patients with not-advanced HB compared to without HB.

Myocarditis Patients With Not Advanced AV Block vs. HDAVB

Compared to patients with not advanced AV block, myocarditis patients with HDAVB are sicker with a higher prevalence of cardiogenic shock (26.2% vs. 8.6%, $p = 0.03$), respiratory failure (33.9% vs. 3%, $p < 0.001$) and acute renal failure (29.2% vs. 5.8%, $p = 0.005$) (Table 3). All the 56 mortality cases occurred in the HDAVB group. None of the myocarditis patients with not advanced AV block required steroid therapy or pacemaker placement during their hospital stay. On the other hand, 155 and 72 out of 363 of myocarditis patients with HDAVB underwent temporary and permanent pacemaker placement, respectively (Table 2).

Discussion

Electrocardiographic changes in the heart are not uncommon in myocarditis [2]. In a small study by Nakashima et al., all the 11 patients studied had ST-T wave changes on electrocardiogram. More than half (55%) of these people had AV block [5]. The incidence of HB in patients with myocarditis in our study was 1.7%. The population distribution in our study is similar to previous studies. The mean age of patients with myocarditis studied by Magnani was 47.3 ± 15.7years [7], which is similar to findings in this study. A higher female proportion was also reported in a study by Pulerwitz et al., [8] The reason for a higher proportion of HB and HDAVB among Asians, however, is unclear and needs to be studied further. Higher mortality among patients with HB underscores the burden of this complication in patients with myocarditis. More specifically, all the patients with HB and myocarditis that died had HDAVB.

Of those myocarditis patients with HDAVB who survived to hospital discharge (n = 307), 72 patients (23.5%) received a permanent pacemaker. It is possible that HDAVB was transient in some of these patients and resolved without the need for a permanent pacemaker. The possible transient nature of some HBs is supported by other studies. In a study, 9 of the 11

patients that developed HDAVB experienced resolution within a median time of 5 days [9]. Another review of literature in the paediatric population recorded patients less than 20 years of age with the diagnosis of myocarditis and atrioventricular block. Out of 40 reported cases, 27 patients (67%) were reported to have resolution of HB (with unspecified degree) with an average duration of 3.3 days [10]. This was also the conclusion in other studies, albeit mostly from the paediatric population [10,11].

From the physiologic standpoint, it is conceivable that inflammation and swelling infiltrate the AV node, creating some temporary AV nodal HB that can resolve during the healing process. A similar phenomenon can occur in inferior myocardial infarction (MI), where the initial ischaemia of the AV node creates complete HB that typically resolves within a few days. However, infiltration of the His Purkinje system may result in permanent scarring and infrahisian block that would be life threatening and may not resolve. Some studies have described other clinical, histopathological and biochemical predictors of morbidity and mortality in patients with myocarditis [2,7,8,12–15], this study specifically describes the burden of HB and HDAVB on patients with myocarditis.

Limitations

This is a retrospective study conducted from the largest publicly available hospital care data with discharge-level information and subject to limitations associated with retrospective studies including the possibility of omission and bias. The database does not contain laboratory results and therefore severity of illness could only be assessed using ICD codes, the true incidence of which may be underestimated due to coding bias. The database is limited to in-hospital events and does not include clinical information such as symptoms from heart failure or HB, or pharmacological treatment. We also could not obtain data on the number of patients with a previously implanted pacemaker before the hospitalisation.

The incidence of other benign HB like first degree AV block was low in the study. It is unclear if they were not documented because of the absence of clinical usefulness from the management perspective. Additionally, the findings in this study can only assume association and cannot determine causality of mortality from HB. The level of the AV block (nodal versus infra-nodal) was also never specified, a finding that carries a prognostic value. Finally, data regarding the patients' baseline electrocardiogram rhythm were not available. Hence, we were unable to determine if the HB was newly developed.

Conclusion

This study reported an incidence of 1.7% for HB and 1.1% for HDAVB in patients with myocarditis. Female gender and Asian race were independently associated with odds for occurrence of both HB and HDAVB. High degree atrioventricular block is independently associated with increased odds for mortality in patients with acute myocarditis.

Grant Support

None.

Conflicts of Interest

None.

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