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Diagnostic Yield of Cardiovascular Magnetic Resonance in Young-Middle Aged Patients with High-Grade Atrio-Ventricular Block

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Conflict of interest

Keywords

List of abbreviations

AVB   Atrio-ventricular block

CMR   Cardiovascular magnetic resonance

ECG   Electrocardiogram

IHD   Ischemic heart disease

LGE   Late gadolinium enhancement

LMNA Lamin A/C

LV   Left ventricle

NIHD   Non-ischemic heart disease

PM   Pace-maker

RV   Right ventricle

TAVI   Trans-catheter aortic valve implantation

TTE   Transthoracic echocardiogram

Abstract

Background: Atrio-ventricular block (AVB) is a rare finding in young or middle-aged adults, often leading to pacemaker implantation (PM) without further investigation. We sought to assess the diagnostic role of cardiovascular magnetic resonance (CMR) in young and middle-aged adults with high-grade AVB.

Methods: We consecutively enrolled young-middle aged (18-65yrs) patients with high grade AVB referred to CMR after standard clinical assessment (history, electrocardiogram and cardiac rhythm monitoring) prior to PM implantation. Cine and post-contrast imaging were performed in a 1.5T scanner.

Results: 34 patients (59% male, mean age 42 ±12 years) with high grade AVB were referred to CMR for suspected ischemic heart disease (IHD)(n=4) and non-ischemic heart disease (NIHD)(n=20); no clear cause was found in 9 patients prior to CMR and 1 patient had suspected lung disease. A pathologic substrate was found on CMR in 15 patients (44%), while a structurally normal heart was reported in 18 (53%). Non-specific findings were reported in 1 patient (3%). There was a fair agreement between CMR and echocardiographic findings (Cohen's kappa 0.243), and CMR provided an entirely new diagnosis in 34% of patients. As compared to the standard clinical assessment, CMR had an additional role in 65% of patients and guided further testing (genetic testing, extra-cardiac imaging) in 9%.

Conclusions: CMR found a pathologic substrate in 44% of patients, mainly NIHD (32%). Half of patients (53%) had a structurally normal heart. When added to the

standard clinical assessment, CMR had an incremental diagnostic role in two thirds of patients.

Introduction

Atrio-ventricular block (AVB) typically shows a bimodal distribution, with a major peak in incidence in the elderly, commonly due to degeneration of the conduction system, and the other in infancy and early childhood, when it is mainly congenital. While the lower-grade AVB is considered benign as it can be observed in up to 1–2% of healthy young people, especially during sleep [1], the higher-grade AVB, such as second degree Mobitz II or complete AVB, is expression of the severity of the underlying cause and more often requires a pacemaker (PM) implantation [2]. Higher grade AVB is uncommon in young or middle-aged adults, but when identified it poses a dilemma, both in terms of diagnosis and clinical management. According to international guidelines [2], patients are frequently offered permanent PM implantation without further investigation, and up to 3-5% of all the patients undergoing PM implantation for AVB are aged 18-55 years [3,4]. PM implantation in young adults is generally recognized as a safe procedure, but it has been associated with peri- and post-procedural complications [5,6]. Ischemic, autoimmune and infiltrative diseases are the recognized causes of complete AVB in young or middle-aged adults [5,6]. Correct identification of the underlying pathophysiologic mechanism has a great impact both on therapeutic strategies and on the prognosis of AVB [4,7]. International guidelines recommend the clinical assessment of patients, comprehensive of clinical history, ECG and cardiac rhythm monitoring, but do not provide indications with regards to the need for cardiac imaging prior to treatment [2]. Cardiac magnetic resonance (CMR) is a well-established diagnostic imaging technique with increasing applications in clinical practice: CMR represents the gold standard for the assessment of biventricular volumes and function [8] and offers a uniquely advanced,

non-invasive, myocardial tissue characterization, providing an accurate assessment of myocardial fibrosis by late gadolinium enhancement, which has been validated against histology [9,10] . We sought to assess the diagnostic role of CMR in young and middle-aged adults with high-grade AVB.

Materials and Methods

We retrospectively enrolled consecutive young and middle-age patients (aged 18-65 years) referred for CMR prior to PM implantation because of higher-grade AVB. Higher-grade AVB was defined as advanced II degree AVB (Mobitz II AVB, 2:1 AVB) and complete or III degree AVB. All patients underwent a 1.5T CMR (Avanto, Siemens Healthcare, Germany), with a comprehensive protocol that included long and short axis cine and late gadolinium enhancement (LGE) images. Steady state free precession sequences were performed to acquire the long and short axis cine images; typical parameters were TR 38 ms, TE 1.07 ms, flip angle 80°, slice-thickness 8 mm, inter-slice gap 0 mm, bandwidth 930 Hz/Px, voxel size 2.0x2.0x8.0 mm and temporal resolution ≤45 ms between phases. For LGE imaging, a standard inversion recovery gradient-echo sequence was adopted. The LGE images were acquired 10-15 minutes after intravenous injection of 0.1 mmol/Kg of body weight of gadolinium-chelate contrast agent (Gadovist 1.0 mmol/ml, Bayer-Schering, Berlin, Germany) in identical short-axis planes to cine images, using an inversion recovery prepared breath-hold gradient-echo technique. Typical image parameters were TR 700 ms, TE 3.15 ms; flip angle 25°; slice thickness 8.0 mm, no interslice gap, bandwidth 140 Hz/Px and voxel size $2.0 \times 1.5 \times 8.0$ mm. The inversion time was progressively optimized to null normal myocardium (typical values,

250–350 ms). Each slice was obtained during a breath-hold of 10–15 s depending on the patient's heart rate.

Ventricular function was assessed with dedicated software (Circle Cardiovascular Imaging, Calgary, Canada), by tracing endo- and epicardial borders on each short axis cine slice in end-diastole and end-systole. All volumes measurements were indexed to body surface area. The presence/absence, localization, and distribution pattern of LGE were assessed visually by a SCMR/ESC level 3 certified individual with > 10 years of experience. Pattern and extent of LGE were assessed by using short- and long-axis views and were defined as present only if they were detectable in two orthogonal planes. The pattern of LGE distribution was defined as subendocardial or transmural, if involving <50% or ≥50% of wall thickness, respectively, and as mid-wall/epicardial if patchy/spotty intra-mural or sub-epicardial enhancement was detected. The presence of LGE at the right ventricle/left ventricle insertion points, in the absence of other LGE distribution patterns, was defined as non-specific findings, as its diagnostic and prognostic meaning is still unclear. All the analysis was carried out in accordance with the recommendation of the Society for Cardiovascular Magnetic Resonance [11]. Based on a standard clinical assessment, including clinical history, ECG and cardiac rhythm monitoring, all patients were referred with a pre-CMR working diagnosis, classified as ischemic heart disease (IHD), non-ischemic heart disease (NIHD), normal heart and unknown cause. The study was reviewed by the local Institutional Research and Innovation Department and in view of the retrospective design of the study, formal ethical approval was waived off. All patients gave written informed consent.

Statistical analysis

Continuous and categorical variables are expressed as mean±SD or median (IQR), and n (%), respectively. Categorical variables were compared by using the chi-square test or Fisher exact test, as appropriate. Inter-rater agreement for categorical variables was assessed by Cohen's kappa coefficient. A p-value of <0.05 was considered statistically significant. Data were analysed with SPSS® version 23 (IBM®).

Results

We consecutively enrolled thirty-four patients (59% male, mean age 42 ±12 years, minimum-maximum 21-61 years) referred to CMR prior to PM implantation secondary to higher grade AVB. Twenty-two patients (65%) had evidence of complete AVB and 12 patients (35%) had second degree Mobitz II AVB. Twenty-three patients (68%) showed intermittent high grade AVB on 24 hours Holter monitoring or on implantable loop recorder monitoring. Eleven patients (32%), all but one presenting with III degree AVB, were admitted to hospital following syncope; they were all haemodynamically stable and underwent CMR as inpatients. Based on the standard clinical assessment, 4 patients were referred for suspected ischemic heart disease (IHD) and 20 for suspected NIHD; no clear cause was identified in 9 patients prior to CMR and one patient had suspected interstitial lung disease. Median LVEF was 64% (IQR 58-68), median indexed left ventricular end-diastolic volume (LVEDV) was 88 ml/m^2 (IQR 77-109) and median indexed left ventricular end-systolic volume (LVESV) was 31 ml/m^2 (IQR 27-54). On tissue characterization, LGE was found in twelve patients (35%), mainly with a mid-wall/epicardial pattern (7/12 patients, 58%); LGE had a septal distribution in 5 patients (42%). Based on CMR findings, a pathologic substrate was found in 15 patients (44%): 4

patients (12%) were diagnosed with IHD and 11 (32%) with NIHD. A structurally normal heart was found in 18 patients (53%) and non-specific findings were reported in 1 patient (3%). Among patients presenting findings consistent with NIHD, myocarditis was the most common (5 patients, of which 2 were diagnosed with cardiac sarcoidosis, Figure 1A and B), followed by athlete's heart and valvular heart disease (moderate aortic regurgitation and severe pulmonary regurgitation) which were each reported in 2 patients, respectively; dilated cardiomyopathy (Figure 1C and D) and left ventricular non-compaction were each found in 1 patient. CMR findings are listed in Table 1.

Standard clinical assessment *vs* CMR findings

Based on clinical and family history and on ECG findings, IHD was suspected prior to cardiac imaging in 4 patients and NIHD in 20 patients; no clear cause could be identified in 9 patients and 1 patient was diagnosed with suspected lung disease. CMR had an additional role in re-defining the final findings in 22/34 (65%) patients, mainly by re-defining the final diagnosis in 4 patients and by ruling out an underlying structural heart disease in 18 patients (Table 2). Among the 20 patients with a pre-imaging diagnosis of suspected NIHD, CMR diagnosed IHD in 2 patients and found a structurally normal heart in 9 patients. Among the 9 patients with no clear cause for AVB prior to imaging, CMR found a structurally normal heart in 7 patients and NIHD in one.

Diagnostic performance of CMR and TTE

Trans-thoracic echocardiogram (TTE) data were available in 29/34 patients (85%). A pathologic substrate was found on TTE in 3/29 patients (10%): one patient (3%) was

diagnosed with IHD and 2 (7%) with NIHD. There was no significant difference between the ability of CMR and TTE to identify a pathologic substrate, but there was a trend in favour of CMR (15/34 vs 3/29, p=0.539). A structurally normal heart was found on TTE in 21 patients (73%) and non-specific findings were reported in 5 patients (17%). CMR and TTE provided the same diagnosis in 17/29 patients (59%) with an overall fair agreement (Cohen's kappa 0.243, p=0.019); CMR had mainly a role in re-defining patients diagnosed with normal heart and those with non-specific findings on TTE, overall providing a new diagnosis in 10/29 patients (34%). Out of 21 patients diagnosed with normal heart on TTE, 5 (24%) received a different diagnosis on CMR: one patient had findings of IHD and 4 of NIHD. CMR was diagnostic in all 5 patients with non-specific findings on TTE: three patients had findings consistent with NIHD, one with IHD and one with structurally normal heart (Table 3).

Discussion

The main findings of our study were: 1) CMR identified an underlying pathologic substrate in nearly half of patients, 2) the most prevalent underlying conditions was NIHD (32%); 3) CMR demonstrated a significant incremental diagnostic value (in 65% of patients) when added to standard clinical work-up of patients with AVB; 4) when added to transthoracic echocardiography CMR provided an entirely new diagnosis in 34% of patients.

Higher grade AVB is rare in young or middle-aged adults and the underlying etiologic mechanisms are multiple and different from the degenerative process mainly responsible for AVB in the elderly [12]. To the best of our knowledge this is the largest study

investigating the role of CMR in patients with high-grade AVB, and its added value to the current standard clinical practice. In our cohort, CMR could identify an underlying pathologic substrate in nearly half of patients (44%). We found a 12% incidence of IHD, which is in keeping with previous studies on middle-aged (45-65 years) patients presenting with AVB [13] and on patients with severe LV systolic dysfunction after acute myocardial infarction [14]. More than a third (32%) of our patients had evidence of NIHD on CMR; as confirmed by endomyocardial biopsy (EMB) studies in patients with high grade AVB [15-17], we have also found that myocarditis is the most common non-ischemic cardiomyopathy. It has been shown that Lamin A/C gene mutation in dilated cardiomyopathy accounts for 33% of AVB [18] cases, but similar scenarios are also seen in cases of LV non-compaction and hypertrophic cardiomyopathy, as also confirmed in our cohort. Infiltrative diseases are frequently associated with AVB, which often represents the first and most common clinical manifestation, as in the case of cardiac sarcoidosis [19]. Although cardiac sarcoidosis commonly results in AVB, it is a rare disease, and its prevalence in the spectrum of AVB is not well known [20]. Based on CMR findings we diagnosed cardiac sarcoidosis in 2 patients (6%, 18% of the NIHD). Other causes of high grade AVB in young-middle aged patients include cardiac amyloidosis [21,22] and can be rarely encountered among trained athlete's [23,24], where it is usually considered pathological.

CMR *vs* standard of care clinical assessment

In patients presenting with AVB, international guidelines recommend a clinical assessment, comprehensive of clinical history, ECG and cardiac rhythm monitoring, but

there is no indication with regards to the need for cardiac imaging prior to treatment [2]. Patients are thus often offered a PM implantation without further investigation, although the underlying pathology has important implications on prognosis. CMR showed an additional role in 65% of patients when added to the standard clinical assessment, mainly by re-defining the final diagnosis in 4 patients and by ruling out an underlying structural heart disease in 18 patients (Table 2). European guidelines on cardiac pacing [2] do not recommend TTE in the work up of high-grade AVB patients. Nevertheless, nearly all of our patients (85%) underwent a TTE in addition to the standard clinical assessment. TTE could identify a pathologic substrate in 10% of patients, which was lower compared to CMR (44%) although it did not reach statistical significance, most likely because of the small sample size. The agreement between TTE and CMR findings was fair, and CMR provided an entirely new diagnosis in 10/29 (34%) patients, mainly by re-defining diagnosis among patients with a structurally normal heart (5/21, 24%) and being diagnostic in all 5 patients with non-specific findings on TTE.

Clinical Implications

Although CMR did not change the final treatment strategy with regards to AVB, as all patients received a PM, information provided by CMR, as compared to both the standard clinical assessment and TTE, had a clinical impact in patients' management with direct implications on their treatment strategies.

The superior diagnostic capability of CMR in our cohort was mainly related to the analysis of LGE sequences: LGE was found in 35% of patients, mainly with a non-ischemic distribution pattern (58%) and with a septal location in 42% of patients. It is

well established that LGE distribution pattern allows non-invasive identification of the structural aetiology of cardiomyopathies [25-27], with a diagnostic accuracy in some cases exceeding that of trans-thoracic echocardiogram and even of EMB [28]. The advanced tissue characterization provided by CMR has also been shown to allow the identification of genetic variants of common cardiomyopathies [29,30]: a recent study by Holmstrom et al. demonstrated that 88% of asymptomatic or mildly symptomatic carriers of Lamin A/C (LMNA) mutations causing dilated cardiomyopathy had typical myocardial fibrosis, involving the mid-myocardium of the basal septum (Figure 1D, white arrow) [29]. The fibrosis was observed in all individuals with an AV conduction defect and LGE-pattern was typically linear with involvement of less than 50% of the area of the segment. In our series, a patient showed mildly dilated LV with the typical mid-wall fibrosis of the basal antero-septum on CMR (Figure 1D, white arrow): late genetic testing was positive for LMNA mutation. Moreover, in our patients cohort, CMR diagnosis of cardiac sarcoidosis triggered further testing, leading to the finding of extra-cardiac manifestations of the disease in both patients.

Finally, it has been shown that CMR is able to detect myocardial infarction in a non-negligible proportion of patients (approximately one third) in which the diagnosis was missed on non-CMR imaging [31]: although this was not the case in our patients' cohort, finding evidence of unknown IHD on CMR in patients with high-grade AVB might lead to diagnostic invasive coronary angiogram, as underlying coronary artery disease can explain the conduction disorder [13].

Study Limitations

The main limitation of the present study is the limited number of patients; nevertheless, AVB in this age group (18-65 years) is a very rare condition and to our knowledge, this is the first and largest series of young and middle-aged patients with high-grade AVB referred for CMR. Half of our patients were found to have structurally normal hearts. It is acknowledged that transient tissue damage, in the form of reversible myocardial oedema, as in the few Tako-Tsubo cases reported in literature [32,33], may induce atrio-ventricular conduction abnormalities; T2-weighted sequences for myocardial oedema were not performed in our cohort, so transient acute tissue damage could not be assessed. We might speculate that this aspect might explain the high prevalence of structurally normal hearts in our cohort. A structurally normal heart on CMR reflects the absence of gross ischemic or non-ischemic abnormalities, but cannot exclude the presence of microscopic, ultra-structural abnormalities, which are below the resolution of the technique. EMB is the gold standard to assess ultra-structural abnormalities, but carries non-negligible complications, and is not routinely performed in clinical practice, and we had no histologic data in our patients' cohort. Finally, LGE imaging accurately allows the identification and characterization of focal fibrosis; however, exploring the presence of diffuse fibrosis on T1 mapping technique [34] might provide a new insight in the aetiology of high-grade AVB. Further studies, to assess tissue characterization with more advanced sequences, such as the T1 and T2 mapping, could provide additional insight on interstitial changes in this patients' cohort.

Conclusions

In young patients presenting with high grade AVB, CMR demonstrated incremental

diagnostic yield by identifying a pathologic substrate in 44% of patients. There was a fair agreement between CMR and TTE final diagnosis, and CMR provided an entirely new diagnosis in 34% of patients. When added to the standard clinical assessment (history, ECG and cardiac rhythm monitoring) CMR had an additional diagnostic role in two thirds of patients. Our results show that CMR could be a valuable test to be included in the clinical work-up of patients with AVB.

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Tables

Table 1. CMR Findings

CMR Findings	n (%)
LVEF, %, median (IQR)	64 (58-68)
LVEDV, ml/m2, median (IQR)	88 (77-109)
LVESV, ml/m2, median (IQR)	31 (27-54)
LGE, n (%)	12 (35)
Ischemic Heart Disease, n (%)	4 (12)
Non-ischemic Heart Disease, n (%)	11 (32)
- Myocarditis, n	5
- Dilated cardiomyopathy, n	1
- Athlete's heart, n	2
- Aortic/pulmonary valve regurgitation, n	2
- Left ventricular non compaction, n	1
Structurally Normal Heart, n (%)	18 (53)

LVEF, left ventricular ejection fraction; LVEDV, left ventricular end-diastolic volume;

LVESV, left ventricular end-systolic volume; LGE, late gadolinium enhancement.

Table 2. CMR findings vs standard clinical assessment

		CMR				
		IHD	NIHD	Non-specific Findings	Structurally Normal Heart	TOTAL
Standard Clinical Assessment	IHD	2	1	0	1	4
	NIHD	2	9	0	9	20
	Non-specific Findings	0	1	1	7	9
	Other	0	0	0	1	1
	TOTAL	4	11	1	18	34

Comparison between pre-CMR working diagnosis based on the standard clinical

assessment (history, ECG and cardiac rhythm monitoring) and CMR findings. Boxes in

bold show the number of patients that received the same diagnosis before and after CMR.

CMR, cardiovascular magnetic resonance; IHD, ischemic heart disease; NIHD, non-

ischemic heart disease.

Table 3. Diagnostic performance of CMR and trans-thoracic echocardiography

		CMR				
		IHD	NIHD	Non-specific Findings	Structurally Normal Heart	TOTAL
TTE	IHD	1	0	0	0	1
	NIHD	1	1	0	0	2
	Non-specific Findings	1	3	0	1	5
	Structurally Normal Heart	1	4	1	15	21
	TOTAL	4	8	1	16	29

Comparison between CMR and TTE findings. Boxes in bold show the number of patients that received the same diagnosis on both imaging modalities. CMR, cardiovascular magnetic resonance; TTE, trans-thoracic echocardiogram; IHD, ischemic heart disease; NIHD, non-ischemic heart disease.

Figure Legend

Figure 1.

Complete atrio-ventricular block (AVB) (A) in a patient with prominent mid-wall/epicardial late gadolinium enhancement in the basal inferoseptum (B, black arrow); a suspicion of cardiac sarcoidosis was raised and confirmed on laboratory testing. Complete AVB (C) in a patient with lamin A/C dilated cardiomyopathy; on late gadolinium enhancement sequences, septal enhancement was noted (D, white arrow).

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