HLA-B27 and an Electrocardiographic Peculiarity

James Ker
Department of Physiology, University of Pretoria, South Africa

Abstract

Introduction: An increased cardiovascular mortality has been described in patients with spondyloarthropathies due to HLA-B27. Numerous cardiovascular afflictions are currently known to be associated with HLA-B27. These include aortic root dilation, aortic regurgitation, mitral regurgitation, myocarditis, heart failure, pericarditis, pericardial effusion, atrioventricular conduction block and more recently, the presence of J-waves.

Materials and methods: 48 HLA-B27 positive patients (23 men and 25 women) were included in this observational study. A 12-lead electrocardiogram and a signal-averaged electrocardiogram was recorded in every patient in order to detect any possible J-waves and ventricular late potentials respectively.

Results: 27 out of these 48 patients demonstrated a visible J-wave in the inferolateral leads. It was revealed that there is a likelihood ratio of 11.386 (p=0.00074) to demonstrate a visible J-wave if the duration of low-amplitude signals is less than 20 ms.

Conclusion: HLA-B27 positive patients have a high incidence of inferolateral cardiac J-waves. There is a high probability of demonstrating such a J-wave on the 12-lead electrocardiogram if the duration of ventricular late potentials is less than 30 ms. The possible mechanisms of this electrocardiographic paradox is discussed.

Keywords: HLA-B27, Ventricular; Late potentials; J-wave

Introduction

In 1973 the strong association between the immunogenetic marker HLA-B27 and ankylosing spondylitis was described [1,2]. More than 11 subtypes or polymorphisms of HLA-B27 have been described since, each one varying in frequency in different ethnic groups, with HLA-B*2705 the so-called "parent" allele, common in all racial groups [3].

It was subsequently realized that HLA-B27 is common to the entire spectrum of seronegative spondyloarthropathies, such as ankylosing spondylitis, Reiter’s syndrome, psoriatic spondylitis, spondylitis in association with inflammatory bowel disease, juvenile spondyloarthropathy, undifferentiated spondyloarthropathy and acute anterior uveitis [2,3]. This spectrum can range from the majority of individuals who have no disease at all to isolated skin, eye or joint involvement to full-blown ankylosing spondylitis [3].

It has been reported that there is an increased cardiovascular mortality in patients with spondyloarthropathies [4]. In fact the first reported case of cardiac involvement in spondyloarthropathy already appeared in 1936 [5,6]. Aortic root involvement is echocardiographically detectable in 61 % of patients with ankylosing spondylitis [4,7,8] presenting echocardiographically as thickening of the posterior aortic wall with occasional aortic root dilation [4,7,8]. Aortic regurgitation is a known complication of HLA-B27 spondyloarthropathy as a result of cusp thickening and aortic root dilation [4,9]. A study by Roldan et al 10 found mitral regurgitation in 30 % of 44 patients. The predominant reason being basal thickening of the anterior mitral leaflet [4,10]. Another classic echocardiographic feature is the so-called “subaortic bump”-hyperechoic thickening of the aortic-mitral junction [4,8,11]. Myocardial and pericardial involvement in spondyloarthropathy is a well described entity with myocarditis, heart failure, symptomatic pericarditis and pericardial effusion known sequelae [2,4,12,13]. More interesting and much more common is involvement of the cardiac conduction system in HLA-B27 positive patients [2,4]. Atrioventricular conduction blocks have been reported since the 1940’s as a complication of ankylosing spondylitis and is regarded as the most common cardiac complication [2,14]. It has been suggested that as many as 20 % of male patients with permanent pacemakers may have an HLA-B27 related disease as the underlying cause for the pacemaker [2,15,16].

An important feature of atrioventricular block in HLA-B27 positive patients is that there is a tendency for these blocks to occur intermittently and it has been stated that this feature supports the notion that a reversible inflammatory process, rather than fibrosis is the cause of the conduction blocks in these patients [2,17-19].

Ker [20] detected a high incidence of inferior J-waves on the electrocardiograms of asymptomatic HLA-B27-positive patients. Might this be evidence that HLA-B27 positivity may be a risk factor for sudden cardiac death as it has been reported that J-waves in the inferior electrocardiographic leads is associated with an increased risk of death [21].

Materials and Methods

48 HLA-B27-positive patients (23 men and 25 women) were included in this study. All of these patients were chosen in a retrospective manner from a cardiology practice. Only patients where no comorbidities were present were chosen for the study. They all had a normal echocardiographic study. This was done to exclude the possibility that any concomitant disease could affect the electrocardiogram. A 12-lead electrocardiogram was then recorded in...
Figure 1:

Figure 2:
The incidence of J-waves in the inferior and inferolateral leads and is associated with a moderate level of risk. Type 3 demonstrates J-waves globally in the inferior, lateral and right precordial leads and can be associated with electrical storms. The fourth type represents Brugada syndrome with J-waves limited to the right precordial leads.

The observed J-waves in this population of HLA-B27 positive patients thus fits the criteria for type 2 (Figure 1). The incidence and electrocardiographic pattern of observed J-waves in this study corresponds to that of a previous study in HLA-B27 positive patients [20]. But, what might the underlying physiological reason be for these type 2 J-waves in HLA-B27 positive patients? Cardiomyopathy was reported in patients with ankylosing spondylitis 31 years ago already [28]. In a series of studies in such patients with cardiomyopathy, but without aortic regurgitation or conduction abnormalities-other known sequelae of HLA-B27—early diastolic dysfunction was found [29,30] with histological examination showing a mild and diffuse increase in interstitial connective tissue [29]. It was shown that the myocardium can develop histopathological abnormalities in the small arteries-an obliterative intimal proliferation-this obliterative arteritis is also found in the tissues adjacent to affected joints, the sinus node artery, the atrioventricular nodal artery and the vasa vasorum of the proximal aorta [2]. It is thus suggested that the high incidence of J-waves in this population is related to such histopathological abnormalities in the myocardium of afflicted patients.

Signal averaged electrocardiography is designed to detect low amplitude signals in the terminal part of the QRS complex and early ST segment by the elimination of noise which contaminates the surface electrocardiogram [31]. The principal clinical indication for this method is for the detection of ventricular late potentials [31]. Ventricular late potentials are microvolt signals that are part of the terminal QRS complex and persist into the ST segment [31]. These late potentials correspond to areas of delayed ventricular activation due to slowed conduction velocity [31]. On such a signal averaged electrocardiogram (SAECG) the so-called root-mean-square voltage of the terminal at 40 ms (RMS40) represents the relative amplitude of the late potential component and the low amplitude signal (LAS) is the duration of the signal whose initial value is less than 40 μV [32].

(Figure 2) is the signal averaged electrocardiogram of the patient with the prominent inferolateral J-waves as seen in (Figure 1). On the SAECG in this case (Figure 2) the duration of the low amplitude signal is 16 ms. As shown by the two-by-two table the likelihood of demonstrating J-waves on the 12-lead ECG is 11.386 (p=0.00074) if the low amplitude signal duration is less than 30 ms.

Current opinion favours the concept that the J-wave is a marker of early repolarization [26] and that low amplitude signals (or ventricular late potentials) correspond to areas of delayed ventricular activation (depolarization) [31]. It is therefore physiologically plausible that in cases where low amplitude signals has a low duration, that earlier repolarization is possible and thus the higher probability of observing a J-wave on the 12-lead ECG.

However, as both these entities (J-waves and late potentials) have been shown to be electrocardiographic risk markers for arrhythmia, this study raises the possibility that HLA-B27 positive patients displays a double risk for arrhythmia—either early repolarization or late potentials.

It is proposed that this question merits an observational study of

---

### Table 1: Electrocardiographic characteristics.

| LAS duration < 30 ms with J-wave present: 18 | LAS duration > 30 ms with J-wave present: 9 |
| LAS duration < 30 ms with J-wave absent: 4 | LAS duration > 30 ms with J-wave absent: 17 |

Likelihood ratio=11.386 (p=0.00074)

LAS denotes low amplitude signal

---

### Results

Out of these 48 patients a total of 27 demonstrated a visible J-wave on the 12-lead electrocardiogram. All observed J-waves was seen in the inferolateral leads (leads II, III, aVF and V3-V6) (Figure 1).

All of the signal-averaged electrocardiograms were within normal limits according to current published criteria. However, when scrutinizing both the 12-lead surface electrocardiograms and the signal-averaged electrocardiograms it was seen that almost all observed J-waves occurred in the SAECG’s of patients where the low-amplitude signal (LAS) duration was less than 30 ms.

A two-by-two table was then used to calculate the likelihood ratio to observe J-waves in cases where the LAS duration is less than 30 ms.

The two-by-two table (Table 1) revealed a likelihood ratio of 11.386 (p=0.00074) to demonstrate a visible J-wave on the 12-lead electrocardiogram if the low-amplitude signal (LAS) duration is less than 30 ms on the signal-averaged electrocardiogram (SAECG).

---

### Discussion

The J-point marks the end of the QRS complex and the J-wave is a low frequency deflection at the end of the QRS complex [22]. Currently, it is not clear whether the J-wave represents ventricular depolarization or early repolarization [22]. However, for the clinician it may become one of the most important electrocardiographic risk markers for cardiovascular death: Haissaguerre [23] found a J-wave in 31 % of survivors from idiopathic ventricular fibrillation versus only 5 % in control subjects [22,23]. Tikkkanen [24] found a strong association between an inferior J-wave and risk for cardiac death among 630 middle aged subjects. Recently, Sinner [25] published a prospective study of 2063 subjects between the age of 35 and 74 years. It was found that the prevalence of a J-wave was 18.5 % and this was associated with an increase in cardiovascular mortality [22,25].

Thus, according to available data the J-wave is associated with a dispersion of repolarization within the ventricular myocardium with a subsequent risk for cardiac arrhythmia [26]. A recent classification scheme for cardiac J-waves divides the electrocardiographic pattern into four possible types [26,27]: Type 1 demonstrates J-waves in the lateral precordial leads. This pattern has a low level of risk for arrhythmic events and is prevalent among healthy male athletes. Type 2 demonstrates J-waves in the inferior and inferolateral leads and is associated with a moderate level of risk. Type 3 demonstrates J-waves globally in the inferior, lateral and right precordial leads and can be associated with electrical storms. The fourth type represents Brugada syndrome with J-waves limited to the right precordial leads.
adequate size and duration to answer the specific question of whether the presence of HLA-B27 is a risk factor for death to due cardiac arrhythmia.

References

1. Schiothstein L, Terasaki PI, Bluestone R, Pearson CM (1973) High association of an HL-A antigen, W27, with ankylosing spondylitis. N Engl J Med 288: 704-706.
2. Bergfeldt L (1997) HLA-B27-associated cardiac disease. Ann Intern Med 127: 621-629.
3. Reveille JD (1998) HLA-B27 and the seronegative spondyloarthopathies. Am J Med Sci 316: 239-249.
4. Vinsonneau U, Brondex A, Mansourati J, Saraux A, Cornily JC, et al. (2008) Cardiovascular disease in patients with spondyloarthopathies. Joint Bone Spine 75: 18-21.
5. Mallory TB (1936) Case reports of the Massachusetts General Hospital. N Engl J Med 214: 690-698.
6. Tolat A, Krishnan S, Lippman N, Delf’Orfano J, Berns E (2010) Advanced heart block and atrial flutter in a patient with HLA B27 spondyloarthropathy. Europace 12: 903-904.
7. Armaso NA, Patel AK, Rahko PS, Sundstrom WR (1996) Transthoracic and transesophageal echocardiographic evaluation of the aortic root and subvalvar structures in ankylosing spondylitis. J Rheumatol 23: 120-123.
8. O’Neill TW, King G, Graham IM, Molony J, Bresnihan B (1992) Echocardiographic abnormalities in ankylosing spondylitis. Ann Rheum Dis 51: 652-664.
9. Graham DC, Smythe HA (1958) The carditis and aortitis of ankylosing spondylitis. Bull Rheum Dis 9: 171-174.
10. Roldan CA, Chavez J, Wiest PW, Qualls CR, Crawford MH (1998) Aortic root disease and valve disease associated with ankylosing spondylitis. Am J Cardiol 32: 1397-1404.
11. Tucker CR, Fowles RE, Calin A, Popp RL (1982) Aortitis in ankylosing spondylitis. Early detection of aortic root abnormalities with two dimensional echocardiography. Am J Cardiol 49: 680-686.
12. Wilkinson M, BywaterSEG (1958) Clinical features and course of ankylosing spondylitis. As seen in follow up of 222 hospital referred cases. Ann Rheum Dis 17: 209-228.
13. Doran MF, Brophy S, Mackay K, Taylor G, Calin A (2003) Predictors of long-term outcome in ankylosing spondylitis. J Rheumatol 30: 316-320.
14. O’Neill TW, Bresnihan B (1992) The heart in ankylosing spondylitis. Ann Rheum Dis 51: 705-706.
15. Bergfeldt L, Edhag O, Vedin L, Vallin H (1982) Ankylosing spondylitis: an important cause of severe disturbances of the cardiac conduction system. Prevalence among 223 pacemaker-treated men. Am J Med 73: 187-191.
16. Bergfeldt L (1983) HLA B27-associated rheumatic diseases with severe cardiac bradycardhythmias. Clinical features and prevalence in 223 men with permanent pacemakers. Am J Med 75: 210-215.
17. Kinsella TD, Johnson LG, Sutherland IR (1974) Cardiovascular manifestations of ankylosing spondylitis. Can Med Assoc J 111: 1309-1311.
18. Bergfeldt L, Edhag O, Vallin H (1982) Cardiac conduction disturbances, an underestimated manifestation in ankylosing spondylitis. A 25-year follow-up study of 68 patients. Acta Med Scand 212: 217-223.
19. Cass RM, Richeson JF, Akiyama T (1991) Reversible complete heart block. Hosp Pract (Off Ed) 26: 51.
20. Ker J (2010) HLA-B27-associated J-wave—a new variant of HLA-B27-associated cardiac disease? Int J Cardiol 145: 637.
21. Tikkkanen JT, Anttonen O, Junttila MJ, Aro AL, Kerola T, et al. (2009) Long-term outcome associated with early repolarization on electrocardiography. N Engl J Med 361: 2529-2537.
22. Surawicz B, Macfarlane PW (2011) Inappropriate and confusing electrocardiographic terms. J-wave syndromes and early repolarization. J Am Coll Cardiol 57: 1584-1586.
23. Haissaguerre M, Derval N, Sacher F, Jesel L, Deisenhofer I, et al. (2008) Sudden cardiac arrest associated with early repolarization. N Engl J Med 358: 2016-2023.
24. Tikkkanen JT, Anttonen O, Junttila MJ, Aro AL, Kerola T, et al. (2009) Long-term outcome associated with early repolarization on electrocardiography. N Engl J Med 361: 2529-2538.
25. Sinner MF, Reinhard W, Müller M, Beckmann BM, Martens E, et al. (2010) Early repolarization pattern on ECG with risk of cardiac and all-cause mortality: a population based prospective cohort study (MONICA/KORA). PLoS Med 7: e1000314.
26. Antzelevitch C, Yan GX, Viskin S (2011) Rationale for the use of the terms J-wave syndromes and early repolarization. J Am Coll Cardiol 57: 1587-1590.
27. Antzelevitch C, Yan GX (2010) J wave syndromes. Heart Rhythm 7: 549-558.
28. Takkanen J, Vuopala U, Isomäki H (1970) Cardiomyopathy in ankylosing spondylitis. I. Medical history and results of clinical examination in a series of 55 patients. Ann Clin Res 2: 106-112.
29. Brewerton DA, Gibson DG, Goddard DH, Jones TJ, Moore RB, et al. (1987) The myocardium in ankylosing spondylitis: A clinical, echocardiographic and histopathological study. Lancet 1: 995-998.
30. Gould BA, Turner J, Keeling DH, Hickling P, Marshall AJ (1992) Myocardial dysfunction in ankylosing spondylitis. Ann Rheum Dis 51: 227-232.
31. Jarrett JR, Flowers NC (1991) Signal-averaged electrocardiography: History, techniques and clinical applications. Clin Cardiol 14: 984-994.
32. Breithardt G, Cain ME, El-Sherif N, Flowers NC, Hombach V, et al. (1991) Standards for analysis of ventricular late potentials using high resolution or signal averaged electrocardiography. A statement by a Task Force Committee between the European Society of Cardiology, the American Heart Association and the American College of Cardiology. Circulation 83: 1481-1488.