

HLA-B27 and an Electrocardiographic Peculiarity

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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 30 ms.

Conclusion: HLA-B27 positive patients has 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

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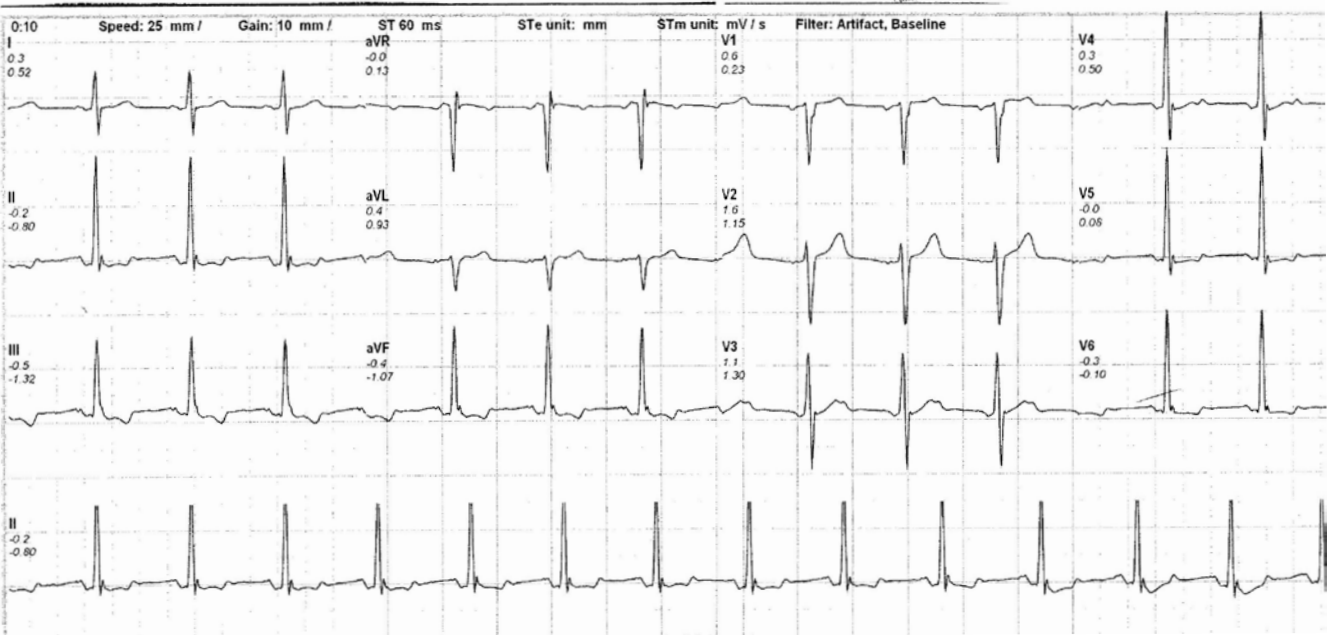


Figure 1:

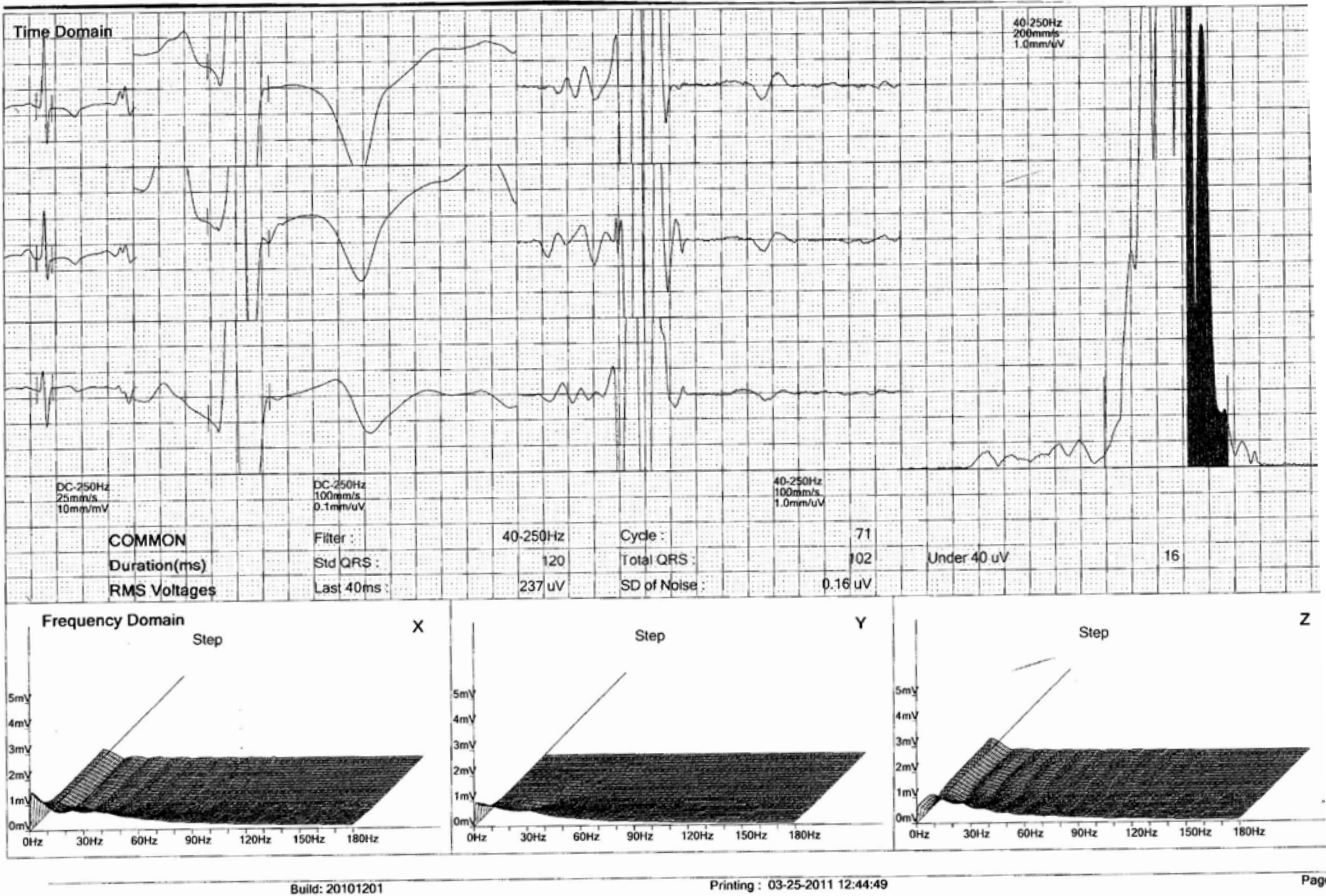


Figure 2:

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

Table 1: Electrocardiographic characteristics.

every patient and the presence of any J-waves noted. Subsequently a signal-averaged electrocardiogram was recorded in every patient.

The aim of this observational study was to describe the signal-averaged electrocardiographic features in HLA-B27 positive patients and to detect any possible differences between the group of HLA-B27 positive patients with and without J-waves on the 12-lead electrocardiogram. It has been shown before that a high prevalence of inferolateral J-waves exist in HLA-B27 positive patients, but no there is currently no data on the possibility of cardiac late potentials in this patient population.

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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 SAEKG'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 that 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 that 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]. Tikkanen [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 or 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 vasora 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 μ V [32].

(Figure 2) is the signal averaged electrocardiogram of the patient with the prominent inferolateral J-waves as seen in (Figure 1). On the SAEKG 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

adequate size and duration to answer the specific question of whether the presence of HLA-B27 is a risk factor for death due to cardiac arrhythmia.

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