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ARTYKUŁ SPECJALNY / *STATE-OF-THE-ART REVIEW*

Viral heart disease

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INTRODUCTION

Viral heart diseases (VHDs) are defined as heart muscle diseases associated with the presence of virus in the myocardium. VHDs are classified into four major forms: a) virus presence in the myocardium, without myocarditis and with normal left ventricular ejection fraction (VNEF), b) viral myocarditis with normal left ventricular ejection fraction (MNEF), c) viral inflammatory cardiomyopathy (VIC), and d) viral cardiomyopathy (VC).

Viral heart diseases may be suspected based on clinical presentation, non-invasive imagining techniques, and invasive procedures. Since the pathological conditions take place at the cellular level, it should be remembered that VHDs can be clinically only suspected but not diagnosed. All clinical methods including imaging techniques may be misleading if viruses are involved. Accurate diagnosis requires simultaneous histologic, immunohistochemical, and molecular biological workup of the tissue. Therefore, the gold standard for *in vivo* diagnosis of the virus presence in the heart is endomyocardial biopsy (EMB), the importance of which is increasing due to its relevant impact not only on the proper diagnosis but also prognosis and therapeutic decisions.

THE DEFINITION OF DIFFERENT FORMS OF VIRAL HEART DISEASES

Viral heart disease differentiation is critical for their proper diagnosis, treatment, and prognosis. Nowadays, it can only be achieved with EMB and subsequent histological, immunohistological, and molecular investigation (polymerase chain reaction [PCR], gene sequencing, and real-time PCR) of the biopsy samples (Table 1) [1–3].

The following terms are currently used: 'virus in the myocardium without myocarditis with normal ejection fraction' is defined as viral persistence (positive PCR for viral RNA or DNA) in a heart with normal left ventricular ejection fraction. This scenario is observed mainly in patients with BP19V or HHV-6 nucleic acid present in cardiac tissue. Virus in myocardium may be accompanied by myocardial inflammation and is then termed 'viral myocarditis with normal ejection fraction' [4]. 'Myocarditis' (MC) is characterised by inflammatory infiltrate (≥ 14 leukocytes/mm^2, with the presence of lymphocytes T CD3+ ≥ 7 cells/mm^2 and ≤ 4 monocytes/mm^2) of the myocardium with necrosis and/or degeneration of adjacent cardiomyocytes of non-ischaemic origin (Dallas and immunohistochemical criteria) [5–8]. The lack of cardiomyocyte necrosis and/or sparser inflammatory infiltrate allows to diagnose borderline MC [9, 10]. 'Viral cardiomyopathy' is defined as a viral persistence in a dilated heart. The term viral cardiomyopathy should be applied if just viral RNA or DNA without inflammation is present [2, 10]. If viral RNA or DNA is accompanied by myocardial inflammation it should be termed 'viral inflammatory cardiomyopathy' [1, 2, 10].

AETIOLOGY AND EPIDEMIOLOGY OF VHD

In the past, the most commonly identified viruses in EMB samples from patients with suspected VHD were enteroviruses (HEV: especially Coxsackie A and B viruses) and adenoviruses (HAdV). Additionally, influenza viruses A and B, rubella virus, and paramyxoviruses (mumps virus and parainfluenza virus) were often found [11–13]. Currently, parvovirus B19 (PB19V), human herpesvirus 6 (HHV-6), cytomegalovirus (CMV), and Epstein-Barr virus (HHV-4) are considered to be the most common (Table 2) [1, 4, 9, 10, 13–15]. Coexistence of nucleic acids of several viruses in one biopsy is reported more frequently, with PBV19 and HHV-6 being the most common connection [10]. In patients with concomitant PVB19 and HHV-6 infection, HHV-6 DNA is eliminated more often than PVB19 DNA from the myocardium. Recent investigations revealed the presence of viral nucleic acids in 19–96% of examined EMB samples, including explanted hearts and healthy control samples [16]. Viral nucleic acids were present in up to 67% of patients' myocardial biopsies with idiopathic left ventricular dysfunction undergoing EMB [13]. Moreover, Dallas criteria of active or borderline MC were not fulfilled in this population [15]. Therefore, it is presumed that the presence of viral nucleic acids in the myocardium does not automatically imply their direct role in the pathogenesis of VNEF, MNEF, VIC, and VC. Probably in some cases the viral nucleic acid found in the myocardium, especially in case of normal left ventricular function, is only an innocent bystander, present in the heart as a consequence of an earlier infection, typically occurring during childhood or adolescence [2]. Our experience indicates the possibility of the presence of viral nucleic acid also in patients with coronary artery disease [17].

Table 1. Viral heart disease (VHD) classification based on echocardiography and histological, immunohistochemical and molecular investigation. Adapted from [11, 12, 13]

VHD classification	Immunohistological inflammation	Positive PCR	Dilated cardiomyopathy
Virus in myocardium without myocarditis	–	+	–
Viral myocarditis with normal EF	+	+	–
Viral inflammatory cardiomyopathy	+	+	+
Viral cardiomyopathy	–	+	+

EF — ejection fraction; PCR — polymerase chain reaction

Table 2. Aetiology and epidemiology of myocarditis and inflammatory cardiomyopathy

Cardiomyotropic viruses		Prevalence [%]
RNA viruses	Picornaviruses: Enterovirus (Coxsackie A and B virus, Polio virus)	1–33 [14, 15]
	Hepatovirus (HCV)	0.1–10 [10, 11]
	Orthomyxoviruses: Influenza A and B virus	1–2 [16]
DNA viruses	Parvoviruses: Parvovirus B19	2.5–96 [19]
	Adenoviruses	2–23 [14, 15]
	Herpesviruses: Human herpes 6 virus (HHV-6)	8–30 [10]
	Cytomegalovirus (HHV-5);	1–5 [5]
	Epstein-Barr virus (HHV-4)	0.5–5 [5]
	Human herpes 1 virus (HHV-1);	< 1 [16]
	Varicella-zoster virus (HHV-3)	< 1 [16]

Currently, one of the most important issues is the identification of patients with viral nucleic acids present in EMB samples that should be diagnosed with VHD and treated. The exact incidence of MC remains unknown as the diagnosis is rather based on exclusion than explicit confirmation. MC occurs more commonly among young people — it was recognised in 46% of children with dilated cardiomyopathy (DCM) and in up to 42% of autopsy studies of people who died of sudden cardiac death before age of 35 [10, 18]. In individuals with immunodeficiency viral infection was observed in up to 50% of autopsy studies. Higher incidence of viral infection is observed among men [19]. 20–30% of patients with acute MC develop DCM during three-year follow-up. The development of DCM in these patients is associated with poor prognosis [20, 21]. In adults with unexplained DCM the incidence of MC was estimated as 9–16%. It should be emphasised that in the quoted literature MC diagnosis was made based on EMB and histological evaluation only.

PATHOMECHANISM OF THE VHD

Cardiomyotropic viruses can be divided into two main groups. The first group consists of HEVs and HAdVs for which cardiomyocytes are the most important target cells. HEVs usually show low risk of persistence, but in some cases their RNA remains detectable in myocardial cells a long time after the acute infection. On the other hand, HAdVs reveal long-term presence in lymphadenoid tissue, which can be a reservoir of HAdVs and a constant source of low-level adenoviral viraemia. The second group comprises PB19V and β-herpesviruses that invade both cardiomyocytes and endothelium. They present high risk of persistence.

The viral infection triggers the triphasic cascade, which may progress to an autoimmune phase after the initial infection and then finally progress to DCM.

In the first phase HEVs and HAdVs reach cardiomyocytes with bloodstream from other, usually primary sites of infection, in the form of cell-free virion or within infected leukocytes [22]. Then, viruses invade the cardiomyocytes by connecting with the specific coxsackie-adenovirus receptor (CAR) and co-receptors (DAF, CD55) for HEV internalisation or αv-type integrins for adenovirus penetration [23]. PB19V exploits P-receptor and co-receptors (integrins, KU80) on the endothelial cells to enter the cells and pass to the state of persistent infection in the endothelium of various organs, including the heart [24]. Acute viral infection is dominated by Th1 response [25, 26]. Activation of the Th2 immune reactions is necessary for the development of chronic viral infection with fibrosis and dilatation of the left ventricle [27]. The innate immunity activates the inflammatory process via toll-like receptors (TLRs) as the first line of defence against the virus [28]. The innate immunity regulates inflammation, infiltration, and production of the cytokines (TNF-α, IFN-γ, IL-1, IL-2, IL-6, IL-10) [28]. The activation of the non-TLR sensors like retinoid acid inducible gene I (RIG-I) and melanoma differentiation associated protein 5 is another way to induce the immune response. RIG-I-like receptors maintain the production of interferon-β, which is very important for limiting the viral presence in the heart. Its absence or decrease in expression leads to mortality increase. Dendritic cells, natural killer cells, and macrophages migrate to the heart in response to the massive cytokine production and minimalise virus propagation, mostly via direct cytotoxic effect [28]. Inactivation of T-cells and associated cytokines after clearance of viral infection is necessary for complete recovery.

The acute phase lasts for only a few days and can cause virus elimination from the heart and renovation of the damaged tissue (spontaneous improvement in 50–57%), lead to non-inflammatory damage of the myocardial cells, or result in heart failure or death due to the direct cytopathic effect of the active replication [9, 25]. It can be manifested by fever, weakness, rash, joint and muscle pain, or symptoms of respiratory or gastrointestinal viral infection.

The second stage of the infection is subacute and it lasts weeks to months. Signals from the innate immunity system activate specific T and B lymphocytes. The cytotoxic T-cells, responsible for the lysis of virus-infected cells, as well as, B-cells, which produce antibodies destroying viruses, react with the

structures of the human heart and can damage the myocardium. Consequently, specific cellular antigens from necrotic myocytes such as β1-adrenergic receptors, myosin, or M2 muscarinic receptors are released [29]. The above-mentioned cellular antigens can activate autoimmune reactions because of the molecular mimicry. It is considered that direct viral injury, cytokine context, and the level of the proinflammatory immune reaction are altogether responsible for determining the severity of viral infection and the probability of drift from acute to subacute stage [28]. The activation of the acquired immunity results in chronic inflammatory response in the myocardium and may lead to its dysfunction due to fibrosis and remodelling. The patient may present dyspnoea, chest pain, arrhythmias, fatigue, increased sweating, and fainting.

The last stage of the infection is the myopathy phase. In case of the persistent inflammatory response, DCM may develop. A pathogenic role may be played by a) antibodies against sarcolemma, myolemma, β-receptor, acetylcholine receptor, laminin, and cardiac conducting tissue release of cytokines, b) release of viral proteins, c) activation of matrix metalloproteinases, and d) activation of osteopontin and matricellular protein, which predispose to fibrosis and cardiac dilatation [4, 26, 30]. The development of DCM is observed in 14–52% of patients with acute MC [31].

Additionally, the presence of the virus or its components in the cardiac tissue without concomitant local immune response at a detectable level, as determined in standard histopathological examination, can also elicit fibrosis, hypertrophy, and degeneration of cardiomyocytes observed in DCM [12].

DIAGNOSIS

The evaluation of patients with suspected VHD includes detailed history and careful physical examination oriented towards features that may provide clues to the aetiology. Electrocardiogram, chest X-ray, blood tests, non-invasive imaging techniques, and coronary angiography should be performed in most cases. Nevertheless, the most important tools for VHD diagnosis and classification are cardiac magnetic resonance (CMR) and EMB.

CLINICAL PRESENTATION

Viral heart disease symptoms may vary in different phases of the disease. It is presumed that genetic predispositions, type of the immune response, virus type, and the viral load (number of genome equivalents [ge] per microgram of isolated nucleic acids) influence the clinical presentation [10, 12, 13]. Viral infection can affect individuals with and without genetic predisposition [6, 7, 32]. The VHD can be preceded by upper respiratory or gastrointestinal infection with fever, fatigue, and joint pain [31, 33, 34]. The viral infection, often unnoticed, is followed by the latent phase lasting from several days to several weeks. The diversity of clinical scenarios is typical for VHD [33–35]. Clinical presentations include: asymptomatic (or barely symptomatic) disease with exercise tolerance worsening or dyspnoea during exercise/at rest, peripheral oedema, pulmonary congestion or typical chest pain, pleuritic chest pain, supraventricular and ventricular arrhythmias, treatment resistant ventricular tachycardia and torsade de pointes, high-grade atrioventricular blocks, or sudden cardiac death [9, 33–36].

According to The European Study of Epidemiology and Treatment of Cardiac Inflammatory Diseases (ESETCID) the most commonly presented symptoms by patients with suspected MC were dyspnoea (72%), chest pain (32%), and rhythm disorders (18%) [9]. The course of the disease in children was more often fulminant and the myocardial injury was often more severe in male patients [33]. 4.7-year mortality in patients with MC reaches 19.2% [37]. The percentage is even higher in case of some types of viruses, in patients with regions of late gadolinium enhancement on CMR and in DCM [10, 37].

CARDIOVASCULAR MAGNETIC RESONANCE IMAGING

Cardiovascular magnetic resonance should be considered in patients with clinical suspicion of MC, and usually before EMB is performed. However, it should not replace EMB [38]. It is recommended that three imaging methods be used in the study protocol: T2-weighted imaging and early (EGE) and late (LGE) gadolinium enhancement T1-weighted imaging. T2-weighted imaging enables assessment of areas of increased water content and thus identification tissue oedema. It allows determination of the severity of the inflammatory process. EGE images assess total hyperaemia and vascular permeability [39]. LGL enables location of irreversible myocardial injury and fibrosis. In VHD LGLs are spotted, located mainly in subepicardial and intraepicardial areas, and unrelated to the anatomy of the coronary arteries [39]. Fulfilment of MC criteria (myocardial oedema and LGL presence) is characterised by high specificity (95%) but unfortunately very low sensitivity (< 25%) [31]. It should be emphasised that myocardial oedema, as an inflammation feature, is present only in the early stage of inflammation. Therefore, CMR study in patients with chronic VHD has significantly lower sensitivity and specificity. Moreover, it is not able to identify patients with persistent viral genomes in EMB, who constitute up to 40% of patients with DCM and require antiviral treatment.

ENDOMYOCARDIAL BIOPSY

The gold standard for the diagnosis of VHD is EMB, which was introduced to clinical practice in 1980 [10]. It should be underlined that EMB performed by an experienced operator is associated with a low rate of serious complications of below 1% [1]. Currently, the use of EMB is defined in the ESC recommendations (Table 3) and in the Statement of the ESC Working Group on Myocardial and Pericardial Disease [10, 20]. EMB is the only method that allows for the final determination of the

Table 3. Indications for myocardial biopsy. Adapted from [24]

CR	LE	Form	Myocarditis history	Clinical presentation
I	B	Acute HF	< 2 weeks, impaired left ventricle function	Left ventricle normal or dilated
I	B	Acute HF	2–12 weeks or lack of response to standard HF treatment	DCM, ventricular arrhythmias, second- or third-degree atrioventricular block
IIa	C	Chronic HF	> 3 weeks or lack of response to standard HF treatment	DCM, new ventricular arrhythmias
IIa	C		Regardless of time	DCM (allergic, eosinophilic) Toxic injury (anthracycline) Idiopathic DCM in children Unexplained RCM Suspected cardiac tumours
IIb	B	Acute HF	2–12 weeks, with good response to treatment	Acute DCM without arrhythmias
IIb	C	Chronic HF	> 3 weeks, with good response to treatment	DCM without arrhythmias
IIb	C		Regardless of time	HCM Suspected ARVD Unexplained ventricular arrhythmias

CR — class of recommendation; LE — level of evidence; HF — heart failure; DCM — dilated cardiomyopathy; RCM — restrictive cardiomyopathy; HCM — hypertrophic cardiomyopathy; ARVD — arrhythmogenic right ventricular dysplasia

aetiology, type of inflammation, and prognosis in VHD. It is also necessary for the use of immunosuppressive and antiviral therapy. Increasing interest in this method and approval for its use may contribute to its wider use in diagnosing VHD.

During the procedure, 8 to 10 EMB samples are taken from the left or right ventricle, depending on the localisation of abnormalities [10]. Usually, two biopsies are used for histological and two for immunohistochemical analysis, and the next ones — depending on the centre — are used for electron microscopy, and molecular and virological studies [10]. The histological diagnosis of myocardial inflammation based on the Dallas criteria are limited by variability in interpretation (39% among pathologists examining the same EMB sample), lack of prognostic value, and low sensitivity (MC absence in 50% of EMB samples with virus positive PCR), partly due to sampling error [9, 34]. To address the shortcomings, in 1999, the World Health Organisation and International Society and Federation of Cardiology updated the conventional histological criteria for diagnosis of MC by the introduction of a immunohistochemical method that enables accurate identification of inflammatory cells by staining surface antigens, such as: CD45 (leucocyte antigen common), CD3 (T cell marker), CD4 (helper T cell marker), CD8 (cytotoxic T cell marker), CD68 (macrophages), and CD20 (B-lymphocytes) [1, 36]. The value of ≥ 14 leukocytes/mm^2 with the presence of T lymphocytes (e.g. CD3) or activated T-cells (CD45ro) ≥ 7 cells/mm^2 has been considered a realistic cutoff to diagnose MC [32]. Immunohistochemical methods are characterised by higher sensitivity and presumably higher predictive value [34]. However, many observations confirm that routine histological and immunohistochemical analysis is not sensitive enough to detect myocardial inflammation accurately in the acute phase of disease, as well as in the chronic phase. It should be emphasised that in many studies, despite establishing the virus presence by PCR, there are no histological features of active or borderline inflammation, and although immunohistochemical analyses show increased presence of T cells, macrophages, intercellular adhesion molecule-1 (ICAM-1), and human leukocyte antigen 1 (HLA-1) the quantitative criteria for diagnosis of the MC are often not met [13].

The introduction of molecular analysis with DNA-RNA extraction and amplification of the viral genome increases the sensitivity and specificity of the virus assessment in EMB samples. Additional diagnostic values of PCR are a) precise aetiological diagnosis and b) the identification of virus titre and the degree of its replication.

For the time being, determination of VHD aetiology relies on direct methods, mainly detecting specific surface antigens by immunohistochemical examination and viral nucleic acids by PCR in EMB samples, and rarely on electron microscopy [20]. Our experience indicates that electron microscopy could be a helpful diagnostic tool not only for the investigation of ultrastructural changes but also for the localisation of viruses in EMB samples [40, 41].

According to the current recommendations, as well as EMB, peripheral blood samples should also be investigated for virus presence by PCR [20]. Based on our data the detection of viral nucleic acid in peripheral blood samples seems to be irrelevant for identifying viral infection in patients with low virus load in the myocardium [42]. It is suspected that the blood samples from the ventricle could be more appropriate for prediction of viral nucleic acid in the myocardium [42].

CONCLUSIONS

With the introduction of molecular biological techniques an important improvement in the quantitative diagnosis of VHD has been achieved. Nevertheless, it should be kept in mind that only a full spectrum of diagnostic methods can enable proper diagnosis of VHD.

Viral heart disease diagnostics should be performed in centres with experience in EMB and its full analysis with histological, immunohistochemical, and molecular methods.

Conflict of interest: *none declared*

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