



Mechanisms of Cardiovascular Defects due to Endotheliotropic Virus Infection

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Abstract

In this article, the literature on some endotheliotropic viruses such as parvovirus B19 (PVB19) and human herpesvirus-6 (HHV-6) was reviewed to update the current information on the pathogenesis of cardiovascular dysfunction. PVB19 targets exclusively endothelial cells in microvasculature by binding to P antigen receptors and co-receptors such as $\alpha 5 \beta 1$ integrin and Ku80 autoantigen, whereas HHV-6 targets all cardiovascular cells by utilising CD46 and CD134 to infect predominantly cardiomyocytes. The activation of endothelial cell by PVB19 produces upregulation of some adhesion molecules, cytokine release and recruitment of inflammatory cells in acute phase. In chronic phase, there occurs pro-inflammatory environment in microvasculature which is associated with reduced production of nitric oxide (NO), impaired vasodilatory capacity, occurrence of ischaemia in cardiomyocytes and development of cardiomyopathy. On the other hand, HHV-6 infection not only induces cardiac defects due to ischaemic insult by endothelial/microvasculature dysfunction like PVB19, but also produces myocardial abnormalities by directly affecting cardiomyocytes by inducing chromosomal integration as well as promoting infiltration of immune cells and pro-inflammatory cells. Such alterations in cardiomyocytes by HHV-6 virus as a consequence of ischaemic conditions, mitochondrial dysfunction, Ca^{2+} -handling abnormalities, inflammatory environment and immune processes are considered to explain the occurrence of cardiac apoptosis as well as cardiac fibrosis, structural damage and cardiac dysfunction. In view of these observations indicating similarities and differences in the mode of cardiovascular defects induction by PVB19 and HHV-6 infections, extensive research needs to be carried out for fully understanding the exact mechanisms of viral cardiomyopathy.

Key words: Viral cardiomyopathy; PVB19 virus; HHV-6 virus; Mitochondrial dysfunction; Ca^{2+} -handling abnormalities; Inflammation; Immune cells.

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Introduction

Cardiovascular disease remains the leading global cause of death and is responsible for approximately 18 million deaths worldwide annually.^{1, 2} Although the occurrence of this disease is attributed mainly to metabolic and lifestyle-related risk factors, viral infections are recognised as

important contributors to both acute and long-term cardiovascular morbidity. A diverse group of cardiotropic and systemic viruses including human immunodeficiency virus (HIV), influenza viruses, adenoviruses, parvovirus B19 (PVB19), enteroviruses (Coxsackievirus B), cytomegalo-

virus, Epstein–Barr virus, human herpesvirus-6 (HHV-6B), Zika virus, Dengue virus) and coronaviruses (eg SARS-CoV-2) have been implicated in cardiovascular pathology. These infections are associated with a wide spectrum of cardiovascular manifestations, such as myocarditis, dilated cardiomyopathy, arrhythmias, acute coronary syndrome, heart failure, thromboembolic complications and valvular abnormalities. Many of these complications may coexist and interact clinically, such as arrhythmia-associated thromboembolism in atrial fibrillation.³⁻⁸

Endomyocardial biopsy and molecular studies have demonstrated the presence of viral genomes in a substantial proportion of inflammatory cardiomyopathies, highlighting the significant contribution of viral pathogens to cardiovascular disease.⁹⁻¹¹ Among various cardiotropic pathogens, HHV-6B and PVB19 have been most frequently detected in patients and autopsy samples with unexplained acute myocarditis and progressive dilated cardiomyopathy.^{9, 12, 13} PVB19 is consistently identified as the most frequent viral genome detected in “idiopathic” left ventricular dysfunction, often presenting concurrently with HHV-6 in aggressive, multi-viral infections that have poor prognosis.^{9, 14-16} Despite their shared prominence in the aetiology of cardiomyopathy, these two DNA viruses possess entirely divergent cellular tropisms, utilising unique receptor complexes to infect distinct compartments of the myocardium.^{17, 18} Consequently, they trigger heart failure via distinct ischaemic and non-ischaemic mechanisms, acting in a time dependent chronological order.¹⁸⁻²¹

The divergent clinical manifestations of PVB19 and HHV-6 are anchored in their initial receptor-mediated entry. PVB19 is an exclusively endotheliotropic virus in the adult human heart.²² It targets cardiac microvasculature-specifically endothelial cells of capillaries, venules and small arterioles- by binding to the blood group P antigen (globoside) as its primary cellular receptor, supplemented by co-receptors such as $\alpha 5 \beta 1$ integrin and Ku80 autoantigen.^{23, 24} Since adult cardiomyocytes lack the P antigen and are thus resistant to the direct action of PVB19 infection.²⁵ On the other hand, HHV-6 utilises the ubiquitous complement regulatory protein CD46 or the specific T-cell receptor CD134 to directly infect interstitial helper T-lymphocytes and cardiomyocytes themselves.^{26, 27}

Since the pathogenesis of virus-induced cardiomyopathy requires the understanding of temporal sequence of infarct-like injury which acts as the acute instigator to pave the way for chronic, non-ischaemic remodelling,^{28, 29} this article discusses the phases in which they proceed to drive the development of cardiovascular abnormalities. Accordingly, this narrative review was computed from articles indexed in *PubMed*, *Google Scholar* and *Scopus* using search words such as endothelial viruses, HHV-6 and PVB19 mechanisms of cardiovascular and endothelial damage, subcellular and molecular strategies of HHV-6 and PVB19 infections as well as immune mechanisms of HHV-6 and PVB19 induced cardiovascular and endothelial damage.

General consideration of PVB19 and HHV-6B cardiomyopathy

While both PVB19 and HHV-6 viruses drive the heart towards heart failure, they do so through opposing pathways. PVB19 acts on the endothelium and induces functional ventricular impairment via “outside-in” approach, where endothelial death and downstream microvascular schema deprive the healthy cardiomyocytes of oxygen.^{18, 30-32} On the other hand, HHV-6 utilises an inside-out process characterised by a variant-dependent tropism. One variant of HHV-6 acts by targeting the cardiomyocytes via CD46 receptors, inducing productive lytic cycles, cellular syncytial formation and host-cell apoptosis that cause cytopathic destruction and cellular degradation of myocardium. The other variant HHV-6 targets the vascular endothelium, mimicking microvascular injury patterns like PVB19.¹⁴ It has been established that about 1 % of the population carries chromosomal integrated HHV-6 in their germline genome which gets reactivated from within the host-cell itself under conditions of immunosuppression or systemic stress. This finding is another evidence to support its inside-out action approach.³³

Cardiovascular magnetic resonance (CMR) imaging observations have revealed that PVB19-induced damage typically manifests as patchy subepicardial late gadolinium enhancement predominantly in the lateral wall of the left ventri-

cle, aligning with microvascular perfusion zones. In contrast, HHV-6 infection characteristically presents with mid-myocardial late gadolinium enhancement concentrated in the anterior and septal walls, reflecting diffuse myocellular necrosis and interstitial infiltration. It is important to note, however, that similar patterns can be mimicked by other viruses like coxsackievirus, so CMR doesn't solely serve as a definitive viral fingerprint.^{34,35} Furthermore, while single PVB19 infections or low-load HHV-6 infections frequently show a high rate of spontaneous recovery, complex viral profiles-such as high-load HHV-6, or combined (PVB19/HHV-6) persistent co-infections are prone to progressive clinical deterioration towards systolic heart failure.^{16,36}

Both endothelial/microvascular ischaemia (caused by PVB19 infection) and cardiomyocyte destruction (caused by HHV-6A infection) are considered to result in non-ischaemic remodelling of the heart. The persistent viral presence and low-grade reactivation maintain an inflammatory environment, characterised by cytokines like TNF- α and IL-6, which induce diffuse interstitial fibrosis instead of focal scarring. This chronic damage indirectly triggers electrical remodelling in the myocardium. While viral targeting of gap junctions remains unproven, local inflammation and hypoxic stress are established drivers of connexin 43 (Cx43) lateralisation and ion channel (Ito, ICa, L) dysregulation.³⁷ Ultimately, this mechano-neural uncoupling can potentially create an arrhythmogenic substrate and mechanical asynchrony and thus may contribute to the progression of inflammatory dilated cardiomyopathy.³⁸

Implications of PVB19 and HHV-6 viral infections

PVB19-induced endothelial and microvascular injury

PVB19 infection is the well-established model of endothelial-predominant viral cardiac injury, in which microvascular dysfunction, tissue viral persistence and patchy inflammatory remodelling appear to be more central than direct cardiomyocyte cytolysis. Unlike classical cardiotropic viruses that have been shown to directly infect cardiomyocytes, PVB19 demonstrates a strong tropism for cardiac microvascular endothelial

cells, with viral genome predominantly localised within endothelial cells rather than cardiomyocytes.³⁹ Following endothelial infection, PVB19 induces endothelial activation and injury, characterised by upregulation of adhesion molecules, cytokine release and recruitment of inflammatory cells. Mechanistically, the viral NS1 protein has been shown to activate STAT3 signalling in endothelial cells, promoting pro-inflammatory gene expression and sustaining endothelial activation.⁴⁰ Activation of STAT3 signalling is further associated with increased endothelial permeability and disruption of vascular barrier integrity.⁴¹ In parallel, endothelial activation has been linked to impaired nitric oxide (NO) signalling and reduced vasodilatory capacity, providing a mechanistic basis for endothelial-dependent dysfunction and altered coronary vascular tone.⁴²

Collectively, these endothelial alterations contribute to impaired coronary microvascular function and myocardial injury due to ischaemia despite minimal direct cardiomyocyte infection by PVB19. Biopsy-based and functional studies have also demonstrated that PVB19 persistence is associated with endothelial dysfunction and impaired coronary microcirculation.⁴³ This vascular phenotype is further supported by observations of abnormal vasomotor responses and coronary vasospasm in patients with PVB19-associated myocarditis, producing localised ischaemia-like conditions within the myocardium.⁴⁴ Importantly, microvascular impairment in PVB19 infection has downstream electrophysiological consequences. Regional hypoperfusion and endothelial inflammation promote spatial heterogeneity in myocardial conduction and repolarisation, which are key components of an arrhythmogenic substrate.⁴⁵⁻⁴⁷ Although mechanistic studies linking PVB19 and electrophysiological abnormalities are largely absent, clinical observations in inflammatory cardiomyopathy suggest that myocardial inflammation and microvascular dysfunction are associated with increased susceptibility to arrhythmias and conduction disturbances.^{16,48}

Clinically, PVB19-associated myocarditis has been limited to atrial and ventricular arrhythmias as well as conduction abnormalities in paediatric cohorts, often in the context of inflammatory cardiomyopathy rather than overt structural heart disease.^{16,32,48} One longitudinal study also found a significant proportion of the PVB19-infected patients manifesting acute lymphocytic damage.⁴⁹

These observations support the concept that arrhythmogenesis in PVB19 infection is primarily mediated through inflammation and microvascular dysfunction rather than direct cardiomyocyte injury. Over time, persistent endothelial injury and inflammation may contribute to interstitial fibrosis, which stabilises the arrhythmogenic substrate and increases the risk of sustained arrhythmias.^{50, 51}

Some clinical studies further support a link between PVB19 infection and structural remodelling that may predispose to conduction abnormalities. Endomyocardial biopsy analysis has demonstrated that viral persistence, rather than mere viral presence, correlates with chronic inflammation, endothelial activation and progression to adverse cardiac remodelling.^{9, 52} In these cohorts, persistent viral activity is associated with worse clinical status and progressive myocardial dysfunction. However, it is important to note that mechanistic studies linking PVB19-induced endothelial infection to fibrosis-driven conduction system disease remain limited. Much of the current understanding is derived from correlative clinical and histopathological evidence, where viral persistence, microvascular dysfunction and fibrotic remodelling coexist rather than from definitive causal pathway studies.^{9, 52, 53} This represents an important gap in the literature and underscores

the need for integrated studies combining viral localisation, fibrosis mapping and electrophysiological assessment. A schematic representation of events during the development of cardiomyopathy by PVB19 is shown in Figure 1.

Chromosomal integration and electrophysiological remodelling due to HHV-6

HHV-6 represents a model of viral cardiac injury in which myocardial involvement and conduction system remodelling are clinically prominent. Furthermore, in contrast to PVB19, HHV-6 demonstrates broader cellular tropism, including cardiomyocytes, endothelial cells as well as immune cells and is characterised by its ability to establish lifelong viral persistence with periodic reactivation. As a result, arrhythmogenic mechanisms in HHV-6 infection arise from a combination of viral presence, chronic inflammatory signalling and progressive structural and electrophysiological remodelling rather than a single dominant pathway.^{5, 14} Some studies have identified HHV-6 in patients presenting with atrioventricular block, bundle branch block and other conduction abnormalities, supporting a relationship between HHV-6-associated myocardial injury and conduction system dysfunction.⁵⁴ In some cases, HHV-6-associated myocarditis presents a high-grade atrioventricular block or intermittent

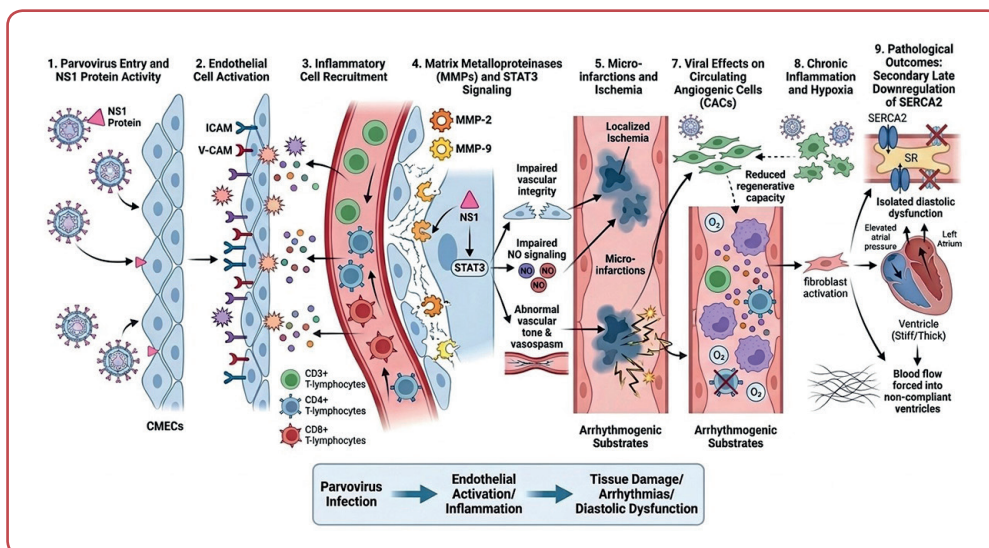


Figure 1: Parvovirus B19 (PVB19) associated endothelial dysfunction and cardiomyopathy

The figure represents entry of B19V NS1 protein and subsequent attack on cell adhesion molecules and immune-mediated damage which impairs endothelial cell integrity. It also shows activation of STAT3 signalling in endothelial cells resulting in impaired NO signalling leading to vasospasms and subsequently ischaemic damage within the microvasculature of heart. It also affects CACs which prevents regeneration of endothelial cells and reducing oxygen supply to cardiomyocytes. These processes collectively activate fibrotic remodelling over a long period. SERCA2 is downregulated via NS1 protein as well as cellular stress pathways. This figure is generated by using AI tools (FigureLabs). CMECs: cardiac microvascular endothelial cells; ICAM-1: intracellular adhesion molecule 1; VCAM-1: vascular cell adhesion molecule 1; SERCA2: sarco/endoplasmic reticulum Ca^{2+} -ATPase; CACs: circulating angiogenic cells; NS1 protein: non-structural 1 protein

tachycardia requiring pacing support, highlighting its ability to disrupt cardiac electrophysiological pathways even in the absence of extensive structural disease.^{55, 56}

Viral activity within myocardial tissue promotes sustained inflammatory signalling, cytokine release and immune cell infiltration, creating a pro-arrhythmic environment that evolves over time rather than arising from an acute focal insult.⁹ This inflammatory milieu alters cardiac electrophysiology by disrupting electrical coupling and Ca^{2+} -handling, thereby increasing susceptibility to both atrial and ventricular arrhythmias.^{57, 58} One of the unique features of HHV-6 infection is its ability to integrate into host chromosomal DNA, specifically at telomeric regions, a property not observed in most cardiotropic or endothelial-tropic viruses.^{59, 60} Unlike PVB19, which persists primarily in an extrachromosomal form and RNA viruses such as SARS-CoV-2, which do not integrate into the host genome, HHV-6 is considered to establish long-term persistence through stable chromosomal integration.⁶¹ Its reactivation in mononuclear cells and cardiac tissue has been linked to heart failure symptoms.¹²

From a pathophysiological perspective, HHV-6

chromosomal integration into host telomeric regions provides a unique mechanism for prolonged viral persistence.^{61, 62} In the setting of myocardial infection, such persistence may contribute to sustained low-grade inflammation and progressive myocardial remodelling, with potential downstream effects on the cardiac conduction system. The site-specific integration of HHV-6 into host telomeres is recognised by the cell as double-strand break, activating the DNA damage response (DDR) pathway-specifically via ATM/ATR kinase signalling.⁶³ In cardiomyocytes, this DDR activation triggers p53-dependent cellular senescence and the secretion of senescence associated secretory phenotype, characterised by pro-inflammatory cytokines (eg IL-6, TNF- α) and matrix metalloproteinases.^{64, 65} Chronic inflammatory milieu promotes interstitial fibrosis and disrupts Cx43 gap junctions. Consequently, the loss of electrical coupling creates zones of slow, heterogenous conduction establishing a substrate for arrhythmias. However, mechanistic evidence linking HHV-6 chromosomal integration specifically to conduction abnormalities or arrhythmia generation remains limited. Current understanding is derived primarily from observational and clinical studies demonstrating an association between persistent HHV-6 genome,

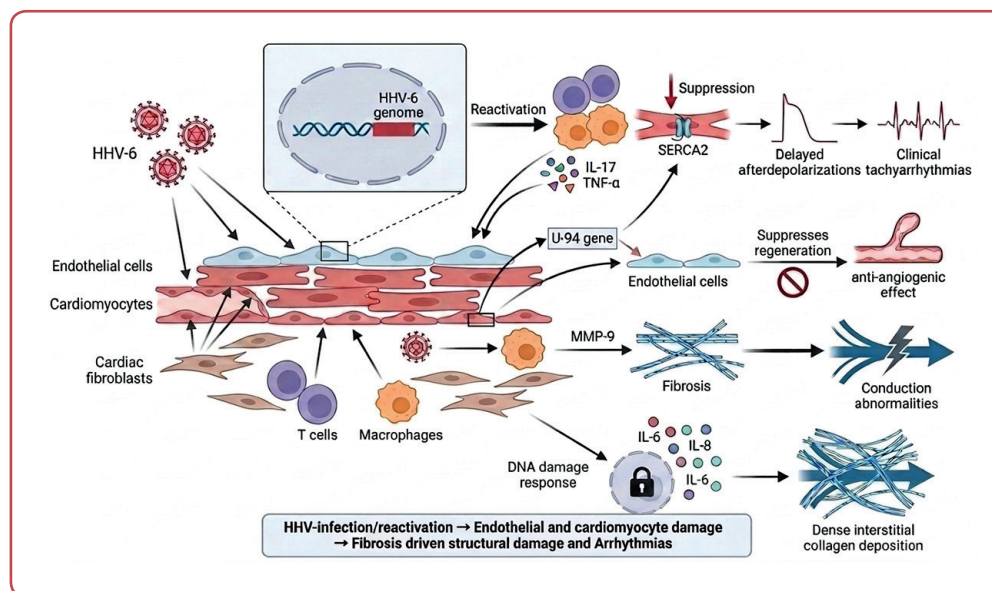


Figure 2: Human herpesvirus 6 (HHV-6) associated endothelial dysfunction and cardiac cytotoxicity via activation of cell death and immune-mediated pathways

This figure represents HHV-6 reactivation leading to activation of inflammatory cytokines which suppress transcription of SERCA2 and leading to electrical abnormalities due to Ca dysfunction. Active viral replication also leads to activation of DNA damage response in endothelial and cardiac cells. These senescent cells express SASP profile that leads to deposition of collagen around electrical tracts and triggers arrhythmias and cardiomyopathy. The dotted lines connecting the endothelial cells also extend to cardiomyocytes -because HHV-6 can be integrated in the genome of cardiomyocytes as well. This figure is generated by using AI tools (FigureLabs). SERCA2: sarcoplasmic reticulum Ca^{2+} -ATPase; SASP: senescence associated secretory phenotype

myocardial inflammation and ventricular dysfunction, rather than clearly defined causal pathways.^{4, 14, 66} A schematic representation of events during the development of cardiomyopathy due to HHV-6 is shown in Figure 2.

Taken together, HHV-6 infection reveals a persistence-driven pattern of viral arrhythmogenesis in which chronic infection, immune-mediated injury and potential conduction system involvement represent important contributors. When considered alongside PVB19 and SARS-CoV-2, these findings support the concept that viral-induced arrhythmias may arise from overlapping but differentially dominant mechanisms, ranging from cardiomyocyte injury to endothelial-mediated microvascular dysfunction and immune-driven electrical remodelling.

Mechanisms for the development of endotheliotropic virus-induced cardiomyopathy

Mitochondrial dysfunction due to PVB19 and HHV-6 infections

At the subcellular level, viral protein interactions with the mitochondrial network dictate the metabolic decline observed in viral cardiomyopathies, though distinct structural footprints left by PVB19 and HHV-6. In PVB19-dilated cardiomyopathy (DCM), ultrastructural endomyocardial biopsy analysis has revealed severe, localised disruption of the mitochondrial architecture even in the complete absence of active tissue inflammation.⁶⁷ PVB19 interaction with non-structural protein 1 induces substantial morphological decay, characterised by a profound loss of inner mitochondrial cristae, complete interruption of the outer mitochondrial membrane and a pathologic clustering of mitochondria immediately adjacent to abnormally expanded sarcoplasmic reticulum.⁶⁸ This structural collapse of mitochondria promotes the uncontrolled release of reactive oxygen species (ROS) and forces the cell to destroy its own energy networks (mitophagy) and depressing the heart muscle ATP.^{67, 69}

On the other hand, HHV-6 induces metabolic dysfunction through its complex integration into the host telomeres, which operates as a chronic nuclear distress mechanism rather than direct

structural tearing. Because it integrates into host telomeres and damages the T-loop structure of chromosomes, it triggers a nuclear DNA damage response (DDR). This chronic distress may force the cell into a state of premature aging (senescence), causing it to continuously release toxic inflammatory proteins. Such a signalling paralyzes the mitochondrial electron transport chain complexes, dropping the membrane potential and depriving the contractile machinery of energy. When applied to cardiomyocyte context, this metabolic change is compounded by the HHV-6 early viral protein, U95. As demonstrated by Yeo et al,⁷⁰ U95 directly binds to host GRIM-19, a critical structural subunit of mitochondrial respiratory chain Complex I. In cardiac cells, this molecular alteration blocks the Complex I assembly, causing mitochondrial swelling and complete collapse of membrane potential. This drives the cardiomyocyte of severe electromechanical failure, cause ROS leakage and thereby triggering intracellular stress pathways that degrade the Cx43 gap junctions. It has been suggested that this is an alternative cell death mechanism where the cell simply expires from energy starvation instead of undergoing caspase-dependent apoptosis.⁷⁰⁻⁷² Importantly, this secondary pathway of oxidative stress and gap junction failure due to HHV-6 parallels PVB19 pathophysiology, even though these have different upstream triggers. It is noteworthy that neither virus has been shown to directly target or mutate Cx43 but instead, both indirectly cause downstream tissue damage.

In HHV-6 pathogenesis, mitochondrial dysfunction is a primary, proximal consequence of parenchymal infection; during early viral reactivation, HHV-6-encoded small non-coding RNAs (sncRNAs) rapidly alter the host transcriptomic landscape to drive mitochondrial fragmentation and metabolic disruption.⁷³ Conversely, because PVB19 targets the cardiac endothelium rather than the cardiomyocytes themselves, its initial phenotype is dictated by chronic inflammatory and mechanical stress.⁷⁴ This manifests as a primary structural and functional uncoupling of the cell's microdomains—such as diastolic Ca²⁺ leaks, rather than an immediate, transcriptional failure of the metabolic or contractile machinery. While both viral pathways eventually converge on the same end-stage downregulation of SERCA2a and global energetic bankruptcy.⁷⁵ HHV-6 may initiate an immediate transcriptomic and organelle-level shutdown, whereas PVB19 may operate through progressive structural degradation.^{37, 76}

Intracellular Ca^{2+} -handling alterations subsequent to PVB19 and HHV-6 infections

The disturbance of intracellular Ca^{2+} homeostasis serves as a major mechanisms of contractile failure and arrhythmogenesis for both pathogens, ultimately converging on same destructive endpoint—oxidation and destabilisation of ryanodine receptor (RyR2) complex and initiating this defect through different structural versus genetic pathways that are transcription-mediated.^{77, 78} In PVB19 infection, Ca^{2+} -handling defects are primarily initiated by a mechanical and geometric rearrangement of the cellular architecture. An endomyocardial biopsy study by Brola et al⁷⁹ has experimentally shown this structural disruption, demonstrating that the physical expansion of the sarcoplasmic reticulum and its abnormal proximity to damaged mitochondrial membranes may compromise the structural integrity of the Ca^{2+} -microdomain. This spatial uncoupling could break down the strict synchronisation between L-type Ca^{2+} channels (ICa,L) on T-tubules and RyR2 on the sarcoplasmic reticulum. L-type Ca^{2+} channels may no longer interact smoothly with RyR2 receptors across the widened gap.⁷⁹⁻⁸¹

The immediate wave of ROS production by damaged mitochondria may also oxidise the RyR2

complex and thus induce macromolecular instability, causing Ca^{2+} to constantly leak out from the sarcoplasmic reticulum during diastole.⁸² Importantly, while chronic PVB19 infection ultimately may result in a secondary, late-stage downregulation of SERCA2a in a manner similar to other types of failing hearts,^{75, 83} its initial phenotype may be driven by an inflammatory and oxidative disruption of excitation-contraction coupling. This is characterised by a diastolic Ca^{2+} leak through hyperphosphorylated RyR2 channels rather than an isolated pump failure.⁸⁴ Such a defect would deplete the intracellular Ca^{2+} reserve upon the activation of Na^+ - Ca^{2+} exchanger for the removal of Ca^{2+} and thus may compromise cardiac contractile function.^{85, 86} Accordingly, Ca^{2+} -handling defects due to ROS-mediated and inflammation-associated mechanisms, have been proposed for the development of arrhythmias and cardiac dysfunction as a consequence of PVB19 infection.^{30, 87-89}

On the other hand, for HHV-6-associated myocarditis and subsequent tachyarrhythmias, the underlying pathology is initiated by an immediate upstream genetic and inflammatory suppression of Ca^{2+} -recycling machinery. Clinical profiling has demonstrated that while chromosomal integration remains pathologically silent, active HHV-6 viral transcription alters host cellular-transcript networks, resulting in a global disruption of

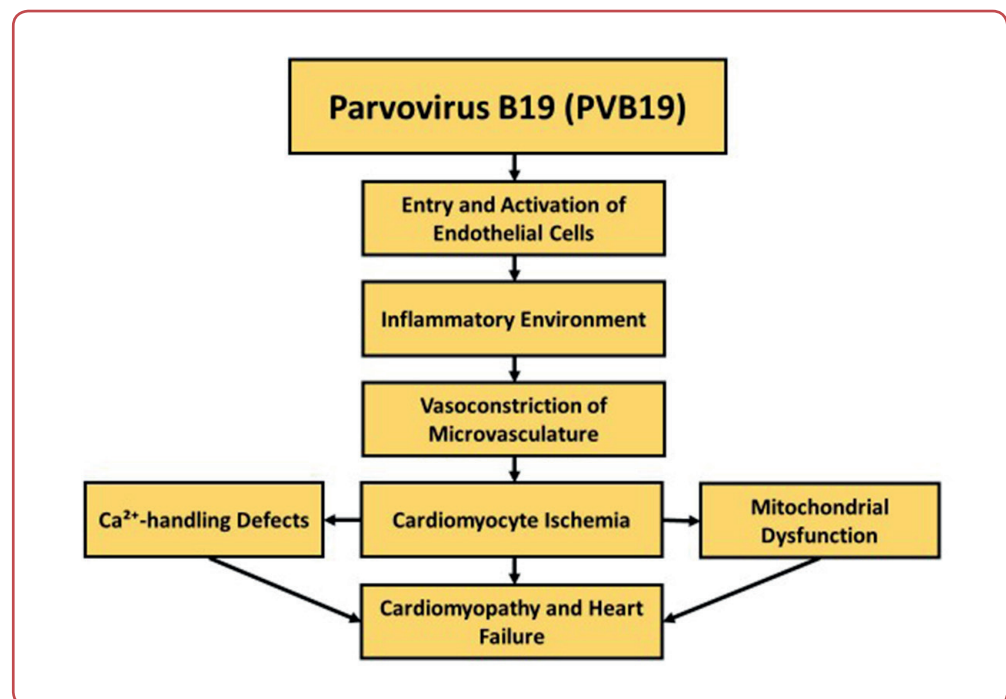


Figure 3: Proposed mechanisms for the induction of cardiomyopathy due to parvovirus B19 (PVB19) infection

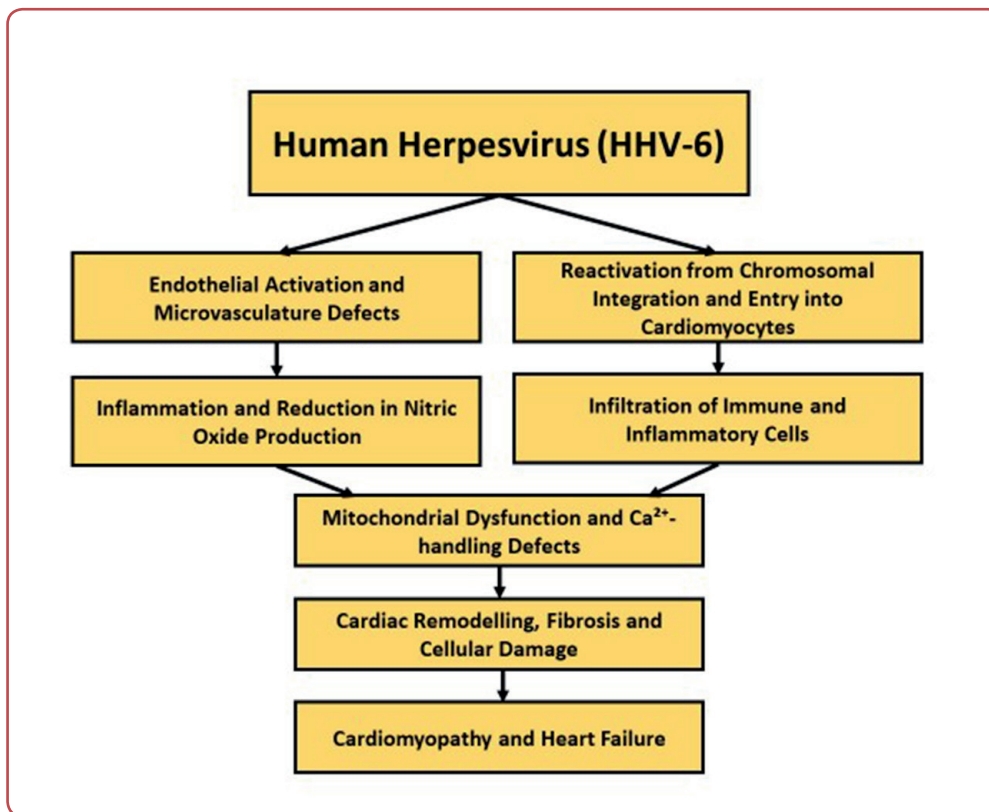


Figure 4: Proposed mechanisms for the induction of cardiomyopathy due to human herpesvirus 6 (HHV-6) infection

functional cellular pathways.¹² This persistent viral state is considered to establish a high-grade chronic inflammatory profile due to increased level of cytokines. At the molecular level, some specific inflammatory cytokines (IL-17 and TNF- α) have been shown to suppress the primary transcription of SERCA2a and disrupt the regulatory control of phospholamban (PLN) complex in cardiomyocytes.⁹⁰⁻⁹³ Specifically, increased level of cytokines blunts host β -adrenergic signalling, preventing protein kinase A (PKA)-mediated phosphorylation of PLN and suppressing SERCA2A pump as well as activation in Na⁺-Ca²⁺exchanger. Such changes in Ca²⁺-handling are considered to destabilise the resting membrane potential, trigger delayed afterdepolarisations that ultimately manifest as tachyarrhythmias.⁹⁴ Simplified mechanisms for the induction of cardiomyopathy due to PVB19 and HHV-6 are shown in Figures 3 and 4, respectively.

Divergence of cellular tropism in PVB19 and HHV-6 induced cardiomyopathy

The expression of the cytotoxic PVB19 capsid component VP1-unique region (VP1u) and its intrinsic phospholipase A2 like enzymatic activity inflict structural damage upon the coronary microvasculature.^{22, 95, 96} This leads to endothelial cell apoptosis, impaired nitric oxide (NO) bioavailability and intense microvascular vasospasm. The resulting presentation simulates microvascular angina, producing widespread, patchy micro-infarctions and localised ischaemia that leave downstream post-mitotic cardiomyocytes starved of oxygen and prone to necrotic loss.^{30, 97} One study has shown that even the mere presence of high viral loads without active repletion can cause endothelial damage.⁹⁸ On the other hand, HHV-6 displays a strict tropism for the myocardial microvasculature. Active viral rep-

lication drives acute, high-grade tissue damage via cytokine production. It has been shown that HHV-6 also infects microvascular endothelial cells and increases their ability to secrete proinflammatory chemokines.⁹⁹ Thus, both PVB19 and HHV-6 viruses produce ischaemia by constricting the microvasculature either by endothelial (as with PVB19) or by endothelial microvascular dysfunction (as with HHV-6). The resulting chronic narrowing of the coronary capillary beds precipitates low-grade ischaemia, driving the progressive loss of functional contractile units and replacing the downstream tissue with dense, ischaemic-type replacement fibrosis.^{100, 101} Furthermore, both variants of HHV-6 have also been shown to inhibit angiogenesis by inducing human leukocyte antigen G (HLA-G).¹⁰²

While the development of cardiomyocyte damage due to PVB19 and HHV-6 can be explained on the basis for the occurrence of myocardial ischaemia, the development of cardiac remodelling and the occurrence of fibrosis underpins the global cardiac dilation and mechanical failure. It may be noted that PVB19 cardiomyopathy is sustained by a chronic, auto-reactive immune cycle. The resulting progressive degradation of the structural collagen skeleton permits the mechanical slippage of myofibril bundles, leading to the ventricular wall thinning, spherical chamber distortion and global systolic failure seen in dilated cardiomyopathy.¹⁰³⁻¹⁰⁵ On the other hand, cardiac remodelling driven by HHV-6 is governed by telomeric disruption generates a persistent host DNA damage response (DDR) that locks cardiac endothelial cells and interstitial cardiac fibroblasts into a state of permanent cellular senescence.¹⁰⁶⁻¹⁰⁸ Rather than destroying cells instantly, these senescent cells express a destructive Senescence-Associated Secretory Phenotype (SASP) profile that continuously deposits dense interstitial collagen surrounding the conduction tracts. This diffuse, non-ischaemic interstitial fibrosis electrically isolates individual cardiomyocytes, breaking down the normal physical architecture of the myocardium and converting healthy tissue into a highly uncoupled, remodelling-prone substrate.¹⁰⁹

Another crucial, pathway observed in these viral environments is the activation of the endothelial-to-mesenchymal transition (EndMT). In PVB19 and HHV-6 microvascular infections, chronic inflammatory signalling cascades (most notably mediated through the elevated secretion of TGF- β or IL-6) force the capillary endothelial

cells to lose their vascular identity. These cells downregulate typical endothelial markers, such as Vascular endothelial cadherin (VE-cadherin) and CD31 and transform into active, migratory myofibroblasts expressing α -smooth muscle actin (α -SMA). This structural conversion reduces capillary density while accelerating the uncontrolled synthesis of interstitial collagen. EndMT serves as a major subcellular mechanism that links active microvascular viral replication directly to progressive cardiac stiffening, diastolic dysfunction and the development of a highly fibrotic substrate that disrupts normal electrical propagation throughout the heart.^{22, 110-112}

Potential biomarkers for endotheliotropic viral-induced cardiomyopathy

Although various miRNA levels are generally associated with different types of cardiomyopathies, miRNA profiling in endotheliotropic viral myocarditis is largely unexplored. For PVB19, endothelial-derived miR-126 represents a plausible candidate for reflecting the microvascular dysfunction as well as for the development of arrhythmogenesis in manner similar to that in myocardial infarction, showing its essential role in maintaining coronary microvascular homeostasis.¹¹³ Loss or dysregulation of miR-126 in the setting of endothelial viral injury was considered to amplify the microvascular dysfunction and impaired coronary flow reserve described in PVB19 cardiac pathology.^{114, 115} Furthermore, it is pointed out that miR-146a was shown to modulate endothelial activation in response to inflammatory stimuli as it reduced the expression of NF- κ B-dependent cytokine production and collagen synthesis.¹¹⁶ Restoration of miR-146a has been demonstrated to attenuate inflammatory and fibrotic remodelling, supporting its role as a candidate mediator linking endothelial dysfunction to interstitial fibrosis.¹¹⁶⁻¹¹⁸ The chronic inflammatory milieu associated with HHV-6 infection shares features with other conditions of sustained immune activation and dysregulation of miR-146a which have been shown to promote cardiac fibrosis and structural remodelling in different experimental models.¹¹⁹⁻¹²¹ Thus, it is evident that miR-146a may serve as a biomarker for the diagnosis of viral cardiomyopathy.

Conclusion

This review emphasises the critical role of endotheliotropic viral infections, particularly PVB19 HHV-6, as primary drivers of cardiac microvascular dysfunction, myocarditis, cardiomyopathy and activity alterations. PVB19 primarily causes endothelial-centred myocardial injury and ischaemic damage due to its endothelial dominance, while HHV-6 induces chronic electrophysiological remodelling, cellular senescence and fibrosis through latency and chromosomal integration. Ultimately, both pathogens converge on subcellular mechanisms, severely disrupting mitochondrial function and Ca^{2+} handling as well as promoting non-ischaemic remodelling via pathways like the EndMT. While existing research highlights the systemic impact of these infections, significant knowledge gaps remain. Current evidence suggests the urgent need for studies targeting specific viral proteins to understand their precise role in endothelial dysfunction, especially concerning NO availability and their contributions to both inflammatory and non-inflammatory mitochondrial dysfunction and cardiac remodelling. Furthermore, there is a notable lack of data exploring the long-term effects of these viral proteins on critical cardiac cell death pathways.

Importantly, while the electrophysiological properties of the heart and the involvement of proteins, such as SERCA2a in heart failure are well-established, the effects of endotheliotropic viruses on these targets are yet to be empirically tested. This makes it difficult to distinguish between upstream and downstream pathways activated upon viral activation or reactivation. Much of our current understanding of virus-induced electrical and structural remodelling relies on inferences from basic electrophysiology and general heart failure mechanisms. To move beyond general heart failure models, the research in this field must prioritise, mechanistic studies on specific viral proteins to understand their exact roles in endothelial dysfunction, especially regarding NO bioavailability and microdomain signalling. While structural remodelling and failure-associated proteins including SERCA2a are well-mapped in general cardiology, empirical testing is urgently needed to observe how these specific viruses alter cardiac electrical prop-

erties and Ca^{2+} handling. Establishing these direct associations is crucial for accurately distinguishing between upstream viral triggers and downstream secondary failure pathways. Addressing these gaps also requires a renewed focus on the chronic timeline of infection. There is a paucity of data regarding the long-term effects of PVB19 and HHV-6 viral proteins on specific cardiac cell death pathways. Alongside mechanistic investigations, future clinical frameworks must validate circulating miRNAs as reliable, minimally-invasive biomarkers. Identifying these biomarkers will allow clinicians to detect active, endotheliotropic viral reactivation before irreversible structural disease, ischaemic damage and life-threatening arrhythmogenesis occur.

Ethics

The study was based on the analysis of the existing literature and did not directly involve with human participants or experimental animals. Therefore, the ethics approval was not required for this article.

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Conflicts of interest

The authors declare that there is no conflict of interest.

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Data access

The data that support the findings of this study are available from the corresponding author upon reasonable individual request.

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