Etiopathogenesis of Lyme Carditis

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Abstract

The development of Lyme carditis is largely mediated by the direct invasion of the myocardial tissue and the subsequent triggering of pro-inflammatory changes. *Borrelia spp.* modulates the expression of proteins, including outer surface adhesins and complement inhibitor proteins, to facilitate pathogenesis; causing the common manifestations of Lyme carditis including atrioventricular block, other arrhythmias, myocarditis, pericarditis, endocarditis and dilated cardiomyopathy via a plethora of mechanisms.

Keywords

Lyme carditis • Myocardial spirochete invasion • Inflammatory response • Autoimmune response

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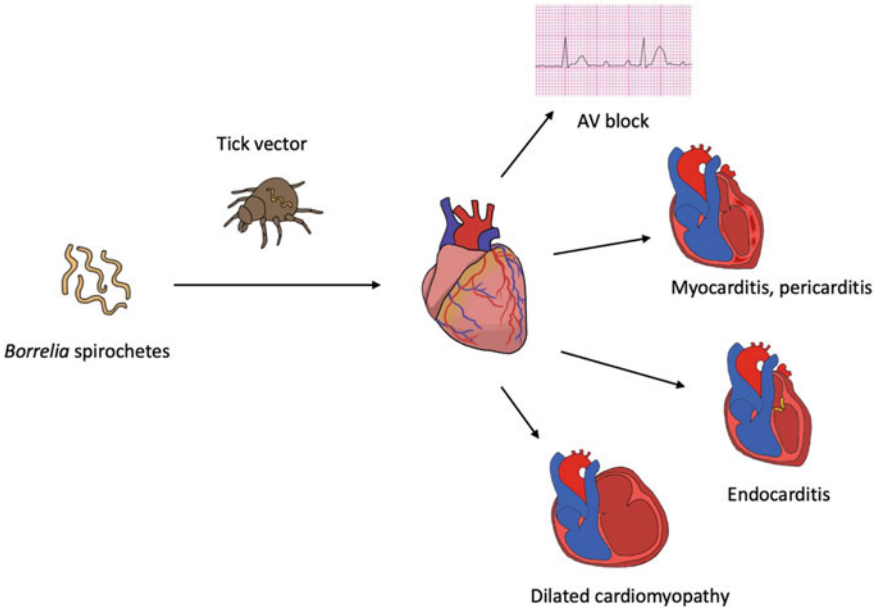
A. Baranchuk et al. (eds.), *Lyme Carditis*,
https://doi.org/10.1007/978-3-031-41169-4_3



Central illustration

1 Introduction

Lyme disease (LD) is one of the most prevalent tick-borne multi-systemic diseases globally. It is estimated that over 14% of the world's population has suffered from LD, concentrating around Central and Western European as well as Eastern Asian regions [1]. Lyme carditis (LC) occurs when the bacteria enter heart tissues and causes interference with electrical activation and/or propagation, notably at the atrioventricular (AV) node, causing heart block and cardiac injury [2]. Approximately 0.3–4% and 1.5–10% of Lyme infected patients suffer from carditis in Europe and the United States (US), respectively [3]. However, given the prompt use of antibiotics during the early phase of infection, LC is now becoming an increasingly uncommon manifestation. Recent data suggest that the incidence may be at 1% in the US [4].

Lyme carditis is rarely lethal, but sudden cardiac death has been described. One of the most common manifestations of LC is AV block, occurring in up to 90% of cases [5]. AV block typically fluctuates heavily, with the potential of shifting from first-degree to second-degree or complete block and vice versa within minutes. While conduction abnormalities in LC usually involve the AV node, they can occur in other regions of the heart, including the sinoatrial node and bundle branches [6]. In addition to cardiac conduction abnormalities, LC patients may also present with endocarditis, pericarditis, myocarditis or pancarditis [7].

Although the occurrence of carditis is low amongst patients with LD, the incidence of LD is increasing. Rapid recognition of the disease is important as it can be ameliorated by antibiotics and temporary pacing to avoid progression and complications. Permanent pacemaker implantation may be required in severe cases of LC with delayed antibiotic treatment [8]. To avoid this and other complications, understanding the pathogenesis is essential as it will guide clinical decisions made in practice when Lyme carditis does arise.

2 Pathogenesis

2.1 Transmission of Lyme Disease to Human

LD is caused by the *Borrelia spp.*, most commonly *Borrelia burgdorferi*, although it can also be caused by species such as *B. garinii, B. spielmanii,* and *B. afzeii.* In the US, the main causative agent is *Borrelia burgdorferi* and infrequently *Borrelia mayonii.* Meanwhile, in Europe and Asia, Lyme disease is mainly caused by *Borrelia afzelii*, *Borrelia garinii*, and less commonly *Borrelia burgdorferi* [9]. *Borrelia burgdorferi* is a Gram-negative fastidious microaerophilic spirochete. The spirochetes can invade various tissues in vertebrates, thus infection can manifest in multiple organs around the body [10]. The *Borrelia* genus can be classified by their transmission by hard-bodied or soft-bodied ticks. They can also be classified according to their phylogenetic and comparative genomic analysis. *Borrelia burgdorferi* is further subclassified into different genomospecies, which are associated with respective clinical presentations of LD.

The reservoir for the *Borrelia burgdorferi* includes mammals and some species of birds. For instance, in the US, mammals such as the white-footed mouse (*Peromyscus leucopus*), the western grey squirrel (*Sciurus griseus*), and the eastern grey squirrels (*Sciurus carolinensis*) were suggested as infectious hosts. The bacteria are then transmitted to humans through the Ixodes tick, most commonly by the deer tick *Ixodes scapularis* [11]. The vectors carrying the bacteria vary geographically. While *Ixodes scapularis* and *Ixodes pacificus* are the main transmitters in the US, *Ixodes persulcatus* and *Ixodes ricinus* are the known vectors of Asia and Europe, respectively [12]. The *Borrelia spp.* are capable of surviving in ticks via several mechanisms. For example, the outer surface adhesins OspA and OspB allow *Borrelia burgdorferi* to thrive in the midgut of the ticks [13]. Moreover, the bacteria also express molecules, such as complement inhibitor proteins and TSLPI, to facilitate its dissemination and transmission. Furthermore, the migration of the bacteria to the salivary gland of the tick is regulated by RpoN-RpoS [14].

The ticks transmit the bacteria to humans via their saliva at the location of the bite. The infected ticks generally require 2–3 days of feeding to transmit *Borrelia burgdorferi* to the hosts [15]. The transmission process is influenced by various factors, including the proportion of infected ticks in certain geographical areas, the stage of the life cycle of the ticks, and the environmental exposure to the ticks. Once transmitted, the bacteria can resist the host immune response by

modulating the expression of surface proteins. *Borrelia* upregulates complement regulator-acquiring surface proteins to resist complement-mediated elimination and downregulates outer surface protein C to evade the adaptive immune system [16]. During the early disseminated phase of infection, the bacteria can spread via the circulatory and lymphatic systems, thus reaching organs such as the heart and the skin.

2.2 Direct Invasion of Myocardial Tissues

Following the initial tick-borne infection, where the *Borrelia* spirochetes are injected and deposited into the dermis, they proliferate locally, then disseminate to various distant sites within the host. During the early disseminated phase, the accumulating spirochetes can colonise a range of tissues, including cardiac tissues, causing LC. *Borrelia burgdorferi* has shown significant cardiac tissue tropism following dissemination within infected hosts, and have shown to persist within for months to years [14]. In particular, the spirochetes were seen to discriminatorily infiltrate connective tissue at the base of the heart, interventricular septum, and perivascular areas in murine studies [17–19]. These sites of infiltration could thus explain why heart conductive disorders occurs in Lyme carditis.

There is evidence for the necessity of vascular interactions, such as those involving borrelial adhesins, for successful attachment and subsequent colonisation of the spirochetes at secondary infection sites. Specifically, adhesins such as decorin-binding proteins and *p66* have been identified as crucial constituents for cardiac tropism. *Borrelia burgdorferi* expresses a plethora of surface adhesins that can bind with components found within the extracellular matrix of targeted tissues, including glycosaminoglycans (GAG), collagen and decorin. Decorin is upregulated in humans during the remodelling process after myocardial infarction or any myocardium insult [14]. Notably, the adhesin decorin-binding protein A (DbpA) that binds decorin, heparin and dermatan sulphate GAG has been postulated to play a major role in the invasion of cardiac tissues. Animal studies found reduced infectivity and colonisation of the heart with mutant *Borrelia burgdorferi* that lacked *DbpA* compared to wild-type *Borrelia burgdorferi* [16]. However, obtained results vary in the in vivo study between inoculation and tick bites, adding to the complexity of the pathogenic process.

Another adhesion protein of equal significance is *p66*, an integrin-binding protein. It is postulated that not only does *p66* contribute to cardiac tropism, it also promotes the dissemination of spirochetes into the bloodstream [8]. Its expression is inactive within the tick vector, only activating once the tick begins feeding and persisting throughout the mammalian infection, suggesting its importance in pathogenesis [17]. Indeed, an animal study has demonstrated that heart tropism depends on *p66* by comparing infections between *Borrelia burgdorferi* mutants without functional *p66* and wild-type *Borrelia burgdorferi* [18].

Upon infection, *Borrelia burgdorferi* induces changes in the metabolism of the heart, including the mitochondrial function at a cellular level. The large inoculum of the infective agent downregulates mitochondrial components involved in fatty acid metabolism. It also results in compensatory upregulation of proteins in the tricarboxylic acid cycle and respiratory chain processes [19]. This may result in cardiac dysfunction in the heart secondary to mitochondrial dysfunction [20].

Nonetheless, the exact mechanisms of dissemination, invasion and immune evasion of the spirochetes are complex and are yet to be elucidated, and tissue tropism could be strain-dependent [18, 20]. There are allelic variation of genes encoding the bacterial adhesins, which could be the potential explanation for the distinct tissue tropism of different species and strains of Borrelia, leading to different clinical manifestations [21]. It is evident that the adhesion process is not solely dependent on one adhesin, as the deletion of one adhesin is insufficient to dampen the infectivity and tropic effects of *Borrelia burgdorferi*.

2.3 Inflammation and *Borrelia burgdorferi*

As the number of spirochetes identified in the myocardial tissues was discording with the extent of lymphocytic infiltration, it was proposed that the immune response also plays an important role [22]. The increased inflammatory response to bacterial load and the antigen released in the myocardium might be responsible for LC. Meanwhile, the immune processes triggered by molecular mimicry between the bacterial antigen and self-components might also contribute to autoimmune carditis [23]. It was found that the IgM anti-*Borrelia burgdorferi* cross-reacted to molecules that shared homology with the OspA molecule in *Borrelia burgdorferi*. The OspA, in turn, cause polyclonal activation of the B cells and increases the production of the IgM, which reacts with the self-components [24].

3 Conductive Disease and Arrhythmias

LC is closely associated with conduction abnormalities, which can lead to sudden cardiac death in severe cases [4]. The most common abnormality seen in patients with LC is atrioventricular block, present in 90% of cases [25]. AV block typically fluctuates heavily, with the potential of shifting from first-degree to second-degree or complete block and vice versa within minutes. Colonization of the myocardium by *Borrelia burgdorferi* results in an exaggerated immune response and cardiac injury. Research conducted on mice has revealed a correlation between the presence of conduction abnormalities and the inflammatory response triggered by the bacteria [18]. The immune response induced by *Borrelia burgdorferi* leads to a memory-like response in macrophages and causes transcriptional, epigenetic, and metabolic changes in these cells [26]. It has been shown that macrophages are abundant in the distal AV node, with conducting cells interspersed among them

[27]. The resident macrophages express connexin 43 gap junctions to communicate with cardiomyocytes and mediate their normal electrical coupling [27]. As such, the changes caused by *Borrelia burgdorferi* in cardiac resident macrophages, in particular, may alter electrical activity in the heart and result in conduction abnormalities at the AV node [27].

In addition to AV blocks, LC has been associated with sinus pauses, albeit rarely. As of January 2022, only seven case reports have been published [28]. Sinus pauses can be due to spirochete invasion restricted to the atrium, leading to conduction problems only in the SA node [28]. While the cause of sinus node dysfunction in LC remains unclear, there has been postulation that the pauses are a result of SA exit block but not intranodal electrical automaticity as LC is widely recognised to primarily manifest with conduction abnormalities [29]. Bundle branch blocks and intraventricular conduction delay have been in LC patients, making up around 13% of cases [30]. These cases suggest His-Purkinje system involvement by direct spirochete invasion or inflammation.

LC is also associated with other supraventricular arrhythmias, which were mediated by the anti–*Borrelia burgdorferi* antibodies. The antibodies caused cross-reactivity to induce inflammation and atrial fibrosis, which increase the risks of supraventricular arrhythmias [31]. An example of supraventricular arrhythmia is atrial fibrillation (AF). It is extremely rare to see AF in LC patients, with only fewer than 5 cases reported in the English literature as of 2019 [32].

3.1 Lyme Endocarditis

The most recent review of the literature identified only eight reported cases of Lyme endocarditis, all of which occurred in either the US or Europe [33]. Current diagnostic methods of Lyme endocarditis include histopathology, culture, and PCR of heart valves tissue samples. In four out of the eight cases, universal 16S ribosomal ribonucleic acid (rRNA) PCR and sequencing were successful in identifying the presence of *Borrelia* [33].

Due to the rarity of Lyme endocarditis, the exact pathogenesis of the condition is largely unknown. Despite so, it should follow the three critical steps involved in infective endocarditis: preparation of the cardiac valve for bacterial attachment, attachment of circulating bacteria to the valvular surface, and survival of the bacteria along with the propagation of infected vegetation [34].

The endothelium of the heart and valves are normally resistant to bacterial and fungal infections. As such, two models of adherence could be applied to Lyme endocarditis. The first model is the 'damaged induced' pathway, in which previous endocardial injury leads to a deposition of platelets and fibrin that allow the *Borrelia* bacteria to be trapped in. Another model, which is the direct infection of heart valves, could also be possible. This typically happens only if organisms have high virulence. *Staphylococcus aureus*, for instance, is believed to interact with extracellular matrix binding proteins such as von Willebrand factor as a means of

internalizing into the endothelial cell [35]. *Borrelia burgdoferi* similarly has the ability to adhere to and bypass endothelial barriers under vascular shear stress. Instead of targeting insoluble matrix Fn deposited on endothelial surfaces, the bacteria recruit and induces polymerization of soluble plasma Fn (pFn), which is normally non-adhesive. Yet, under physiological shear stress, the polymerised pFn form mechanically loaded adhesion complexes that facilitate interactions with endothelial cells via a 'catch-bond mechanism' [36]. After successful adherence to the valvular surface, the bacteria can modulate the physical forces and immunity of endothelial cells to travel through their monolayers, allowing growth and propagation [37].

4 Myocarditis and Pericarditis

The myocardium and pericardium can be affected in LC, either independently or both sites concurrently. Most cases are self-limiting, although there have been a few cases which resulted in mortality, largely in immunocompromised individuals [38–40]. The *Borrelia* spirochetes are known to cause transmural inflammation within the heart, likely through direct invasion and subsequent immune modulation processes described above. Myopericardial involvement in LC has been shown in the murine study by Armstrong et al. [18]. Similarly, in an autopsy report of fatal cases of LC, spirochetes infiltrates were identified in the epicardium and myocardium [38]. Additionally, increased interstitial collagen deposition was found within these infiltrates. This not only highlights the spirochetes' gravitation towards extracellular matrix-like environments, but also indicating their ability to alter the composition of the tissue they reside in, which could explain the colonisation of the myopericardial tissues.

The *Borrelia* spp. is documented to be a potent immunomodulator. This extracellular pathogen is unable to release exotoxins or endotoxins [41]. However, the spirochetes was shown influence the expression of major histocompatibility complex, leading to suppression of the local immune response and evading the host immune surveillance [42]. In the autopsy report, a predominance of lymphocytic cells is found in the infiltrate, which is similar in composition to that in viral myocarditis [38]. In a mouse model of viral myocarditis, humoral and cellular immune responses mainly consisting of macrophages and T-lymphocytes were initiated, eliminating the infectious agent [43]. However, inflammation persisted in the heart for longer in susceptible mouse strains, likely due to secondary autoimmune reactions following infection, progressing into chronic infection [44]. *Borrelia* infections could potentially result in myocarditis and pericarditis in a similar fashion. Myocarditis and pericarditis tend to occur much later than the initial infection [45]. The spirochetes are likely to be able to persist within the myocardium due to the changes induced to the macrophages, then subsequently generate pathogenic cardiac autoantibodies directed against the myocardial proteins.

5 Dilated Cardiomyopathy

A possible long-term consequence of untreated or poorly treated LD is dilated cardiomyopathy (DCM). This topic will be discussed further in Chap. 14.

While the pathophysiological mechanisms behind *B. burgdorferi*-associated DCM are not fully understood, three mechanisms have been proposed: direct invasion of myocardial tissue, maladaptive immune response, and auto-immune responses that lead to exaggerated inflammation [46]. Existing literature is conflicting, and thus it is currently unclear whether *Borrelia* is the cause of DCM, or whether the proceeding inflammatory processes is attributable.

Borrelia burgdorferi defends itself against the host immune system and continues to thrive within cardiac tissues. The spirochete may be able to do so by interfering with all three activation pathways of the complement cascade, through various modalities such as manipulation of its surface proteins and adhesins, and recruitment of certain proteins [47–49]. The inactivation of the complement system reduces continued antigen presentation and thus hyper-affinity maturation, decreasing the capacity of the host to generate effective antibodies against *Borrelia burgdorferi* [50]. The persistence of *Borrelia* in the myocardium can cause chronic inflammation, in turn leading to DCM [51]. Several studies found improving cardiac function and remodelling following the use of antibiotic therapy in patients with suspected *Borrelia*-induced DCM, suggesting that Borrelia may play a direct role in the disease process [46].

However, *Borrelia burgdorferi* may only be present in the myocardium for a temporary period before inducing chronic inflammation that ultimately result in the development of inflammatory DCM [18]. Autoimmunity has also been implicated in the pathogenic progression. Individuals diagnosed with autoimmune diseases, such as Crohn's disease, autoimmune thyroiditis, and psoriasis, have a higher occurrence of *Borrelia burgdorferi*-associated DCM [52]. It is uncertain whether Lyme disease triggers these autoimmune conditions or mimics them, or vice versa. Autoimmune responses have been highly associated with cardiac damage, due to chronic upregulation of inflammatory factors [53]. It is possible that cross-reactive IgM antibodies can react with cardiac tissue with consequent injury and functional abnormalities.

6 Conclusion

The *Borrelia spp.* utilise a plethora of mechanisms to modulate the ticks and human bodies to enhance its dissemination and transmission. *Borrelia spp.* causes LC by direct invasion of the myocardial tissues and triggering and modulating the inflammatory responses.

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