

Review

Chronic Infection and Cardiac Aging: a New Perspective on Pathogen-Associated Cardiomyopathy

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Key Words

Chronic infection • Cardiac aging • Inflammaging • Autophagy • Mitochondrial dysfunction

Abstract

Cardiovascular diseases remain the primary driver of global mortality, with advanced age serving the most significant risk factor for their development and progression. Emerging evidence suggests that chronic infections can act as potent catalysts for cardiac decline by prematurely inducing aging phenotypes. Pathogens, including viruses, bacteria, and parasites, that evade host clearance establish a state of permanent inflammaging: a chronic, low-grade inflammatory milieu characterized by persistent cytokine signaling and leukocyte infiltration. This environment directly mirrors the sterile inflammation that drives natural senescence. Mechanistically, chronic infection subverts the heart's homeostatic pathways, triggering cardiomyocyte senescence through the dysregulation of mTOR signaling and the impairment of autophagy. These infections further drive mitochondrial dysfunction and the overproduction of reactive oxygen species (ROS), leading to oxidative DNA damage and metabolic exhaustion within the myocardium. On a structural level, immune subversion, via macrophage polarization and the induction of autoimmunity, accelerates left ventricular hypertrophy, myocardial remodeling, and interstitial fibrosis. By characterizing chronic infection as a modifiable driver of biological aging, we can prioritize anti-infective strategies as essential components of cardiovascular longevity and geriatric care.

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Cell Physiol Biochem Press GmbH&Co. KG

Introduction

Heart disease is the leading cause of death in the United States, accounting for over 600,000 deaths in 2023 (1). Cardiovascular diseases become more common with age in both men and women (2). As the heart ages, left ventricular hypertrophy, myocardial remodeling,

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and cardiomyocyte senescence lead to diseased states such as heart failure, arrhythmia, and atrial fibrillation (3, 4). As such, slowing or preventing age-related cardiac decline is of great interest to prolong life- and health-span for millions while reducing burden on healthcare systems. Age is increasingly understood as an inflammatory process, characterized by chronic low-grade inflammation called inflammaging, which can be influenced by infectious diseases (5, 6). Infectious agents such as viruses, parasites, and bacteria can directly damage the heart via cardiomyocyte infection and secreted virulence factors, and induce inflammation leading to secondary damage to myocardium, such as fibrosis and hypertrophy, via the immune system (7). Many infections can evade clearance by the immune system to enter a chronic state, and continuously inducing a low-grade inflammatory response accelerating cardiac damage (8). Chronic infections promote several aging-related factors, including elevated reactive oxygen species (ROS) production, mitochondrial dysfunction, impaired autophagy, dysregulated mTOR signaling, and metabolic alterations, all of which can contribute to persistent low-grade inflammation (9–13). These intertwined factors may result in a pro-aging milieu advancing cardiovascular aging. By understanding these changes, we can emphasize the importance of proper prevention and treatment of cardiotropic infections and may discover remediation for cardiac damage and senescence. Here, we review recent evidence linking chronic infectious diseases with the development and progression of cardiac aging phenotypes.

Hallmarks of Cardiovascular Aging

The aging heart undergoes pathological structural and functional changes, including left ventricular hypertrophy, myocardial remodeling, heart failure (with or without reduced left ventricular ejection fraction), arrhythmia, and atrial fibrillation (3, 4). At the molecular level, cardiac aging is driven by several interconnected mechanisms including prolonged inflammatory damage, reactive oxygen species (ROS) production and oxidative damage, mitochondrial dysfunction, and impaired autophagy causing cardiomyocyte senescence, tissue damage, fibrosis, and ultimately age-related performance declines such as heart failure (3, 14). Excessive ROS generation leads to DNA and mitochondrial damage, telomere shortening, and disrupted energy metabolism, establishing a vicious cycle of oxidative and inflammatory injury. Additionally, ATP synthesis is reduced, leading to a greater reliance on glycolysis and reduced ATP reserves. Simultaneously, defective autophagy and persistent mTOR activation exacerbate protein aggregation, fibrosis, and cellular stress responses. Chronic infections amplify these factors, accelerating age-related decline in cardiac function.

Among these hallmarks, inflammation is central in driving cardiac aging. Persistent activation of inflammatory pathways contributes to the development of dilated cardiomyopathy (DCM), myocardial fibrosis, and heart failure (15–17). In response to injury or infection, inflammatory cells like macrophages, T-cells, and eosinophils infiltrate the myocardium, releasing proinflammatory cytokines and contributing to pathological cardiac remodeling (15, 17, 18). These cytokines activate nuclear factor kappa B (NF- κ B), a transcription factor which induces transcription of inflammatory mediators and the NLRP3 inflammasome (19, 20). The NLRP3 inflammasome induces pyroptosis, highly inflammatory cell death which releases cell contents into the extracellular space, causing cardiac damage (21, 22). Senescent cardiomyocytes further sustain inflammation through the senescence-associated secretory phenotype (SASP), perpetuating a milieu of cytokine release, mitochondrial dysfunction, and hypertrophy (23). Thus, inflammation, often sustained by chronic infections or autoimmune responses, acts as a key driver of cardiac aging. In the following sections we discuss these changes in more details. Table 1 summarizes the key hallmarks of cardiac aging and highlights analogous pathological features observed across a range of infectious diseases.

Table 1. Similarities between cardiac aging and symptoms of infectious diseases

Cardiac Aging-related Pathways	References	Inducing Pathogens	References
Oxidative Stress	2,3,9,41	SARS-CoV-2, CVB3, T. gondii, T. cruzi	56,105,120,122,127,145, 146,156
Impaired Autophagy	2,3,12,103,112	HHV-6, CVB3	102,111
Impaired mTOR signaling	2,3,10	HHV-6	95
IL-6 + TNF α Signaling	15, 66, 67, 193	SARS-CoV-2, T. gondii, T. cruzi, S. pneumoniae, M. pneumoniae	65,66,67,90,120,122,143,144,148, 190,198,208
NLRP3 Inflammasome Activation	21,22,43	CVB3, M. pneumoniae	105,209
IFN- γ production	27,28	T. gondii, T. cruzi	120,122,141,142,149
ACE2 Depletion	61,62,63	SARS-CoV-2	60
Thrombosis	59,60	SARS-CoV-2, B19V, S. aureus, S. pneumoniae	69,70,91,92,178,203
Endothelial Dysfunction	80	SARS-CoV-2, B19V, T. gondii, S. aureus	69,77,79,81,124,126,178
Dysregulation of Galectin-3 levels	166,167	T. spiralis	162

Immune Changes in Cardiac Aging

As we age, the immune system is affected by a series of changes termed “immunosenescence” including changes to immune cell populations, increased cytokine production, and the formation of autoantibodies (24). The progression of immunosenescence and the resulting chronic inflammation, often called inflammaging, lacks a central marker. Instead, aging patients show an increase in immune signaling overall, as tracked by multiple inflammatory and anti-inflammatory markers (25). In aged mice, the accumulation of activated CD4⁺ T cells promotes chronic low-grade inflammation in the heart. This leads to increased immune cell infiltration, myocardial remodeling, fibrosis, and mild cardiac dysfunction; notably, depletion of lymphocytes or transfer of young immune cells attenuates these age-related cardiac changes (26).

In a recent study, T-cells were collected from the mediastinal lymph nodes which surround the heart of young and aged mice and subjected to single-cell RNA sequencing. Analysis revealed an age-associated increase in cytotoxic CD8⁺ T-cells and effector memory CD4⁺ T cells (27). In both CD8⁺ and CD4⁺ T-cells, from the lymph nodes or myocardium, IFN- γ levels increased, as did expression of IFN- γ response genes (27). This is notable as IFN- γ treatment has been shown to increase the risk of arrhythmia and atrial fibrillation in rats (28). In the same study, CD8⁺ T-cells expressing IFN- γ in patient peripheral and atrial blood were closely associated with atrial fibrillation and post-procedural recurrence thereof, corroborating the rat results (28). It has been suggested that T-cells activate fibroblasts leading to collagen deposition and myofibroblast differentiation (29, 30). T-cell deficient mice were transplanted with naïve, Th1 wild type, and Th1 IFN- γ knockout T-cells following thoracic aortic constriction to induce non-ischemic heart failure. Only mice with mature IFN- γ competent T-cells developed significant perivascular fibrosis, showing that IFN- γ is necessary for T-cell mediated fibrosis (31). Similarly, major histocompatibility complex II (MHCII) was shown to be necessary for age-related cardiac decline, as MHCII knockout rescued age-related decline in fractional shortening and end diastolic area in mice (32). T-cell changes alone cannot replicate an aged-like phenotype, however, as adoptive transfer of aged T-cells to young mice was insufficient to induce cardiac decline (32).

Age-related changes to immune cell populations are not limited to T-cells. Macrophages undergo significant population shifts and are a source of increased inflammation with age. Cardiac macrophages are of one of two lineages: embryonic yolk sac derived macrophages which are present from birth and proliferate *in situ*, and CCR2⁺ monocyte derived macrophages which infiltrate into the myocardium from the bloodstream (17). In a study of young and aged female mice, the total number of macrophages increased with age with a greater proportion of CCR2⁺ monocyte derived macrophages among their number (33).

Among both lineages, multiple inflammatory pathways are upregulated, leading to a more inflammatory phenotype. Many inflammatory signals, including IL-1 β , IL-6, IL-18, and TNF α , have been associated with cardiovascular disease and may induce profibrotic cytokine release (29, 34). While both lineages expressed proinflammatory pathways, infiltrating CCR2⁺ macrophages may be more important to profibrotic pathways, as in mouse models of cryoinjury and repeated ischemic insult, inhibition of macrophage infiltration significantly reduced collagen deposition (i.e. fibrosis) (35, 36).

The inflammatory signals released by infiltrating and resident immune cells, as well as molecular patterns from pathogens or cellular damage recognized by pattern recognition receptors, activate the transcription factor NF- κ B which in turn promotes pro-inflammatory signaling, immune activity, and cell survival (20). In humans and mice NF- κ B activity increases with age and stress which may be mediated by epigenetic regulation of FK506-binding protein 51 (FKBP51), a protein cochaperone which interacts with NF- κ B regulators (37–39). To study the role of NF- κ B in cardiac aging, mice were modified to overexpress myotroponin to induce cardiac hypertrophy. The mice were then treated with a viral vector for small interfering RNA against the p65 subunit of NF- κ B, decreasing heart weight to body mass ratio and left atrial area and increasing ejection fraction and fractional shortening, indicating improved diastolic function (40). In a later study, male mice were treated with D-galactose to induce premature aging via oxidative stress, reducing ejection fraction, fractional shortening, and telomere length and upregulating TNF- α , all of which was prevented by exosome treatment (39). Then, in an *in vitro* senescence model, the same exosome treatment was shown to reduce inflammation and senescence identically to NF- κ B inhibition (39). Taken together, these results suggest that NF- κ B is a key regulator of inflammatory cardiac damage in aging.

Among the genes upregulated by NF- κ B are the components of the NLRP3 inflammasome, a large protein complex which cleaves IL-1 β and IL-18 into their active forms by facilitating the cleavage and activation of procaspase-1 (19). NF- κ B primes the inflammasome by upregulating its components, and then assembly is induced by endogenous signals including ROS released by damaged mitochondria often found in aging cardiomyocytes (41, 42). Expression of related inflammasomes, inflammasome related genes, and IL-1 β , which signals NF- κ B activation, is increased in older patients and correlates with risk for hypertension, pulse-wave velocity (a measure of arterial stiffness), and lower self-reported familial longevity (43). NLRP3 expression is necessary for cardiomyocyte senescence, structural remodeling, and reduced contractile performance from D-galactose treatment in mice hearts and in rat cardiomyocytes (21, 22). Therefore, NF- κ B may mediate inflammatory cardiac aging via the NLRP3 inflammasome. The inflammasome itself is certainly involved in cardiomyocyte senescence, as NLRP3 inhibition attenuated D-galactose induced senescence of H9C2 cardiomyocytes *in vitro* (22). The NLRP3 inflammasome induces pyroptosis which releases cell contents causing severe inflammation which may contribute to further inflammatory damage (19). Fig. 1 summarizes immune alterations occur in cardiac aging.

The Use of Artificial Intelligence-ECG in Predicting Heart Biological Age

Cardiac aging is characterized by the progressive deterioration of cardiac structure and function and is driven by cumulative molecular, cellular, and metabolic alterations (44). Hallmarks of the aging heart include increased myocardial stiffness, impaired diastolic function, mitochondrial dysfunction, chronic low-grade inflammation, and diminished capacity to respond to physiological stress, all of which contribute to an increased risk of cardiovascular disease and heart failure (44, 45). Although chronological age is a major determinant of cardiovascular risk, it does not fully capture interindividual differences in the biological processes that govern cardiac aging (46). To address this limitation, deep learning algorithms trained on large-scale datasets of standard 12-lead electrocardiograms (ECGs) have been developed to estimate biological heart age. Recent advances in artificial intelligence (AI) enable estimation of biological age using ECGs. Unlike conventional ECG interpretation, which relies on overt cardiac abnormalities, AI models capture complex latent waveform

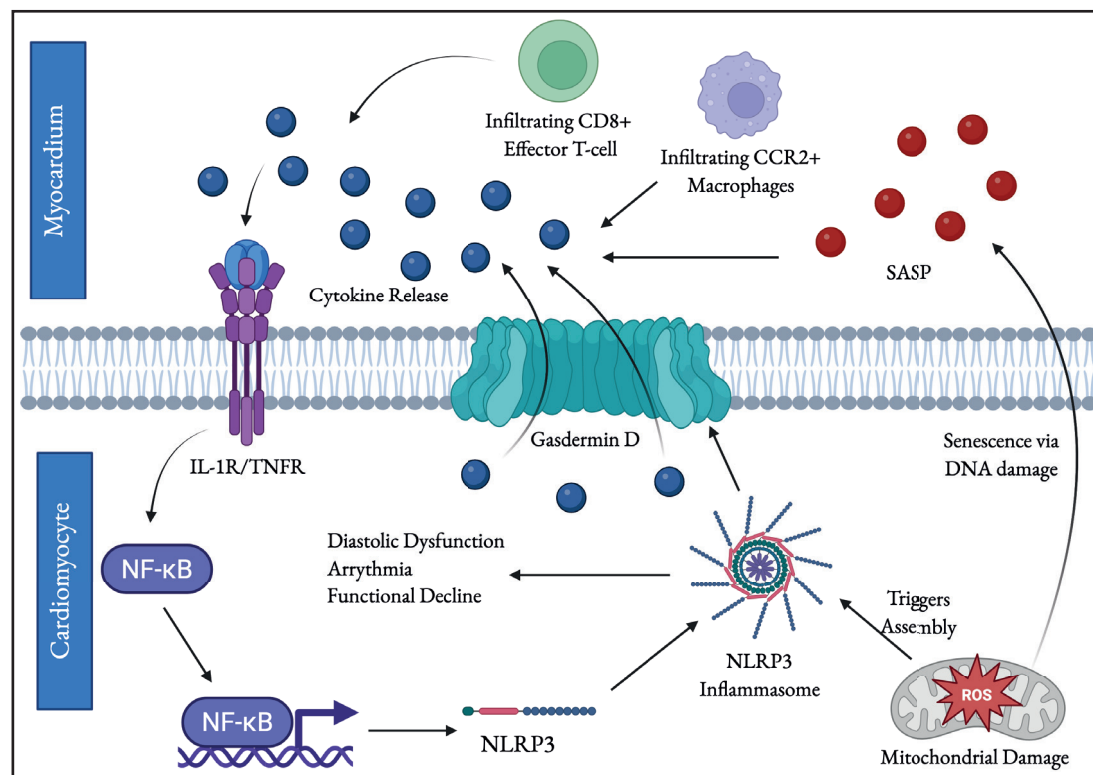


Fig. 1. Immunological alterations contribute to age-related cardiac functional decline. Aging is marked by an increase in cytokine production and a change in T-cell and macrophage populations. The increased release of inflammatory cytokines activates NF- κ B, which activates transcription of inflammatory mediator genes including the NLRP3 inflammasome. Assembly of the components into the active inflammasome can be triggered by endogenous signals like ROS from mitochondrial damage. ROS also induces senescence in cardiomyocytes via DNA damage, which further contributes to cytokine release via the senescence-associated secretory phenotype (SASP). The NLRP3 inflammasome triggers pyroptosis, which releases proinflammatory factors through the formation of gasdermin D pores and is highly pro-inflammatory. NLRP3, NF- κ B, certain cytokines, mitochondrial dysfunction, ROS, and immunosenescence are directly related to age-related functional decline in the heart. Fig. created by BioRender.

features associated with diffuse myocardial remodeling, extracellular matrix deposition, ion channel perturbations, altered repolarization dynamics, and loss of autonomic balance. As a result, AI-ECG can detect subclinical cardiovascular deterioration before the appearance of overt structural disease or measurable declines in cardiac function (47).

When biological age, based on AI-ECG, exceeds chronological age by approximately 6 years, all-cause mortality and cardiovascular event risk increases (48) and age gaps greater than 8 years are associated with significantly higher mortality rate (49), highlighting the utility of AI-derived heart age as a sensitive biomarker of cardiovascular health and aging. Another clinical study evaluated 25,144 adults without pre-existing coronary artery disease, stroke, or atrial fibrillation and followed them for an average of 12.4 years. Compared with individuals whose AI-ECG age was within one standard deviation (SD) of their chronological age, those with an Age-Gap ≥ 1 SD exhibited significantly higher all-cause and cardiovascular disease (CVD) mortality, whereas individuals with an Age-Gap ≤ -1 SD experienced lower all-cause and CVD mortality. Importantly, these associations remained significant after adjustment for traditional cardiovascular risk factors, demonstrating that the AI-ECG age gap is an independent biomarker of biological aging and a powerful predictor of long-term cardiovascular outcomes (50).

Importantly, cardiovascular aging is not a static process but rather a dynamic trajectory that evolves over time. A recent study demonstrated that longitudinal assessment of multiple AI-ECGs substantially improves survival prediction compared with a single ECG measurement. In this cohort of 46,960 patients encompassing 337,415 ECGs and a median follow-up of 4.5 years, it was found that patients whose biological age exceeded their chronological age had a higher hazard of death. Notably, models incorporating serial ECG measurements significantly excelled single-ECG models in predicting all-cause mortality (51). These findings demonstrate that the AI-derived age gap is a dynamic biomarker that captures ongoing physiological changes in cardiovascular health, providing a sensitive measure of age-related decline and a potential tool for monitoring responses to interventions aimed at slowing or reversing cardiac aging.

In chronic infections, a positive age gap may reflect accelerated cardiac senescence. Chronic infections create a sustained microenvironment that accelerates the heart's biological clock through four converging mechanisms. First, unlike acute infections that resolve, chronic infections sustain elevated pro-inflammatory cytokines over months to years. This chronic inflammaging directly damages cardiomyocytes, promotes interstitial fibrosis, and impairs mitochondrial function, all hallmarks of biological cardiac aging that would normally only emerge in older individuals. Second, persistent pathogen burden forces the immune system into a state of exhaustion and metabolic reprogramming (52, 53). This can cause systemic insulin resistance, oxidative stress, and mitochondrial inefficiency that mirror the metabolic profile of an aging heart, even in young patients. The infected heart is forced to operate in a chronically energy-deprived state, accelerating functional decline. Third, repeated cycles of subclinical injury and repair deposit collagen and stiffen the myocardium. This structural remodeling is indistinguishable, at the tissue level, from age-related fibrosis. It alters electrical conduction, increases arrhythmic risk, and reduces diastolic compliance, all features that AI-ECG systems detect as signatures of an older heart. Lastly, chronic infections can impair the autonomic nervous system, reducing heart rate variability and blunting baroreflex sensitivity. Autonomic aging is one of the strongest predictors of cardiovascular mortality, and chronic infection accelerates it substantially. Because gap age can be assessed non-invasively and repeatedly over time, AI-ECG offers a dynamic biomarker for monitoring disease progression and evaluating the effectiveness of interventions targeting aging-associated pathways.

Chronic Infections and Cardiovascular Aging

Viral infections

Viral infections are the major cause of myocarditis and can cause debilitating cardiac tissue damage. The infection can lead to ROS generation, chronic inflammation, and fibrosis. Infection with cardiotropic viruses such as SARS-CoV-2, Human Parvovirus B19, Human Herpes-Virus Type 6, and Cocksackievirus B lead to cardiac functional decline and molecular changes that resemble age-related decline.

SARS-CoV2. COVID-19, caused by SARS-CoV-2, demonstrates a complex pathology that not only causes acute cardiac injury, but also appears to accelerate cardiovascular aging through mechanisms of chronic inflammation, mitochondrial dysfunction, and structural damage (54–57). The heart highly expresses ACE2 (angiotensin-converting enzyme 2), the viral entry receptor of SARS-CoV-2 (58, 59). During SARS-CoV-2 infection, ACE2 dysregulation emerges as a central driver of cardiac dysfunction. As the virus binds to ACE2, it induces its downregulation or cleavage (60), disrupting one of the heart's primary mechanisms for regulating stress responses and vascular tone (61). This feature closely mirrors the physiology of the aging heart, where the gradual age-related loss of ACE2 reduces cardiac resilience and leaves the myocardium increasingly vulnerable to injury and dysfunction (62, 63).

The post-acute sequelae of COVID-19, commonly known as Long COVID, appear to resemble a state of accelerated biological aging (64), primarily through persistent inflammation and immune dysregulation (65). This chronic inflammatory state mirrors inflammaging, characterized by sustained elevations of pro-inflammatory cytokines, particularly IL-6 and TNF- α which are key mediators of age-related cardiovascular disease such as myocardial infarction and heart failure (66, 67). Persistent autoimmunity, exemplified by the presence of antiphospholipid antibodies in COVID-19 patients (68), contributes to vascular injury, thrombosis, and endothelial dysfunction (69), thereby promoting premature vascular aging. Moreover, viral spike protein binds to fibrin and fibrinogen, two central components of the coagulation pathway, which can lead to abnormal protein folding and clot formation in patient blood samples (70). Importantly, serum samples from COVID-19 patients with asymptomatic, mild, and severe disease were found to contain elevated levels of fibrin-targeting autoantibodies (70), potentially influenced by the persistence of spike protein post infection in certain cell types such as monocytes (71).

Mitochondrial dysfunction, a defining hallmark of cellular aging, is increasingly recognized as a central feature of COVID-19 pathology. The virus disrupts mitochondrial structure and function across multiple cell types, leading to loss of membrane potential, excessive ROS generation, and impaired ATP production in monkey kidney and human hepatocarcinoma cells (72). In human stem cell-derived cardiomyocytes, infection reduces mitochondrial number and causes visible swelling, resulting in the cessation of rhythmic beating (73). These changes were associated with induction of cell cycle arrest in infected cardiomyocytes. Moreover, transcriptional profiling of infected cardiomyocytes further reveals a metabolic reprogramming, characterized by the downregulation of oxidative phosphorylation (74). This metabolic dysregulation is reminiscent of the metabolic decline seen in aged cardiomyocytes (75, 76). Compounding this dysfunction, SARS-CoV-2 also inhibits mitophagy, the process responsible for clearing damaged mitochondria, in monkey kidney and human hepatocarcinoma cells (72). The resulting accumulation of defective mitochondria amplifies oxidative stress and accelerates cellular senescence, driving long-term consequences such as reduced global longitudinal strain and diastolic impairment, cardiac features that closely mirror aging (77). Collectively, these mechanisms suggest that SARS-CoV-2 infections initiate and maintain processes indistinguishable from those driving natural cardiovascular aging, effectively accelerating decline in the heart and vasculature.

Human Parvovirus B19. Human Parvovirus B19 (B19V) is increasingly implicated in long-term cardiovascular pathology. While it primarily infects endothelial and erythroid progenitor cells (8), its mechanisms of damage, endothelial dysfunction with impaired regeneration and autoimmunity, significantly augment the biological processes of cardiac aging.

B19V directly targets the vascular system, inducing damage and disrupting the repair processes essential for maintaining normal cardiac function. Although B19V primarily replicates in erythroid cells, it can also infect endothelial cells where viral transcription and protein synthesis lead to endothelial dysfunction and apoptosis (78, 79), a core feature of vascular aging that contributes to arterial stiffness and impaired blood flow (80). The infection further impairs endothelial regeneration by damaging endothelial progenitor cells, impairing vascular repair and angiogenesis in a mouse transplantation model (81). In addition, B19V infects bone marrow-derived circulating angiogenic cells that normally contribute to blood vessel development and repair. By disrupting these cell populations, B19V not only hinders proper vascular regeneration, but also creates conditions that facilitate its spread, ultimately promoting the progression of cardiomyopathy in B19V patients (81). Infected endothelial cells also upregulate Tenascin C and transforming growth factor beta (TGF- β) in human micro-endothelial cells (82), both of which promote cardiac fibrosis and pathological tissue remodeling (83, 84), key structural hallmarks of the aging heart. Moreover, the B19V capsid protein, VP1u, activates stress signaling pathways involving JNK, ERK, c-Jun, and c-Fos in primary rat endothelial cells (85). These molecular cascades

are linked to cardiac remodeling and vascular aging that heighten long-term cardiovascular risk and mortality (86). Together, these mechanisms position B19V as a potent inducer of endothelial senescence and cardiac aging.

Chronic B19V infection may compromise the heart's energy metabolism, a process closely linked to cardiac aging. Transcriptionally active B19V, linked to higher mortality in non-ischemic cardiomyopathy patients (87), directly disrupts the expression of genes that encode essential mitochondrial respiratory chain proteins in endomyocardial biopsies (88). Such mitochondrial dysfunction not only weakens the myocardium's ability to tolerate physiological stress but also drives the progressive decline in cardiac performance characteristic of age-related heart disease (76).

B19V infection may induce a persistent autoimmune response that imitates and amplifies inflammaging. B19V antigens resemble host proteins leading to the generation of cross-reactive antibodies (44). This cross-reactivity can provoke the synthesis of autoantibodies that attack cardiac proteins, such as myosin and troponin, in B19V patients (89). Antibodies directed against the viral VP1u region, for instance, drive robust inflammation through elevated IL-6, TNF- α , and NF- κ B signaling while promoting complement-mediated cardiomyocyte lysis in mice (90). B19V induced autoimmunity resembles antiphospholipid syndrome. This process is characterized by generation of antibodies against the mitochondrial phospholipid cardiolipin and the clotting regulator beta-2-glycoprotein (91, 92). This manifests as excessive clotting, vascular inflammation, coagulation abnormalities, heightened risk of stroke, valvular injury, and coronary artery disease (63, 64), all of which can lead to vascular aging and chronic inflammation.

Human Herpes-virus Type 6. Human Herpesvirus-6 (HHV-6) may accelerate cardiac aging through its ability to establish a persistent infection in the heart (8). HHV-6 infection is linked to myocarditis, DCM, and heart failure in a significant portion of infected patients as detected by endomyocardial biopsy (93). HHV-6 directly targets fundamental biological drivers of senescence, such as mitochondrial dysfunction and inflammation. HHV-6 infection induces mitochondrial alterations including increased fragmentation, and alteration of mitochondrial proteins involved in fatty acid, amino acid and carbon metabolism in human adenocarcinoma cells (94). This creates an energy deficit, weakening the heart's ability to maintain normal contractile and metabolic function; as in cardiac aging (3). Furthermore, infected human T-cells exhibit a metabolic shift toward glycolysis driven by enhanced mTOR signaling (95). This mirrors metabolic changes seen in aged hearts where reduced mitochondrial efficiency forces reliance on less efficient energy pathways, like glycolysis (96). Collectively, these alterations establish a self-perpetuating cycle of energy failure and oxidative stress which may lead to premature cardiac aging.

HHV-6 infection may result in accelerated structural and functional cardiac aging. Recent clinical evidence revealed that HHV-6 infection induces cardiac arrhythmias, ventricular dilatation, and infiltration of immune cells, such as lymphocytes and neutrophils, within the myocardium of affected patients (97, 98). Persistent HHV-6 infection has also been linked to reductions in left ventricular ejection fraction (LVEF) in patients (99), indicating a progressive decline in cardiac performance. Importantly, the pathological influence of HHV-6 extends beyond the heart. Alongside related herpesviruses such as Epstein-Barr virus (EBV), HHV-6 has been implicated in systemic inflammatory conditions; including multiple sclerosis (100), which in turn increase susceptibility to age-associated vascular disorders such as acute coronary syndromes and cerebrovascular disease (101).

HHV6 also interferes with autophagy in human T-cells primarily through the activation of mTOR signaling (95), which naturally becomes overactive with age as autophagy declines (3). By sustaining high mTOR activity, HHV6 effectively locks the cell in a dysfunctional, aged-like state. Evidence of this autophagic blockade includes the accumulation of sequestosome 1 (p62), a marker of impaired protein degradation, in donor peripheral blood mononuclear cells (PBMCs) (102). As p62 and misfolded or ubiquitinated proteins build up, they contribute to proteotoxic stress, a key driver of cardiac aging and pathology seen in dilated and ischemic

cardiomyopathies (103). Thus, HHV6-induced autophagy inhibition not only mirrors natural aging mechanisms but also amplifies cellular dysfunction within the heart.

Taken together, HHV-6 infection promotes cardiac aging through converging mechanisms that span myocardial inflammation, systemic immune dysregulation, mitochondrial dysfunction, and impaired proteostasis. By chronically activating mTOR signaling and inhibiting autophagy, HHV-6 enforces an aged cellular phenotype characterized by proteotoxic stress and declining contractile function. These viral-driven processes resemble and intensify age-related cardiac decline, ultimately increasing vulnerability to heart failure and vascular disease.

Coxsackievirus B. Coxsackievirus B (CVB) is a significant cardiotropic enterovirus strongly associated with human heart diseases, including myocarditis, pericarditis, and DCM (15). The mechanisms of CVB pathology, specifically mitochondrial disruption, subversion of autophagy, and induction of autoimmunity, create a state of chronic damage and dysfunction that accelerates cardiac aging.

CVB directly targets the cellular systems that sustain energy production and mitochondrial quality control, accelerating the metabolic and structural decline typical in the aging heart. CVB3 infection induces upregulation of transferrin receptor protein 1, which disrupts cristae structure and increases membrane density in HeLa cells (104). It has been shown that altered mitochondrial morphology (including abnormal, irregularly arranged cristae and increased vacuole number) precedes cardiac inflammation in CVB3 infection of mice and primary mouse cardiomyocytes (105). Furthermore, CVB3 infection decreased ATP production, increased ROS production, and decreased membrane potential in infected rats and neonatal rat cardiomyocytes (105). These alterations are associated with decreased membrane potential, mitochondrial fragmentation, and an induction of autophagosome formation and mitophagy in infected HeLa cells (106). However, the decrease in membrane potential could not be replicated in H9C2 rat cardiomyocytes except at excessively high multiplicities of infection (MOI 50 or greater)(106). Conversely, one study showed an increase in respiration and ATP production which was dependent on ISG15, a target of interferon signaling, which suppresses viral replication and shifts cardiac metabolism toward oxidative phosphorylation in mice (107). The two studies use different strains of mice, so it is possible that genetic determinants of interferon signaling and susceptibility to subversion are determinants of susceptibility to viral myocarditis and DCM.

The sustained immune response following CVB infection drives long-lasting cardiac pathology that persists even after the virus itself is cleared, leading to chronic age-like decline of the heart. CVB infection triggers an autoimmune response in patients in which antibodies generated against viral proteins cross-react with host cardiac proteins such as myosin, a key component of the contractile machinery (15). This phenomenon fuels autoimmune myocarditis, setting off a cycle of inflammation and tissue injury that progresses from acute myocarditis to long-term DCM and eventual heart failure (15, 108).

Autophagy declines naturally with age, and CVB3 exploits this vulnerability to accelerate cardiac senescence. CVB3 disrupts protein clearance in HeLa cells by cleaving key autophagy-related proteins such as sequestosome 1 (p62) which normally aggregates ubiquitinated proteins and delivers them to autophagosomes for degradation (109–111). This disruption leads to the accumulation of ubiquitinated and misfolded proteins, forming toxic aggregates implicated in age-related cardiac pathologies such as dilated and hypertrophic cardiomyopathies and myocardial ischemia (103, 112). Autophagy protects the heart under stress, and its impairment by CVB3 resembles the dysfunction of an aged myocardium. Beyond general autophagy, CVB3 also hijacks mitophagy with devastating effects on cardiac metabolism. The virus induces mitophagy through the Parkin pathway in mice (113), but redirects autophagosomes to serve as replication niches and vehicles for viral egress rather than for degradation in mouse cardiomyocytes (114–116). This subversion may release damaged mitochondria and mitochondrial DNA (mtDNA) into the extracellular space (117), where mtDNA acts as a potent danger signal that triggers chronic inflammation through

macrophage activation and cytokine release (TNF- α and IL-6). Accumulated mitochondria further generate ROS and apoptotic factors like cytochrome C (3, 103), intensifying oxidative stress and inflammation. Collectively, these processes create a self-perpetuating cycle of cellular damage, metabolic collapse, and inflammaging, converting healthy cardiomyocytes into senescent-like cells and paving the way for fibrosis, chronic inflammation, and heart failure. In Fig. 2 we have summarized the effects of viral infections on cardiovascular aging.

Parasitic infections

Parasitic infections, including *Toxoplasma gondii*, *Trypanosoma cruzi*, and *Trichinella spiralis*, elicit robust inflammatory immune responses and characteristically progress from an acute phase to chronic persistence. Many of these parasites exhibit cardiac tropism, while in other cases sustained systemic and local inflammation leads to collateral myocardial injury. Regardless of the initiating mechanism, chronic parasitic infection imposes prolonged inflammatory and metabolic stress on cardiomyocytes, thereby exacerbating age-associated

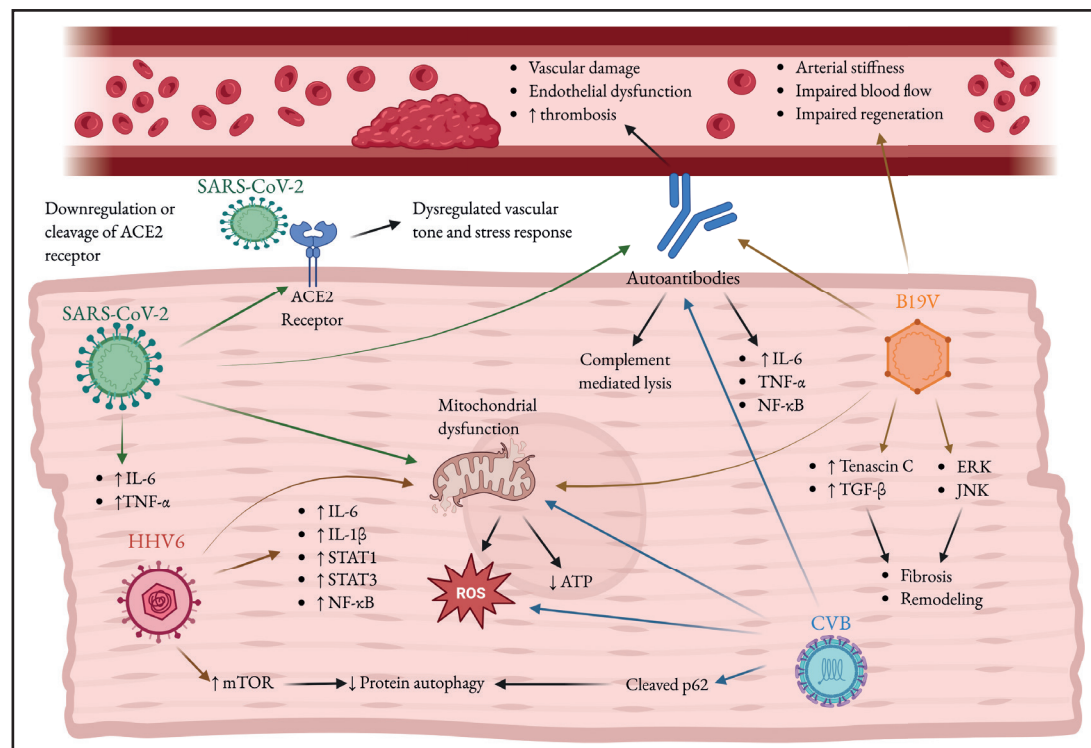


Fig. 2. Viral infections promote cardiac aging and disease. Shown above are SARS-CoV-2, Human herpesvirus-6 (HHV6), Human parvovirus B19 (B19V), Coxsackievirus (CVB) and the mechanisms by which they can contribute to an age-like diseased phenotype in the infected heart. Viral infection cause inflammation and, in the case of B19V, JNK and ERK signaling, which contribute to cardiac fibrosis and pathological tissue remodeling. Many viruses can cause mitochondrial dysfunction, an increase in ROS production and oxidative stress while decreasing ATP reserves, contributing to senescence. SARS-CoV-2 can cause cardiac dysfunction via binding to its viral entry receptor, angiotensin-converting enzyme 2 (ACE2). HHV6 increases mTOR signaling, while CVB cleaves sequestosome 1 (p62). Both inhibit proper autophagy, which contributes to aging and fibrosis. SARS-CoV-2 and B19V cause autoantibody formation, leading to endothelial dysfunction and thrombosis. Autoantibodies also cause inflammation and cell lysis via complement activation. B19V additionally infects endothelial cells, impairing blood flow and arterial regeneration, while promoting arterial stiffness. Fig. created by BioRender.

cellular exhaustion and accelerating pathological cardiac remodeling. In the following sections, we highlight the molecular and cellular mechanisms through which these chronic parasitic infections promote cardiac aging and functional decline.

Toxoplasma gondii. *Toxoplasma gondii* is an obligate intracellular parasite infecting approximately one-third of the global population (118). The parasite utilizes three forms, tachyzoite (rapidly dividing), bradyzoite (tissue cyst), and oocyst (transmission/persistence), and is primarily transmitted through the ingestion of oocysts from contaminated food, water, or soil, or via tissue cysts in undercooked meat (119). Accumulating evidence links chronic *T. gondii* infection to accelerated cardiovascular disease and aging.

The primary link between chronic *T. gondii* infection and cardiovascular disease appears to be sustained immune activation that drives excessive production of ROS, a key mediator of vascular aging. Persistent *T. gondii* infection promotes a prolonged Th1-dominant inflammatory response marked by elevated levels of IFN- γ , TNF- α , and IL-1 β which stimulate ROS generation through mitochondrial dysfunction and activation of NADPH oxidases in immune and endothelial cells from humans and mice (120–122). Sustained oxidative burden overwhelms antioxidant defenses leading to redox imbalance, endothelial dysfunction, and cumulative vascular injury (123). This chronic ROS-rich inflammatory environment closely parallels, and amplifies, inflammaging, thereby accelerating vascular aging and increasing susceptibility to cardiovascular disease. Consistent with this mechanism, latent *T. gondii* infection is associated with elevated circulating biomarkers of endothelial injury vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1) in chronic *T. gondii*-infected individuals reflecting persistent endothelial activation (124). Also, elevated serum levels of endothelin-1, a marker of endothelial dysfunction, have been reported in patients with acute toxoplasmosis (125). Moreover, acute *T. gondii* infection in mice demonstrates direct vascular involvement, inducing endothelial activation, upregulation of adhesion molecules, and structural alterations in cerebral vasculature (126). These changes are accompanied by vascular occlusion and impaired cerebral blood flow indicating functional vascular decline (126). At the cellular level, acute *T. gondii* infection of human umbilical vein endothelial cells (HUVECs) induces DNA damage, S-phase cell-cycle arrest, and cytokinesis failure (127). Although ROS are a well-recognized driver of DNA damage, intrinsic ROS production in infected HUVECs does not appear to account for the early DNA damage observed during infection (127). Importantly, these *in vitro* studies do not account for extrinsic sources of oxidative stress, such as ROS generated by infected macrophages. Therefore, future investigations should assess endothelial injury in more physiologically relevant settings that incorporate immune-endothelial interactions to better define the contribution of *T. gondii* infection to vascular aging.

Epidemiological and clinical evidence consistently demonstrate that *T. gondii* infection is associated with increased cardiovascular risk similar to advanced age. Infected individuals frequently exhibit an adverse biomarker profile including elevated blood pressure, plasma triglycerides, and C-reactive protein (CRP), coupled with reduced HDL cholesterol, markers that typically worsen with age (128). Population-based studies suggest chronic subclinical cardiac involvement. Notably, case-control studies identified a strong association between *T. gondii* seropositivity and cardiovascular diseases, particularly in older adults (129, 130). In addition, another study found that *T. gondii* infection is associated with higher risk of cardiovascular mortality in men (131). Collectively, these findings indicate that *T. gondii* infection may act as a biological catalyst for cardiovascular aging by sustaining chronic inflammation and oxidative stress; which compromise vascular integrity and accelerate atherosclerosis.

Trypanosoma cruzi. *Trypanosoma cruzi*, an intracellular protozoan parasite, is the causative agent of Chagas disease. Chagas diseases is known to be endemic throughout Latin America, however a recent CDC report indicates endemic circulation of the disease in the USA as well (134). Chagas disease is transmitted predominantly through triatomine

insects (kissing bugs) in rural regions where housing conditions favor vector colonization. However, non-vectorial routes such as congenital transmission, blood transfusion, organ transplantation, and ingestion of contaminated food or beverages also contribute to disease spread (132, 135). Following a 1-2 week incubation period, the acute phase typically lasts 4-8 weeks and is often marked by mild, nonspecific symptoms such as fever and malaise (136). If untreated, approximately 20-30% of infected individuals develop chronic Chagas cardiomyopathy (CCC), manifesting as progressive cardiac dysfunction (137, 138). Older individuals are particularly vulnerable, as *T. cruzi* infection in this group is associated with the gradual emergence of new electrocardiographic abnormalities and an increased risk of cardiac-related mortality (139, 140).

CCC represents the most severe manifestation of the chronic phase of *T. cruzi* infection, characterized by persistent parasitic presence and a sustained dysregulated immune response, despite the typically low number of detectable parasites within cardiac tissue. Clinically, CCC presents with a spectrum of debilitating cardiac manifestations including conduction abnormalities like right bundle branch block, arrhythmias, ventricular aneurysms, heart failure, and an elevated risk of sudden cardiac death (137, 138). Mechanistically, *T. cruzi* infection initiates a destructive cycle of immune activation, inflammation, oxidative stress, and mitochondrial dysfunction in the hearts of patients (141, 142) that closely resembles cardiac aging (2). Upon *T. cruzi* infection, parasite-derived molecules, including glycosylphosphatidylinositol (GPI) anchors and nucleic acids, are recognized by host Toll-like receptors (TLRs), particularly TLR2 and TLR9, initiating MyD88-dependent signaling cascades that activate NF- κ B (143). This signaling axis drives the production of key proinflammatory mediators via IL-17 signaling, including IL-12, TNF- α , and IFN- γ which are essential for the development of effective innate and adaptive immune responses and play a critical role in host resistance to *T. cruzi* infection (143, 144). Also, it has been shown robust production of IL-17 promotes Th17 responses which aid resistance against infection and reduce cardiac inflammation in mice (144). IFN- γ enhances macrophage activation and the generation of reactive oxygen and nitrogen species (ROS and RNS) through induction of inducible nitric oxide synthase and NADPH oxidase, which are essential for parasite control, but also contribute to collateral oxidative damage in host tissues; including the myocardium (145, 146). Persistent ROS/RNS production in *T. cruzi* infected patients has been linked to oxidative injury of cardiac lipids, proteins, and DNA; and subsequent functional impairment of the heart. Persistent oxidative and inflammatory stress ultimately drives myocardial senescence, fibrosis, and remodeling leading to contractile dysfunction in rats and H9C2 rat cardiomyocytes (147). Chronic *T. cruzi* infection maintains elevated pro-inflammatory cytokines (IFN- γ , TNF- α , IL-6, and IL-1 β) in CCC patients, correlating with myocardial damage severity, whereas higher IL-10 levels are linked to better outcomes (148).

A key mechanism underlying this immune-mediated pathology is resemblance of *T. cruzi* antigens to its host cells. This can result in a persistent Th1-dominant inflammatory environment promoting autoreactivity against cardiac tissue. Recent studies demonstrate that specific alleles of HLA-DRB1, a type of immune molecule that helps present protein fragments to T cells, found in patients can present peptides with sequence homology between *T. cruzi* antigens and host cardiac myosin (149). This leads to the activation of autoreactive CD4⁺ T cells in CCC patients and enhanced IFN- γ production and cytotoxic gene expression, which are strongly associated with ventricular dysfunction and myocardial fibrosis (149).

During *T. cruzi* infection in humans, the immunoregulatory protein galectin-1 (Gal-1) is upregulated and affects cardiac pathology and immune responses (151). It has two distinct context-dependent functions and is upregulated in infected tissues, particularly the heart (152). On the one hand, Gal-1 helps to limit acute tissue damage by protecting mouse cardiomyocytes from parasite infection and parasite-induced cell death (152). However, by stimulating regulatory T cells (CD4⁺CD25⁺Foxp3⁺) and raising anti-inflammatory mediators like IL-10 and TGF- β 1, it inhibits Th1 and CD8⁺ T cell responses to the parasite in mice (151, 153). This immune suppression lessens the host's capacity to eradicate the infection and promotes parasite persistence. Gal-1 has dose-dependent effects in mouse macrophages; at

low concentrations, it reduces microbicidal activity and promotes parasite survival; at higher concentrations, it triggers macrophage apoptosis and inhibition of parasite replication (151). Overall, Gal-1 contributes to the complex immunopathology of Chagas disease as well as parasite persistence by balancing the protection of cardiac tissue with the suppression of effective anti-parasite immunity.

Elevated levels of IFN- γ and TNF- α are central to the pathogenesis of CCC, driving sustained activation of NF- κ B signaling and upregulation of inducible nitric oxide synthase (iNOS) in patient hearts (141, 142). This inflammatory cascade leads to excessive production of nitric oxide (NO), ROS, and the potent oxidant peroxynitrite within patient cardiomyocytes, resulting in widespread oxidative and nitrosative damage (141, 142). The ensuing oxidative stress disrupts mitochondrial membrane potential, impairs ATP synthesis, and causes depletion of mtDNA, as demonstrated in both the human CCC myocardium and cytokine-treated cardiomyocytes (141, 142, 154). Electron leakage and an overabundance of mitochondrial reactive oxygen species (mtROS) may be caused by an electron transport chain disruption seen in mouse cardiomyocytes (155). The NFE2L2-antioxidant response element pathway is inhibited by the persistent production of mtROS in mice, impairing the antioxidant defenses of the cell and encouraging oxidative adduct accumulation, myocardial fibrosis, and left ventricular dysfunction (156). This persistent mitochondrial dysfunction sustains oxidative stress and energy deficit; resulting in a metabolic profile marked by reduced mitochondrial metabolism and increased immune activation closely resembling age-related heart failure (141, 142, 154, 157). *T. cruzi* infection provides a powerful model for understanding how chronic infections can accelerate cardiac aging, emphasizing the need for therapeutic strategies that simultaneously target persistent infection, metabolic dysfunction, and chronic inflammation.

Trichinella spiralis. *Trichinella spiralis* is a globally distributed zoonotic nematode responsible for trichinellosis with an estimated global incidence of around 10,000 human cases per year (158). Transmission occurs primarily through the consumption of raw or undercooked meat containing infectious larvae (159). *T. spiralis* infection offers a compelling case of how an infectious agent can initiate and exacerbate severe cardiac pathology. In a significant proportion of infected individuals, an estimated 10 to 60%, cardiovascular complications emerge, including eosinophilic myocarditis, pericarditis, and thrombotic events (160, 161). Among these, eosinophilic myocarditis is particularly consequential, often accompanied by elevated cardiac troponin levels and characteristic electrocardiographic abnormalities (161). While *T. spiralis* infection initially triggers acute myocarditis, in the long term it induces a chronic pathological state via immune suppression which resembles inflammaging. Cardiac damage is driven in large part by intense eosinophil infiltration and the release of granule proteins, which perpetuate myocardial inflammation and tissue remodeling in mice (162). *T. spiralis* also employs sophisticated immune evasion strategies, inducing a shift in mouse macrophage populations from pro-inflammatory M1 to anti-inflammatory M2 phenotypes (163, 164); and suppressing pro-inflammatory T cells (165). Although this immunosuppressive shift mitigates overwhelming acute inflammation, it may facilitate parasite persistence and sustain chronic, low-grade inflammation.

A central mediator connecting *T. spiralis* infection to cardiac aging is Galectin-3 (Gal-3), a key regulator of inflammation and fibrosis. Gal-3 is a recognized biomarker and effector molecule in age-related cardiac remodeling and heart failure (166, 167). During acute *T. spiralis* infection in mice, Gal-3 expression rises markedly, although inhibition of galectin receptor interactions exacerbates myocardial inflammation, dysfunction, and fibrosis (162). These findings suggest that Gal-3 may function as a compensatory mechanism, acting to limit excessive inflammatory damage and fibrotic remodeling in the infected myocardium. Furthermore, *T. spiralis* infection perturbs host lipid metabolism in mice, particularly glycerophospholipid pathways (168), while Gal-3 itself promotes hepatic lipid accumulation in mice (169). The convergence of these effects, elevated Gal-3 signaling and disrupted lipid metabolism, synergistically drives fibrotic remodeling and cardiac hypertrophy

in hamsters and H9C2 rat cardiomyocytes (162, 170). Together, these processes create a metabolic and structural environment that closely mirrors the progressive decline of the aging heart, underscoring how infection-induced immune and metabolic dysregulation may emulate and accelerate cardiac aging. Fig. 3 summarizes the effects of parasitic infections on cardiovascular aging.

Bacterial Infections

Bacterial infections can promote cardiac aging by inducing the release of cytokines causing damage to cardiac cells. Bacterial infections such as *Staphylococcus aureus*, *Streptococcus pneumoniae*, and *Mycoplasma pneumoniae* contribute to fibrosis of heart tissue, weakening heart muscle function as in cardiac aging.

Staphylococcus aureus. *Staphylococcus aureus* is a critical Gram-positive pathogen responsible for severe and often life-threatening cardiovascular infections including myocarditis and infective endocarditis (IE). These conditions rank among the most fatal cardiac infections with IE exhibiting a particularly high mortality rate (171, 172). The

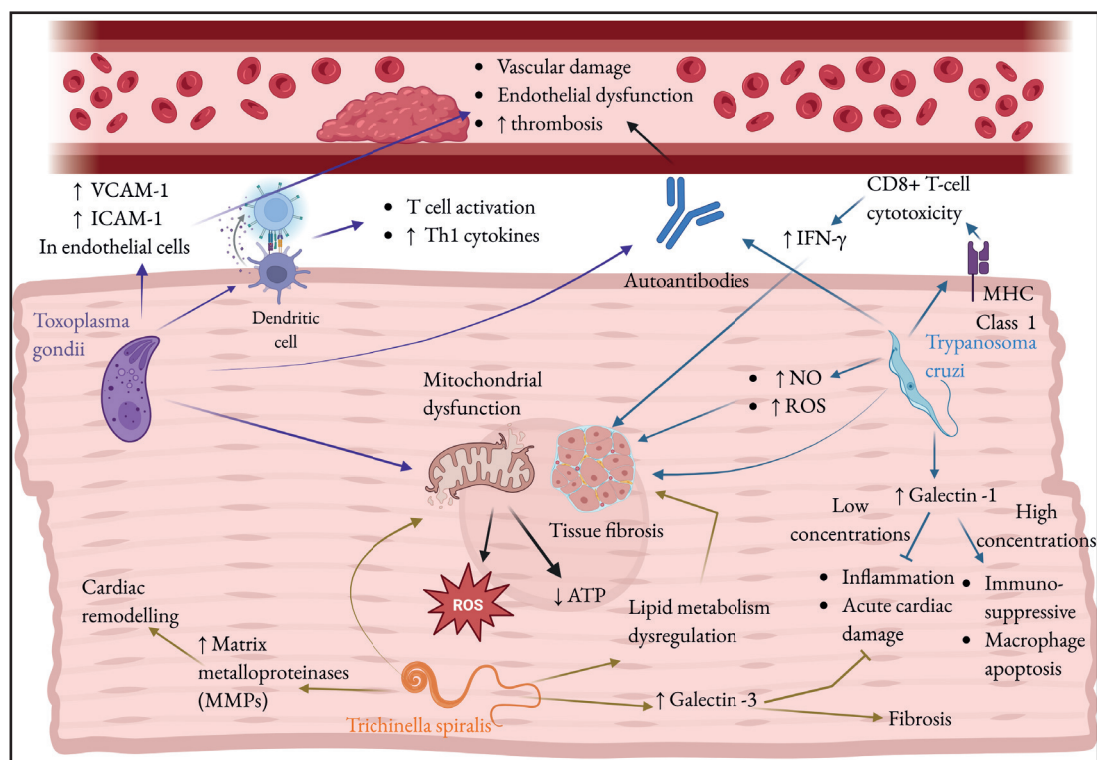


Fig. 3. Parasitic infections promote cardiac aging and disease. The parasites *Toxoplasma gondii*, *Trypanosoma cruzi*, and *Trichinella spiralis* are shown alongside the pathways by which they cause an aged-like diseased phenotype in the heart. Parasitic infections promote inflammation via various pathways, including dendritic cell activation and autoantibody production in *T. gondii*, MHC class 1 upregulation and autoantibody formation in *T. cruzi*, and cytokine production in *T. spiralis*. This inflammation promotes fibrosis in the heart. Autoantibody production also leads to endothelial damage and dysfunction, and thrombosis. *T. gondii* and *T. spiralis* cause mitochondrial dysfunction which increases reactive oxygen species (ROS) production and decreases ATP reserves, contributing to senescence. *T. gondii* decreases nitric oxide production, leading to myocardial stiffening, and VCAM-1, a marker of endothelial activation. *T. cruzi* and *T. spiralis* increase galectin signaling, which decrease acute inflammation and cardiac damage, but suppress the immune response to allow parasite persistence, and promote fibrosis. Additionally, *T. spiralis* upregulates matrix metalloproteinases (MMPs) which mediate pathological cardiac remodeling. Fig. created by BioRender.

pathology and severity of *S. aureus* infections are further intensified by the natural process of cardiac aging, which reduces tissue regeneration and immune competence (42, 173). *S. aureus* employs a range of virulence factors that are especially destructive to the aging cardiovascular system. For instance, *S. aureus* secreted enterotoxins are known to activate host inflammatory pathways inducing multiple forms of programmed cell death including apoptosis, pyroptosis, and necroptosis (174, 175). The pore-forming α -toxin targets epithelial and endothelial cells, leukocytes, and platelets (176, 177) promoting chronic endothelial injury in patients that facilitates thrombogenesis and the formation of a mass of proliferating bacteria shielded by serum molecules and platelets called a vegetation (178). Moreover, *S. aureus* utilizes antibiotic-neutralizing enzymes that enhance antimicrobial resistance resulting in dangerous antibiotic resistant strains (179).

S. aureus infection may lead to infective endocarditis, a disease increasingly associated with advanced age. *S. aureus* is the most frequent pathogen identified in infective endocarditis, as demonstrated in a cohort study of 2,781 patients where it accounted for 31.2% of cases and was commonly linked to mitral and aortic valve damage, heart failure, and complications such as embolization, pulmonary edema, and stroke (180). The rising incidence of infective endocarditis among elderly populations is partly attributed to degenerative valvular diseases, such as calcific stenosis, that provide a damaged surface conducive to bacterial colonization (180). Moreover, *S. aureus* infection is associated with a higher risk of in-hospital mortality, particularly in patients with advanced age, prosthetic valve involvement, or paravalvular complications (180). A study of 221 patients with confirmed infective endocarditis following *S. aureus* bacteremia found vegetations in 65.9% of cases. These vegetations, attached to the endocardium, underscore the rapid progression of the infection (181). Beyond infective endocarditis, *S. aureus* is also the most common bacterial cause of myocarditis in humans characterized by the formation of small abscesses, typically in the left ventricle (182). *S. aureus* myocarditis results in cardiac dysfunction, arrhythmias, myocardial rupture, and purulent pericarditis in infected patients (182). In the aged myocardium, where regenerative capacity is diminished (173), these structural complications are both more frequent and more severe.

Methicillin-resistant *Staphylococcus aureus* (MRSA) refers to highly virulent and drug-resistant strains associated with more severe complications. Clinically, MRSA endocarditis leads to significantly worse outcomes than methicillin-susceptible *S. aureus* infections including higher rates of renal complications, persistent bacteremia, and mortality (183). Alarming, MRSA-related deaths in the United States have surpassed those attributed to AIDS, Parkinson's disease, and homicide (184). Mechanistically, MRSA's resistance to β -lactam antibiotics is mediated by the *mecA* gene which encodes the altered penicillin-binding protein PBP2a (184, 185). Treatment is further challenged by the need for alternative antibiotics such as vancomycin or daptomycin (186), and by the emergence of vancomycin-intermediate and vancomycin-resistant *S. aureus* strains (187). Moreover, MRSA biofilms on mechanical cardiac valves and implanted medical devices perpetuate chronic infection (188). In older adults who are more likely to have implanted devices, this biofilm persistence contributes to recurrent bacteremia and often necessitates aggressive management, including surgical intervention (188).

Streptococcus pneumoniae. *Streptococcus pneumoniae*, a common opportunistic pathogen, has emerged as a significant contributor to cardiovascular disease. The mechanisms of *S. pneumoniae*-induced cardiotoxicity directly intersect with and accelerate cardiac aging by amplifying tissue injury and exploiting age-related vulnerabilities. A key driver of this process is pneumolysin, a pore-forming toxin that induces human and mouse cardiomyocyte death via necroptosis (189–191). Necroptosis is a highly proinflammatory form of programmed cell death mediated by RIPK1 and RIPK3 activation, followed by MLKL-dependent membrane disruption, ion imbalance, and cellular energy loss (192). In the aged heart, already characterized by reduced cardiomyocyte reserves, heightened oxidative stress, and chronic low-grade inflammation (41, 42, 173, 193), this necroptosis-

mediated cell loss can impose a greater burden. In later stages of infection, disrupted cellular membranes release alarmins which amplify inflammation (194). The release of inflammatory signals such as alarmins causes inflammatory damage to the heart leading to the development of heart failure or higher mortality in existing heart failure (16, 17, 195). Moreover, pneumolysin-induced necroptosis drives long-term cardiac remodeling; marked by *de novo* collagen deposition (fibrosis) and reduced fractional shortening in mice and in human and mouse cardiomyocytes (191). Fibrosis and stiffness are hallmarks of the aging myocardium, positioning *S. pneumoniae* infection as an acute insult that hastens the heart's structural and functional transition toward a senescent phenotype.

S. pneumoniae infection is closely linked to acute cardiovascular complications; which occur more frequently and with greater severity in older individuals. Clinical evidence indicates that *S. pneumoniae* infection significantly increases the risk of coronary heart disease, heart failure, stroke, and atrial fibrillation (196), with hospitalizations for pneumococcal disease often resulting from new or worsened heart failure and cardiac arrhythmias (197). The pathogen's success in establishing infection and driving cardiac injury is partly due to immune suppression. During the early stages of infection, pneumolysin suppresses the production of key pro-inflammatory cytokines such as TNF- α , IL-1 β , IL-6, and IL-12 by inducing suppressor of cytokine signaling 1 (SOCS1) in human dendritic cells and mouse macrophages, which inhibits downstream immune signaling and weakens host defense activation (190, 198). This early immune suppression is particularly harmful in the elderly, where immune senescence limits the capacity for efficient immune activation (199–201). As a result, *S. pneumoniae* gains an early advantage-allowing unchecked bacterial proliferation before the onset of destructive late-stage inflammation that further damages cardiac tissue.

The localized cardiac damage caused by *S. pneumoniae* underscores its ability to induce chronic, age-like structural changes in the heart. Studies in humans, mice, and rhesus macaques have identified distinct myocardial microlesions during *S. pneumoniae* infection (202), while *in vitro* experiments show that even at a low multiplicity of infection, approximately 60% of HL-1 mouse cardiomyocytes undergo cell death within just six hours of exposure *in vitro* (197). Although pneumococcal endocarditis and aortitis are relatively uncommon, they progress rapidly when they occur leading to massive thrombus formation and severe valve destruction, most frequently affecting the aortic valve and often necessitating early surgical intervention (203). In non-human primate models, myocardial injury has been confirmed by elevated levels of troponin T and heart-type fatty acid-binding protein accompanied by persistent cardiac scarring even after successful antibiotic therapy (204). This enduring structural damage demonstrates that *S. pneumoniae*-induced cardiac injury extends well beyond the acute infectious phase, leaving behind fibrotic and functional alterations, thereby highlighting the need for therapeutic strategies beyond standard antibiotic treatment.

Mycoplasma pneumoniae. *Mycoplasma pneumoniae* is a small, self-replicating pathogen best known for causing community-acquired pneumonia. Beyond its respiratory tropism, it has the capacity to induce severe multisystemic disease including cardiovascular complications such as pericarditis, myocarditis, congestive heart failure, and, in rare cases, infective endocarditis (205). The mechanisms underlying *M. pneumoniae*'s extrapulmonary effects, spanning cardiovascular, neurological, and dermatological systems (206, 207), closely align with the biological processes that drive cardiac aging, particularly chronic inflammation. *M. pneumoniae* elicits a potent pro-inflammatory response marked by elevated levels of cytokines such as TNF- α , IFN- γ , IL-1 β , IL-4, IL-6, IL-8, and IL-18 (208). In older individuals whose systems already experience inflammaging, this exaggerated immune activation overwhelms homeostatic control, exacerbates endothelial injury, and promotes cardiac remodeling. The resulting fibrosis and stiffness mirror the structural and functional decline characteristic of the aged heart.

M. pneumoniae employs multiple immune-modulation and virulence strategies to enact inflammatory damage to the myocardium, leading to long-term functional decline. Through molecular mimicry, the pathogen produces proteins that closely resemble host molecules such as keratin, fibrinogen, vimentin, and various glycoproteins provoking autoimmunity in patients (209). This autoimmune activation is particularly detrimental to the heart, as chronic, misdirected immune attacks against cardiac tissues, such as the valves and pericardium, lead to age-like damage and fibrosis in *Mycoplasma* patients. Additionally, *M. pneumoniae* secretes the Community Acquired Respiratory Distress Syndrome (CARDS) toxin, which enters mammalian epithelial cells and modifies host proteins via ADP-ribosylation. This induces inflammation via the NLRP3-associated inflammasome; releasing IL-1 β and IL-18 (209). This toxin-driven cellular injury compounds the existing burden of oxidative and replicative stress characteristic of aged tissues, further promoting senescence. Clinically, these pathogenic mechanisms manifest as severe cardiovascular involvement. *M. pneumoniae* has been documented as a rare cause of infective endocarditis in an immunocompetent adult, presenting with fever, elevated troponin-I levels indicative of myocardial injury, and vegetation on the pulmonary valve (205). Its ability to sustain chronic inflammation, trigger oxidative injury, and provoke autoimmunity suggests that, beyond causing acute respiratory illness, *M. pneumoniae* exerts lasting pathological effects that may drive cardiovascular aging. In Fig. 4, we provide an overview of how bacterial infections contribute to cardiovascular aging.

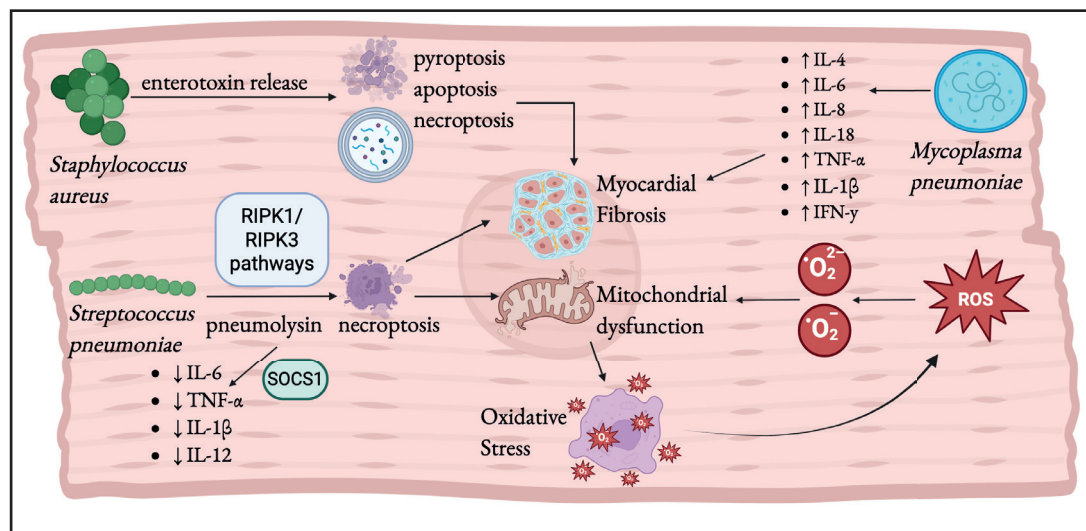


Fig. 4. Bacterial infections promote cardiac aging and disease. The pathogenic bacteria *Staphylococcus aureus*, *Streptococcus pneumoniae*, and *Mycoplasma pneumoniae* are shown alongside mechanisms by which they cause an aged-like diseased phenotype. Bacterial infections cause widespread inflammation, including the release of enterotoxin and pneumolysin. These toxins trigger programmed cell death which increases inflammation and leads to fibrosis. *M. pneumoniae* increases reactive oxygen species (ROS) production, contributing to senescence. ROS and necroptosis caused by *M. pneumoniae* and *S. pneumoniae* respectively cause mitochondrial dysfunction, a hallmark of the aging heart that further contributes to oxidative stress. Fig. created by BioRender.

Concluding remarks

Cardiovascular aging is a multifaceted process driven by a complex interplay of cellular, molecular, and systemic factors that culminate in structural remodeling and functional decline of the heart. Among the key contributors, chronic inflammation and oxidative stress emerge as central mechanisms that accelerate tissue injury, impair repair pathways, and promote fibrosis and metabolic imbalance. Increasing evidence indicates that chronic infections, including viral, parasitic, and bacterial pathogens, can profoundly influence cardiovascular aging. By establishing persistent inflammatory and oxidative environments, these infections exacerbate mitochondrial dysfunction, endothelial damage, and maladaptive immune responses, thereby accelerating age-associated cardiac deterioration. Such processes contribute to a spectrum of cardiovascular pathologies, including atherosclerosis, DCM atrial fibrillation, and myocardial infarction.

Conversely, the aging cardiovascular system itself becomes increasingly susceptible to chronic infection. Age-related declines in immune resilience, redox balance, and cellular repair mechanisms create a permissive environment for persistent pathogens to thrive and inflict further damage. This bidirectional relationship between chronic infection and cardiovascular aging represents a critical yet underexplored dimension of heart disease pathogenesis.

Understanding the molecular networks that link infection, inflammation, and aging offers an opportunity to identify novel biomarkers and therapeutic targets that could preserve cardiac resilience, slowing the trajectory of age-related cardiovascular decline. Future studies integrating systems-level, multi-omics, and spatial approaches are essential to unravel the regional and cell-type-specific vulnerabilities of the aging heart. Such efforts will not only deepen our mechanistic understanding of cardiovascular aging, but also inform strategies to promote healthy cardiac longevity in the context of chronic infectious and inflammatory stressors.

Disclosure Statement

The authors declare that they have no competing financial interests or personal relationships that could have influenced the work reported in this manuscript.

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