REVIEW

Arrhythmogenic Manifestations of Chagas Disease: Perspectives From the Bench to Bedside

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ABSTRACT: Chagas cardiomyopathy caused by infection with the intracellular parasite *Trypanosoma cruzi* is the most common and severe expression of human Chagas disease. Heart failure, systemic and pulmonary thromboembolism, arrhythmia, and sudden cardiac death are the principal clinical manifestations of Chagas cardiomyopathy. Ventricular arrhythmias contribute significantly to morbidity and mortality and are the major cause of sudden cardiac death. Significant gaps still exist in the understanding of the pathogenesis mechanisms underlying the arrhythmogenic manifestations of Chagas cardiomyopathy. This article will review the data from experimental studies and translate those findings to draw hypotheses about clinical observations. Human- and animal-based studies at molecular, cellular, tissue, and organ levels suggest 5 main pillars of remodeling caused by the interaction of host and parasite: immunologic, electrical, autonomic, microvascular, and contractile. Integrating these 5 remodeling processes will bring insights into the current knowledge in the field, highlighting some key features for future management of this arrhythmogenic disease.

Key Words: arrhythmias, cardiac ■ cardiovascular system ■ Chagas cardiomyopathy ■ Chagas disease ■ myocytes, cardiac ■ *Trypanosoma cruzi* ■ ventricular remodeling

C hagas disease (CD), a parasitic infection caused by the intracellular protozoan *Trypanosoma cruzi* (*T. cruzi*),[1] is endemic in regions of Mexico, Central America, and South America, affecting ≈6 to 7 million people.[2] In the United States, it is estimated that 288 000 individuals, predominantly immigrants, are living with CD, which they acquired primarily in Latin American countries.[3] Domestic transmission within the United States through contact with triatomine bugs, the disease's primary vector, is relatively rare.[4]

CD has 2 phases: acute and chronic (Figure 1).[5] During the acute phase, 90% of individuals are asymptomatic or have mild symptoms, while the remaining 10% can exhibit more severe symptoms, which may lead to death from complications such as myocarditis or meningoencephalitis in case the immune system initial reaction fails. If the infection is not treated and cleared, it enters a chronic phase. Approximately 60% of these chronic cases remain with the indeterminate form, without symptoms throughout the individual's life, whereas 40% evolve to determinate chronic CD. This latter group can suffer from significant cardiac and digestive problems due to ongoing inflammation and tissue damage.[1] Both the acute and chronic phases of CD are influenced by various factors, including the virulence of the *T. cruzi* strain, the initial load of the parasite, the route of transmission, the parasite's ability to evade the immune system, the host's genetic background, nutritional status, and immune response.[2] The most common and severe manifestation of chronic CD is Chagas cardiomyopathy (CCM), appearing in nearly one-third of individuals with CD. Notably, CCM has a poor prognosis, with an estimated overall annual mortality of 4%.[6] Despite its prevalence and morbidity, the pathophysiologic understanding of CCM remains to be fully elucidated.

In this review, we will focus on the concept of remodeling that occurs in the cardiovascular system during the progression of CCM. The distinct but intermingled immunologic, electrical, autonomic, microvascular, and contractile remodeling mechanisms all contribute to the phenotypic

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Nonstandard Abbreviations and Acronyms

AP	action potential
BENEFIT	Benznidazole Evaluation for Interrupting Trypanosomiasis
Ca²⁺/CaM	Ca^{2+} bound calmodulin
CaMKII	Ca^{2+}/calmodulin-dependent protein kinase II
CCM	Chagas cardiomyopathy
CD	Chagas disease
Cx43	connexin-43
DAD	delayed afterdepolarization
EAD	early afterdepolarization
I_{Ca-L}	L-type calcium current
IFN-γ	interferon gamma
I_k	delayed K+ current
IL	interleukin
iNOS	inducible nitric oxide synthase
I_{ti}	transient inward current
I_{to}	transient outward potassium current
LV	left ventricular
MPD	myocardial perfusion defect
NCX	sodium-calcium exchanger
NOX2⁻/⁻	nicotinamide adenine dinucleotide phosphate oxidase 2 enzyme
PI3Kinase	phosphoinositide 3-kinase
ROS	reactive oxygen species
RyR2	ryanodine receptor type 2
SCD	sudden cardiac death
SERCA2a	sarcoplasmic/endoplasmic reticulum Ca^{2+}-ATPase
SR	sarcoplasmic reticulum
T. cruzi	Trypanosoma cruzi
TGF-β	transforming growth factor-beta
TNF-α	tumor necrosis factor-alpha
VT	ventricular tachycardia

manifestations of CCM (Figure 2). We propose that the cumulative effects of such structural and functional remodeling of the cardiovascular system evolve into an integrated manner to develop clinically apparent CCM following the long-standing indeterminate form of CD.

CLINICAL ARRHYTHMOGENIC MANIFESTATIONS OF CHAGAS CARDIOMYOPATHY

CCM is often regarded as an essentially arrhythmogenic cardiomyopathy, and nearly, all rhythm disturbances may occur, including sinus node dysfunction, atrioventricular blocks, supraventricular arrhythmias, and most commonly,

a variety of ventricular arrhythmias, such as isolated or coupled premature ventricular contractions, nonsustained ventricular tachycardia (VT), sustained monomorphic VT, polymorphic VT, and ventricular fibrillation.[7] The frequency and severity of ventricular arrhythmias generally correlate with the degree of left ventricular (LV) dysfunction; however, a hallmark of CD consists in the fact that patients with preserved global ventricular function, presenting only with segmental abnormalities, may also experience ominous ventricular arrhythmias and sudden cardiac death (SCD).[8] Not infrequently, both ventricular arrhythmias and conduction system alterations coexist in the same patient.[7]

SCD is the primary cause of death, accounting for 55% to 65% of all cardiovascular deaths in CCM.[9] Sudden death is usually associated with VT or ventricular fibrillation or more rarely with asystole or complete atrioventricular block. Because the clinical course of CCM varies widely, it can be difficult to predict who is at higher risk of SCD. For example, some patients may remain asymptomatic throughout their life span, exhibiting only mild ECG alterations; others have conduction defects, ventricular arrhythmias, and only segmental wall motion abnormalities; others even develop global ventricular dysfunction with only mild symptoms of heart failure or show multiple disturbances of rhythm, thromboembolic phenomena, and severe symptoms of heart failure; and a nonnegligible number of individuals die suddenly with or without previous cardiac symptoms.[10]

Given the dominant arrhythmic profile of CCM and its pivotal relationship with CCM mortality, there has been considerable effort towards risk prediction. In 2006, Rassi et al[6] developed and validated a risk score to predict all-cause mortality and cardiovascular and SCD in CCM. Six independent predictors of mortality were identified, as illustrated in Figure 3. Apart from the incorporation of ventricular arrhythmia (nonsustained VT) in the RASSI score, other electrical indicators of adverse prognosis have been proposed by other authors, including increased T-wave amplitude variability, abnormal T-wave axis deviation, QT interval dispersion, signal-averaged ECG changes (spectral turbulence and filtered QRS), decreased heart rate variability, and increased QRS complex duration.[2] However, these additional factors still lack external validation by independent cohort studies.

CCM outcomes are strongly dependent on the relationship between the host and the parasite, which occurs in an inflammatory milieu.[11] Herein, we present experimental data suggesting the mechanistic underpinnings of the arrhythmogenic remodeling observed in CCM. While we present the data as 5 main mechanistic pillars, it is important to acknowledge that all these mechanisms likely work simultaneously and are interdependent.
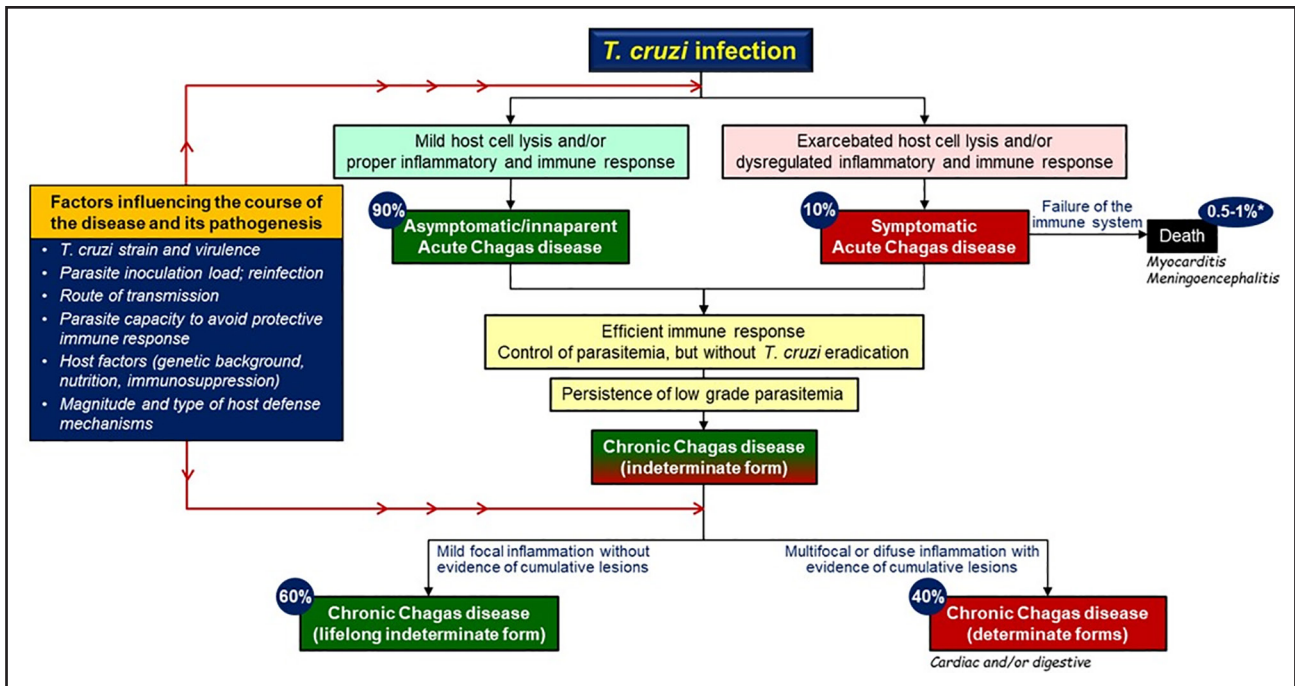
Figure 1. The clinical course of *Trypanosoma cruzi* (*T. cruzi*) infection and influential factors in the pathogenesis and progression of Chagas disease.

*The overall mortality rate for acute Chagas disease, encompassing both asymptomatic and symptomatic cases, ranges from 1 in 100 to 1 in 200 cases.

IMMUNOLOGIC REMODELING IN CCM

Excellent reviews detailing the complex and intricate host immune response following *T. cruzi* infection are available.[12–14] Here, we will provide a synthetic overview of this phenomenon that is fundamental to understand how the remodeling of the host immune system is able to trigger a remodeling at a cellular scale in cardiomyocytes and contributes to the global electrical and mechanical remodeling in CCM.

The variability in the clinical manifestation of CCM can be partly attributed to the heterogeneity of *T. cruzi* strains,
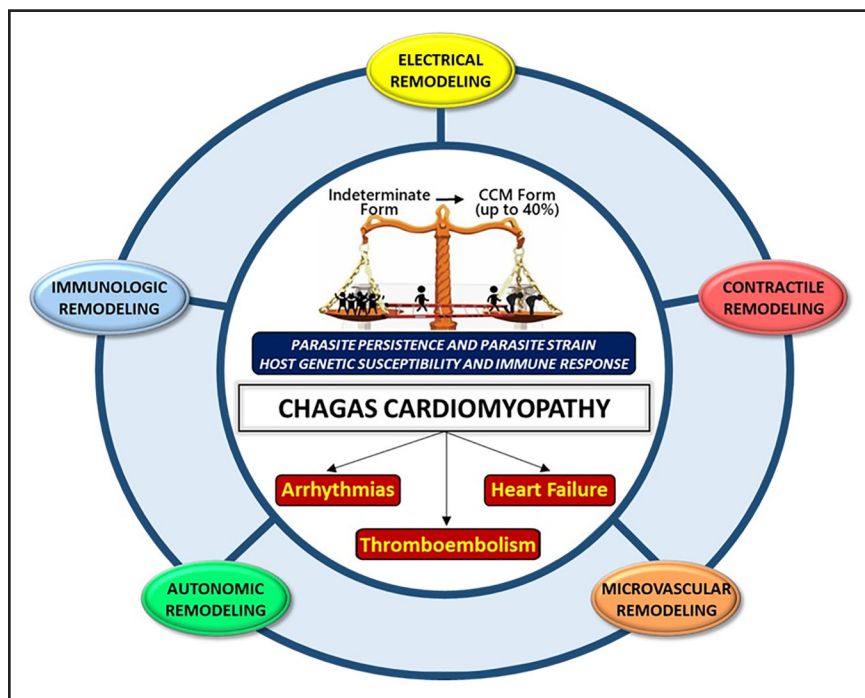

Figure 2. Chagas cardiomyopathy (CCM): a quintet of interrelated remodeling processes.

The progression of Chagas disease from the indeterminate (asymptomatic) form to CCM, which occurs in up to 40% of infected individuals, is guided by 5 intimately linked remodeling processes. These processes collectively shape the pathophysiological landscape of the disease. Central to the pathogenesis of CCM is the interplay among ongoing parasite infection, *Trypanosoma cruzi* strain, the patient's genetic vulnerability, and their immune system's reaction, influencing the clinical progression of the disease into its major syndromes: arrhythmias, heart failure, and thromboembolism.
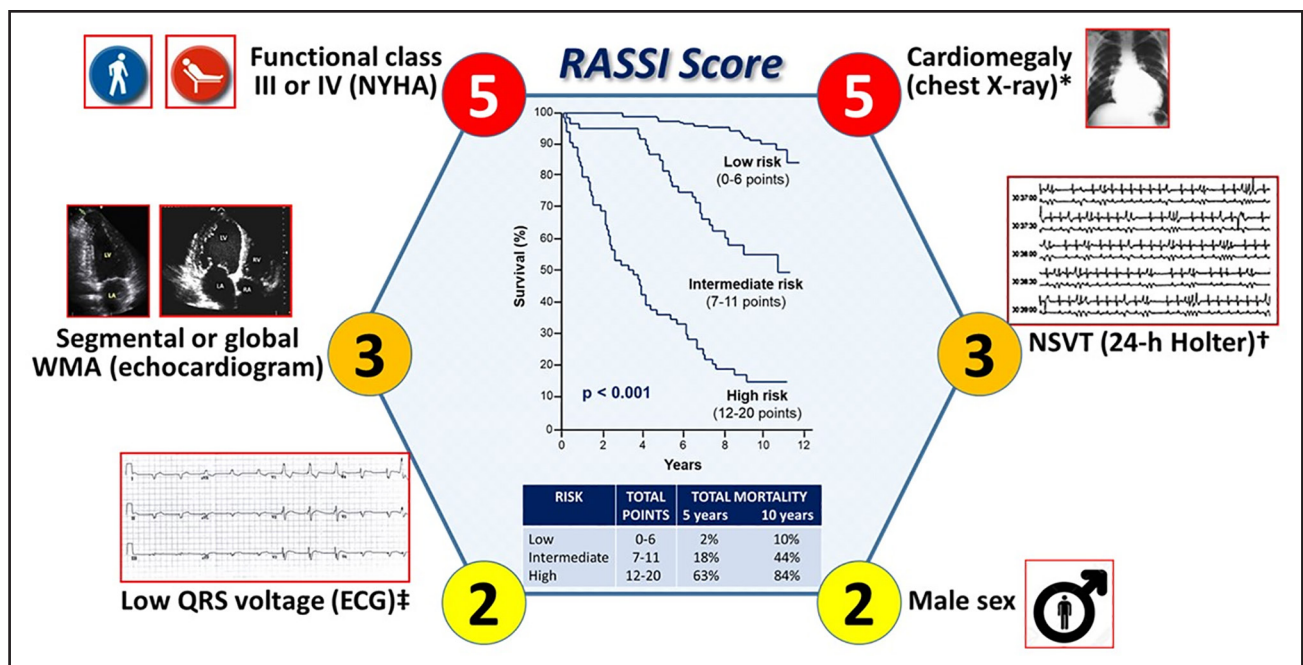
Figure 3. RASSI score.
This illustration presents the RASSI score, comprising 6 independent all-cause mortality predictors, with their associated points inside the circles. It shows the division into 3 risk categories and displays both the 5- and 10-year overall mortality rates, alongside the Kaplan-Meier survival curves for each risk subgroup. Of note, all these variables were also strong predictors of the risk of cardiovascular deaths and sudden cardiac deaths, except for the male sex, which was of borderline significance for the prediction of cardiovascular death, and low QRS voltage, which was of borderline significance for the prediction of sudden cardiac death. HR indicates heart rate; NSVT, nonsustained ventricular tachycardia; NYHA, New York Heart Association; and WMA, wall motion abnormality. *Cardiothoracic ratio >0.50. †≥3 beats and duration <30 s (HR >100 bpm). ‡≤ 0.5 mV in all limb leads.

encompassing a broad spectrum of genotypes and phenotypes.[14,15] However, the precise nature of this relationship remains incompletely understood. The surface of *T. cruzi* is rich in pathogen-associated molecular patterns,[16] while host tissue injury releases damage-associated molecular patterns.[17] Together, these molecular signatures serve as key triggers for activating the host's innate and adaptive immune responses.

This activation plays a critical role in the body's defense mechanisms against the pathogen and influences the course of the disease. Initially, pathogen-associated molecular patterns and damage-associated molecular patterns activate macrophages and dendritic cells to produce IL (interleukin)-12, which, in turn, stimulates natural killer cells to produce IFN-γ (interferon gamma). IFN-γ is a key molecule in this process, as it activates macrophages to produce iNOS (inducible nitric oxide synthase) and NO production, both of which are essential in effectively targeting and combating the *T. cruzi*.[18]

Additionally, another cytokine, TNF-α (tumor necrosis factor-alpha), complements this response by signaling IFN-γ-activated macrophages and *T. cruzi*-infected cardiomyocytes to increase NO synthesis, enhancing the antiparasitic response. This confluence of IFN-γ and TNF-α induces a cytokine storm that prompts infected macrophages to escalate iNOS expression and NO production.[19] Importantly, iNOS and NO play relevant roles in

altering potassium and calcium currents within infected cardiomyocytes, thus impacting the heart's electrical signaling.

Following *T. cruzi* infection, macrophages stimulated by proinflammatory cytokines also increase the production of reactive oxygen species (ROS). These molecules can help in controlling the infection by causing oxidative stress to the parasite. However, similar to NO, high levels of ROS can exacerbate oxidative stress in host tissues, contributing to cell damage, inflammation, and the chronic manifestations of CD.[12,13,17]

It is important to highlight that cytokine production in response to *T. cruzi* infection is not limited to immune cells. Cardiac fibroblasts, endothelial cells, and cardiomyocytes themselves contribute to a wider immunologic response. Cytokines such as IFN-γ, TNF-α, IL-1β, TGF-β (transforming growth factor-beta), and IL-10 are upregulated in heart cells cultured with *T. cruzi*, influencing electrical and contractile functions of the heart muscle and driving the remodeling process that characterizes CCM.[19]

The significance of immune system remodeling to the pathogenesis of CCM is further highlighted by several lines of evidence showing that polymorphisms in genes involved in the structure and function of the immune system are associated with susceptibility to *T. cruzi* infection and development of CCM.[20] For example, a reduction of inflammation and iNOS expression occurs

in IL-18-deficient mice infected with *T. cruzi*, suggesting that the deficiency of IL-18 is cardioprotective during the infection.[21] Table 1 summarizes the principal features of the immunologic remodeling in CCM.

ELECTRICAL REMODELING IN CCM

The current knowledge of the cellular basis of the observed arrhythmias derives mostly from investigations in experimental murine models of CCM and, to a lesser extent, from the heart tissue of patients with CCM. Both animal and human models suggest that myocytes infected with *T. cruzi* exhibit disruptions in several key components of intrinsic cardiac electrophysiology, which includes abnormalities in gap junctions involving Cx43 (connexin-43), potassium channels, and calcium-handling mechanisms. These key features of the cellular machinery related to the electrical signaling remodeling are summarized in Table 2 and illustrated in Figure 4.

Connexin Remodeling

Gap junctions, particularly Cx43, are crucial for uniform anisotropic conduction in the heart, ensuring synchronized cardiac muscle contraction.[22] Studies in both murine[23] and human[24] tissues have demonstrated that *T. cruzi* infection leads to reduction and lateralization of Cx43 expression in gap junctions, which are linked to a high proarrhythmic substrate and can also induce myocardial contractile dysfunction. Elevated levels of proinflammatory cytokines, such as TGF-β and IL-1β, contribute to this reduction. Moreover, genetic mutation with loss of function in Cx43 has been associated with sudden death in human infants[25] and the development of bundle branch block,[26] both of which are observed

in patients with CCM.[5,9] It is also important to note that acute gap junction uncoupling, in which direct cell-to-cell electrical communication is disrupted, causes slowing of the spread of electrical excitation, which facilitates the occurrence of malignant arrhythmias, electromechanical dysfunction, and heart failure.[27]

Potassium Current Remodeling

Alterations in the transient outward potassium current (I_{to}) and in the delayed K+ current (I_k) within cardiomyocytes can significantly impact cardiac electrophysiology and lead to arrhythmias.[28,29] I_{to}, which is responsible for the initial phase of repolarization, is represented by a characteristic notch in the early phase of the human action potential (AP) repolarization. In the normal heart, there is an intrinsic I_{to} density gradient: it is more pronounced in the epicardium and less expressed in the endocardium. Of note, the loss of the notch gradient, particularly in the right ventricle, has been associated with the appearance of life-threatening arrhythmias in humans with diseases of distinct etiologies, such as the Brugada syndrome.[30] The reduction of I_{to} and I_k in *T. cruzi* infection, which results in the prolongation of AP duration, involves a complex interplay of several key mechanisms and was observed in the setting of intense inflammatory infiltrates affecting the heart, in both dog and mice models of *T. cruzi* induced myocarditis.[28,31–39]

The neurohormonal activation, particularly alterations in the adrenergic pathway influenced by factors such as noradrenaline production, plays a significant role in modulating these potassium currents, especially I_{to}. Moreover, the infection-induced immune response leads to heightened oxidative stress and increased production of NO and ROS within the heart tissue.[40] These biochemical changes can

Table 1. Summary of Immunologic Remodeling in CCM

Remodeling Component	Description	Impact on CCM
Host immune response initiation	*T. cruzi* infection triggers innate and adaptive immune responses.	Sets off a cascade of remodeling processes.
T. cruzi strain diversity	*T. cruzi* strains, which are classified into seven discrete typing units, show biological, biochemical, geographic, and genetic diversities.	Partially explains the various expressed phenotypes seen in patients with CCM.
Activation of macrophages and dendritic cells	PAMPs and DAMPs stimulate these cells to produce IL-12, activating NK cells to produce IFN-γ, leading to iNOS and NO production.	Initial step in the immune defense that influences the progression and outcome of CCM.
Cytokine production	Involves various cytokines including IFN-γ, TNF-α, IL-1β, TGF-β, and IL-10, which are crucial in fighting *T. cruzi* infection.	Regulates immune response and influences the electrical and contractile functions of the heart.
IFN-γ and TNF-α mediated responses	These cytokines induce a cytokine storm, enhancing iNOS expression, and NO production, affecting the heart's electrical signaling.	Can lead to alterations in cardiac electrical signaling, contributing to CCM pathogenesis.
Reactive oxygen species	Produced by macrophages, help control the infection but can lead to oxidative stress and tissue damage when in excess.	Contributes to cell damage and chronic manifestations of CCM, influencing its progression.
Contribution of heart cells	Cardiac fibroblasts, endothelial cells, and cardiomyocytes also produce cytokines, affecting the heart's electrical and contractile functions.	Drives the remodeling process in CCM, leading to changes in heart muscle function.
Human genetic susceptibility	Polymorphisms in immune system genes can affect susceptibility to *T. cruzi* infection and CCM development.	May influence the severity and progression of CCM, offering potential targets for therapy.

CCM indicates Chagas cardiomyopathy; DAMP, damage-associated molecular pattern; IFN-γ, interferon gamma; IL, interleukin; iNOS, inducible nitric oxide synthase; NK, natural killer; PAMP, pathogen-associated molecular pattern; *T. cruzi*, *Trypanosoma cruzi*; and TNF-α, tumor necrosis factor-alpha.

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Table 2. Summary of the Various Possible Mechanisms of Electrical Remodeling Observed in CCM, Their Potential Causes, and Their Speculative Implications for Ventricular Arrhythmias

Possible electrical remodeling phenomena	Potential causes	Speculative impact on ventricular arrhythmias
Reduction of Cx43	*T. cruzi* infection leads to inflammatory cytokine release (eg, TNF-α, TGF-β, IL-1β), which downregulates Cx43 expression.	Reduced Cx43 decreases gap junction communication, leading to disordered anisotropic conduction and arrhythmias, and potentially causing myocardial contractile dysfunction.
Lateralization of Cx43	*T. cruzi* infection and associated inflammation cause disorganization of gap junctions.	Misplacement of Cx43 from intercalated discs to lateral cell borders contributes to inhomogeneous electrical conduction and arrhythmogenic substrate formation.
Acute gap junction uncoupling	Cell-to-cell electrical communication disrupted, possibly due to direct effects of *T. cruzi* infection or mediated by inflammation, as well as by calcium overload	Acute uncoupling slows electrical propagation, predisposing the heart to malignant arrhythmias and heart failure.
Attenuation of I_{to}	*T. cruzi* infection-related inflammation and neurohormonal activation; downregulation of Kv4.3 channels by TNF-α.	Reduction of I_{to} alters phase 1 repolarization, diminishing the epicardial-endocardial gradient, which also can lead to life-threatening arrhythmias.
Attenuation of I_k currents	Inflammatory infiltrates, oxidative stress, and CAMKII, modulated by neurohormonal factors and cytokines.	Prolongation of AP duration, depolarization of diastolic membrane potential, and increased susceptibility to reentrant arrhythmias.
Reduced I_{Ca-L}	NO and PI3Kinase pathways activation during *T. cruzi* infection; attenuation of I_{Ca-L} by IFN-γ receptor activation and iNOS.	Decreased I_{Ca-L} disrupts the plateau phase of the AP and cardiac contractility, destabilizing electrical conduction and leading to arrhythmias.
Hyperactivation of CaMKII	*T. cruzi* infection and associated inflammation, oxidative stress, and calcium overload.	CaMKII influences various ion channels, altering repolarization and excitability, and is linked to arrhythmias such as AP alternans and triggered activities (afterdepolarizations).
AP alternans	Hyperactivation of CaMKII due to oxidative stress and calcium overload. *T. cruzi* infection may impair coupling between I_{Ca-L} and RyR2, exacerbating beat-to-beat variations in AP duration.	AP alternans can lead to a significant increase in the dispersion of repolarization, creating a substrate favorable for reentrant arrhythmias.
EADs	Extended AP duration due to reduced potassium currents and altered calcium handling, influenced by CaMKII and oxidative stress.	EADs can disrupt the normal cardiac rhythm by initiating premature AP during the repolarization phase, potentially leading to life-threatening arrhythmias by triggering reentrant circuits or enhanced focal activity.
DADs	Calcium overload, enhanced NCX function, and increased diastolic calcium concentration, modulated by ROS and CaMKII hyperactivation.	DADs can precipitate extra heartbeats, thereby creating a substrate for reentrant arrhythmias and contributing to contractile dysfunction.
Phase 2 reentry	Attenuation of I_{Ca-L} and heterogeneous alteration of potassium currents, particularly I_{to}; observed in phase 2 of the AP.	Phase 2 reentry can lead to life-threatening arrhythmias by allowing reexcitation of myocardial tissue during the AP plateau, contributing to the arrhythmogenic profile of CCM.
Enhanced I_{ti}	Diastolic calcium overload, increased NCX function.	Enhanced I_{ti} prolongs AP, heightens vulnerability to DADs, and facilitates ectopic firing, contributing to the initiation and maintenance of arrhythmias.
Enhanced NCX	Diastolic calcium overload, upregulated by CaMKII hyperactivation and oxidative stress.	Increased NCX function exacerbates calcium imbalance, leading to DADs and arrhythmias.
Calcium overload	Infection-induced inflammatory response, leading to alterations in calcium-handling proteins and increased oxidative stress.	Calcium overload contributes to DADs and EADs, promoting triggered electrical activity and arrhythmias.
Oxidative stress with increased NO and ROS production	*T. cruzi* infection stimulates inflammatory cytokines and ROS-generating enzymes, such as NOX2.	Oxidative stress can trigger CaMKII, affect ion channel function, and promote arrhythmogenic changes in cardiomyocytes, increasing the risk of ventricular arrhythmias.
Increase in action potential duration	Attenuation of potassium currents (eg, I_{to}, I_k), and calcium-handling abnormalities may prolong the AP.	An increased AP duration could enhance the risk of EADs and DADs, leading to a higher susceptibility to tachyarrhythmias and fibrillation events.
Decrease in conduction velocity	Pathological anisotropy, gap junction remodeling, and fibrotic infiltration may slow the propagation of electrical impulses.	A decrease in the conduction velocity might contribute to the initiation and perpetuation of reentrant arrhythmias and can be a substrate for complex arrhythmogenic activity.

AP indicates action potential; CaMKII, Ca²⁺/calmodulin-dependent protein kinase II; CCM, Chagas cardiomyopathy; Cx43, connexin-43; DAD, delayed afterdepolarization; EAD, early afterdepolarization; I_{Ca-L}, L-type calcium current; I_k, delayed K+ current; IL, interleukin; iNOS, inducible nitric oxide synthase; I_{ti}, transient inward current; I_{to}, transient outward potassium current; NCX, sodium-calcium exchanger; NOX2, nicotinamide adenine dinucleotide phosphate oxidase 2 enzyme; PI3Kinase, phosphoinositide 3-kinase; ROS, reactive oxygen species; *T. cruzi*, *Trypanosoma cruzi*; TGF-β, transforming growth factor-beta; and TNF-α, tumor necrosis factor-alpha.
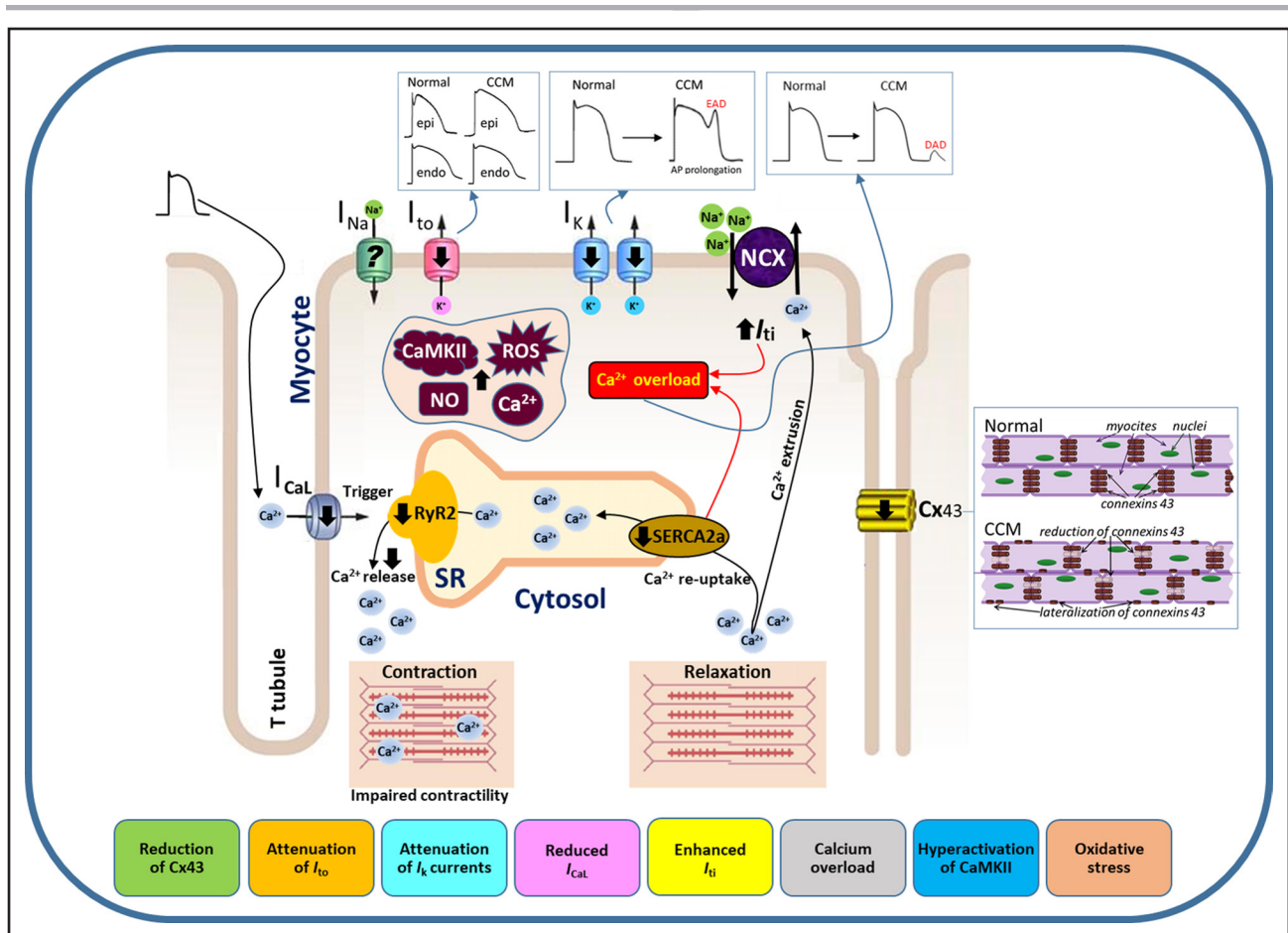
Figure 4. Electrical remodeling and arrhythmogenic mechanisms in Chagas cardiomyopathy (CCM).
The infection with *Trypanosoma cruzi* (*T. cruzi*) initiates a complex sequence of alterations in cardiac myocytes that significantly disrupts the heart's rhythm and contractile function. CCM is characterized by a cascade of events that include impaired calcium influx through attenuated L–type calcium channels (I_{Ca-L}), which is essential for triggering the release of calcium from the sarcoplasmic reticulum (SR) through the RyR2 (ryanodine receptor type 2). This disruption leads to insufficient release of calcium ions during systole, affecting myocardial contractility. Concurrently, the reuptake of calcium by the SR during diastole, mediated by a dysfunctional SERCA2a (sarcoplasmic/endoplasmic reticulum Ca^{2+}-ATPase) pump, causes a harmful cytosolic calcium overload. Additionally, disruptions in the function of potassium channels have also been observed. There is a marked attenuation of the transient outward potassium current (I_{to}) and the delayed rectifier potassium current (I_k) that are essential for the repolarization phase of the cardiac action potential (AP). This dysfunction results in a prolonged AP duration, creating a favorable environment for early afterdepolarizations (EADs). In parallel, the heart's electrical connectivity is impaired due to a reduction in Cx43 (connexin-43) expression, disrupting the spread of electrical impulses and leading to disordered anisotropic conduction and desynchronized myocardial contractions. The compromised ionic balance triggers the activation of compensatory mechanisms, such as the sodium–calcium exchanger (NCX), which acts to expel excess calcium from the cell. This compensatory increase, depicted as enhanced transient inward current (I_{ti}) in the diagram, may inadvertently become counterproductive, potentially precipitating additional electrical irregularities that can provoke delayed afterdepolarizations (DADs) during the heart diastolic phase. Oxidative stress further aggravates the situation, with increased levels of reactive oxygen species (ROS) and NO promoting the hyperactivation of CaMKII (Ca^{2+}/calmodulin-dependent protein kinase II). This enzyme, when overstimulated, can modify the function of ion channels and calcium-handling proteins, further promoting the development of arrhythmias. In summary, arrhythmogenesis in CCM is characterized by calcium mishandling, ionic current imbalances, reduced intercellular communication, and oxidative stress. This comprehensive depiction of electrical remodeling may provide insights into the potential therapeutic targets for mitigating the progression of cardiac arrhythmias and myocardial dysfunction in CCM.

attenuate the potassium currents by impacting the channels' structure and function. During the chronic phase of the infection, TNF-α[38] can also downregulate Kv4.3 channels and function,[28,34,35] which are pivotal for I_{to}, and potentially influence I_k channels, demonstrating the profound effect of cytokine-mediated inflammatory and immune responses on cardiac cellular functions and ion channel expression.

Additionally, specific signaling pathways, such as CaMKII (Ca^{2+}/calmodulin-dependent protein kinase II), are also implicated in this process.[41] CaMKII, which is hyperactivated in CCM (and will be discussed in detail later), can directly modulate potassium channel function and expression, further influencing the cardiac AP and the heart's electrical stability.

Despite the lack of direct evidence linking potassium current disruptions to arrhythmic patients with CCM, it seems plausible to speculate that in those patients, a more severe pathophysiological scenario may indeed be present, similar to what has been described in end-stage heart failure of other etiologies associated with increased circulating TNF-α levels, and in whom the attenuation of I_{to} was already fully documented.[42–44]

L-Type Calcium Current Remodeling

L-type calcium current (I_{Ca-L}) is crucial for the plateau phase of the cardiac AP. This current is responsible for the calcium influx that triggers the release of calcium from the sarcoplasmic reticulum (SR), which, in turn, plays a pivotal role in the contractile function of the cardiomyocytes. In *T. cruzi* infection, there is a significant reduction in I_{Ca-L} density across the heart, affecting both the right and left ventricles during the acute and chronic phases of CD.[31–34,36] This widespread attenuation of I_{Ca-L} also disrupts the heart's electrical stability and contractile function. Studies in the mice model have demonstrated that NO and PI3Kinase (phosphoinositide 3-kinase) pathways are key contributors to I_{Ca-L} attenuation.[35,36,45,46] From these studies, it is plausible to assume that infected cardiomyocytes, through activation of IFN-α receptors, have enhanced NO production through iNOS, which activates the PIK3kinase pathway, resulting in attenuation of I_{Ca-L}, a concept warranting further investigation.

Additional pathways may be involved in the attenuation of I_{Ca-L} during *T. cruzi* infection. NO, through activation of cyclic guanosine monophosphate production, has been reported to regulate the cardiac Cav1.2 channels by various mechanisms, which could lead to activation or inhibition of I_{Ca-L}.[47,48] In one study, it was reported that cardiomyocytes isolated from mice infected with *T. cruzi*, but lacking the NOX2$^{-/-}$ (nicotinamide adenine dinucleotide phosphate oxidase 2 enzyme), have neither attenuation of I_{Ca-L} nor the I_{to} and I_k alterations, compared with normal infected mice.[37] Importantly, NOX2 is fundamental to global ROS generation in cardiomyocytes during stress conditions,[49] and this enzyme is a relevant source of ROS during *T. cruzi* infection.[50]

Interestingly, increased availability of NO was detected in isolated cardiomyocytes of infected NOX2$^{-/-}$ mice, compared with all other groups studied, an effect shown to be associated with an arrhythmogenic cellular profile.[35] Thus, the interaction between NOX2-derived ROS and NO in the context of CCM is intricate and not fully understood. On the one hand, the absence of NOX2 (and, thus, lower ROS production) seems to protect against changes in heart ion currents that are typically seen with *T. cruzi* infection. In contrast, the resulting increase in NO levels associated with NOX2 deficiency could pose risks for the induction of heart rhythm disturbances.

CaMKII, Calcium Overload, Early Afterdepolarizations, and Delayed Afterdepolarizations

The role of CaMKII, a multifunctional enzyme that modulates various aspects of cardiomyocyte function, was studied in an experimental model of CCM.[41] In this model, where hyperactivation of CAMKII is triggered by *T. cruzi* infection, most mice exhibited recurrent arrhythmic manifestations, such as triggered activity from ectopic foci, including atrial and ventricular extrasystoles, along with other ECG abnormalities commonly observed in patients with CCM. Furthermore, these cardiomyocytes demonstrated a highly arrhythmogenic profile, notably characterized by AP alternans, a beat-to-beat oscillation in AP duration. This phenomenon is linked to impaired coupling between I_{Ca-L} and RyR2 (ryanodine receptor type 2), potentially exacerbating the alternans phenotype, which was previously documented to occur in experimental CCM.[35]

AP alternan is believed to contribute significantly to the prolongation of AP duration and to the dispersion of the QT interval, thereby creating a favorable environment for arrhythmias.[51] Notably, an increase in QT interval dispersion is an adverse prognostic indicator in patients with CCM, underscoring the proarrhythmic nature of AP alternans.[52]

Hyperactivation of CaMKII may result from increased oxidative stress and calcium overload, conditions also described in human CCM cases.[53,54] Pharmacological inhibition of CaMKII has been shown to block arrhythmogenic mechanisms, such as AP alternans and I_{ti}, a transient inward current characterized by a brief flow of ions into the cardiomyocyte during diastole, influencing the late phase of the cardiac AP in infected cardiomyocytes. Moreover, inhibiting the Ca^{2+}/CaM (Ca^{2+} bound calmodulin)-CaMKII axis with the molecule KN-93 reversed the arrhythmogenic propensity in *T. cruzi*-infected ex vivo hearts, thus corroborating previously reported in vitro findings.[41] The important role of CaMKII in CCM pathogenesis is further highlighted by its established hyperactivation in various human heart diseases through excessive ROS, contributing to diverse arrhythmias and SCD.[55]

Another proposed mechanism for malignant arrhythmias in CCM involves afterdepolarizations, specifically early afterdepolarizations (EADs) and delayed afterdepolarizations (DADs), arising from multiple foci and spreading through cardiac tissue. These phenomena, well-documented in experimental *T. cruzi* infection,[37,41,56] are supported by a reduction in potassium currents, which extends AP repolarization and is commonly related to EADs. This reduction in potassium current is consistently

observed in *T. cruzi* experimental infections. Additionally, other currents, such as the late sodium current, might also play a significant role, akin to their contribution to hereditary arrhythmogenic cardiomyopathies, such as the long-QT syndrome type-3,[57] although their involvement in CCM needs further evaluation.

DADs are primarily associated with I_{ti}, resulting from cytoplasmic calcium overload in cardiomyocytes, leading to a depolarizing influence adjacent to the sodium-calcium exchanger (NCX). Increased diastolic calcium concentration, a hallmark of *T. cruzi* infection in both experimental models[37,56] and humans[53] with CCM, clearly exacerbates this condition.

Isolated cardiomyocytes from *T. cruzi*-infected mice exhibited numerous EADs and DADs, attributed to enhanced NCX and I_{ti}, both modulated by CaMKII.[41] Notably, oxidative stress present in early CCM can activate CaMKII, contributing to the attenuation of the potassium current. Thus, the low-grade but persistent inflammatory response in early CCM likely amplifies cardiomyocyte oxidative stress, altering intracellular signaling pathways and leading to CaMKII hyperactivation. The hyperactivation of this enzyme, in turn, alters ion current functions in cardiomyocytes, modifying cellular excitability. The aforementioned impaired calcium dynamics coincide with reduced potassium currents in *T. cruzi* experimental infections,[32,35,36] which is also associated with a depolarized membrane potential in isolated cardiomyocytes. A more depolarized resting membrane potential increases the likelihood of afterdepolarization-triggered activities by lowering the threshold amplitude for EADs/DADs, thus facilitating the spread of arrhythmogenic events to neighboring cells.

Finally, phase 2 reentry, a potential mechanism for life-threatening arrhythmias in CCM, involves the electrotonic spread of current from areas displaying spike-and-dome APs, reexciting regions where the AP dome is lost. This reentry is facilitated by the heterogeneous alteration of potassium currents, especially I_{to}, crucial for the spike-and-dome AP shape in humans.[58] Experimental *T. cruzi* infection causes attenuation of I_{Ca-L} and provides a favorable environment for phase 2 reentry. This phenomenon, coupled with AP alternans, also observed in experimental CD, may exacerbate reexcitation.[51] The similarity between the arrhythmogenic mechanisms of phase 2 reentry in CCM and Brugada syndrome, where structural cardiac remodeling is absent, underscores the need for focused research on phase 2 reentry's role in CCM.

I_{ti} and NCX

As previously mentioned, a prominent feature in CD is the occurrence of diastolic calcium overload within cardiomyocytes, a condition that is consistent across human patients[53,54] and animal models,[37,41,56] manifesting in both the acute and chronic phases of the disease. Central

to these disturbances is the enhancement of I_{ti}, which is intricately closely linked with the increased function of NCX, a critical membrane protein that regulates the exchange of sodium and calcium ions across the cardiomyocyte membrane.

In another investigation, a tachycardia protocol mimicking an AP from infected and noninfected mice was simulated,[41] and enhanced I_{ti} was observed in CD cardiomyocytes compared with control noninfected cardiomyocytes. This finding has significant implications for therapeutic strategies targeting electrical remodeling in CCM. It indicates that simply restoring the AP waveform is not sufficient to stabilize the diastolic membrane potential, which is often found depolarized in CCM. Addressing only the AP waveform falls short of correcting the arrhythmogenic propensity inherent to CCM, pointing to the need for a more comprehensive therapeutic approach.

Moreover, the combined effects of diastolic calcium overload, enhanced I_{ti}, and increased NCX function lead to a prolongation of the AP duration during the repolarization phase. This slower repolarization process is crucial because it keeps the cardiomyocytes in a prolonged state of vulnerability.[59] Specifically, such disturbances can lead to DADs, initiating reentrant circuits, a primary mechanism behind the arrhythmias observed in CCM.

In addition, using a well-known blocker of NCX current (INCX; SEA0400), an abnormal AP waveform was reversed and led to attenuation of I_{ti}, suggesting an important involvement of NCX in the arrhythmogenesis seen in CCM.[56] Finally, I_{ti} also plays a significant role in other arrhythmogenic diseases associated with SCD such as congenital long-QT syndrome type-3.[57]

AUTONOMIC REMODELING IN CCM

The first suggestion that the cardiac autonomic system was involved in the arrhythmic manifestations of CCM appeared when Carlos Chagas and the cardiologist Eurico Villela described a blunted chronotropic response to atropine in patients with CCM along with severe ECG alterations, such as ventricular arrhythmias and atrioventricular block.[60] At the time, they hypothesized that cardiac autonomic impairment was involved in the causation of sudden death that they observed in patients with CCM. The mechanistic underpinnings of that hypothesis remained elusive until recently when significant work was done to further understand the cardiac autonomic remodeling observed in CCM.

Pathological Evidence of Cardiac Autonomic Denervation

At autopsy, patients with CCM were found to have intense neuronal depopulation in the parasympathetic cardiac intramural ganglia.[61,62] Investigations in animal models of

experimental infection with *T. cruzi* also showed marked cardiac neuronal depopulation, with parasitism associated with intramural parasympathetic periganglionitis and degeneration of neural cells and fibers.[63–66]

Although parasympathetic neuronal depopulation is not specific to CD, several studies directly comparing autopsy materials from patients with inflammatory rheumatic and noninflammatory heart diseases (endomyocardial fibrosis, dilated cardiomyopathy, and hypertensive cardiomyopathy) showed that cardiac intramural denervation was much more prominent in autopsied patients with CCM.[67–69] There is evidence both in humans and experimentally infected animals that at least 3 pathogenetic mechanisms are responsible for neuronal loss in Chagas heart disease that is deemed to occur predominantly during the acute phase of the infection: necrosis induced by direct parasitism of neurons, degeneration caused by periganglionic inflammation, and antineuronal autoimmune reaction.[70,71]

Evidence of Functional Abnormalities Caused by Cardiac Autonomic Denervation

Studies have demonstrated that in most cases, individuals with CD are deprived of the tonic inhibitory action normally exerted by the parasympathetic system on the sinus node.[72] As a consequence, patients with CD constitute a natural model for studies of an autonomic remodeling of the heart functionality[73,74] because they lack the parasympathetic mediated mechanism to respond with rapid bradycardia or tachycardia to transient changes in blood pressure or venous return.[72]

The dysautonomia in Chagas patients can be typically detected before the development of ventricular dysfunction and in all phases and forms of the disease, including the indeterminate and digestive forms.[75–77] In addition, it is mostly irreversible and distinct from the nonspecific autonomic impairment that occurs in heart failure of whatever cause, which is due to neurohumoral activation and postsynaptic desensitization of neural pathways[78,79] and has been shown to be at least partially reversible with clinical compensation of heart failure.[80]

Consequences of the Autonomic Remodeling in Chronic CCM

Given that neuronal depopulation and aperistalsis are considered to be the essential pathogenetic mechanism of digestive CD,[81,82] it was postulated that CCM would be caused by lack of vagal influence on the heart for 2 reasons.[83,84] First, it was thought that long-standing autonomic imbalance would eventually lead to catecholamine-induced cardiomyopathy.[61,62] Second, it was hypothesized that structural changes would occur due to impairment of the heart to adapt to transient changes in venous return and blood pressure.[72,85] However, tilt table tests performed

under baseline conditions and after selective blockade with atropine and propranolol showed that although less conspicuous, there is also impairment of the adrenergic innervation of the sinus node in chronic CD.[85] These findings showing attenuated sympathetically mediated sinus node responses were corroborated by studies employing power spectrum analyses focusing on the depressed vagal and adrenergic influences that are responsible for reduced heart rate variability in patients with CCM.[86,87]

Nevertheless, potentially even more important is the role of autonomic remodeling in the development of ventricular arrhythmias. There is now evidence of disturbances of sympathetic innervation at the ventricular level, which are clearly associated with serious ventricular arrhythmias. These investigations used single-photon emission computed tomography myocardial scintigraphy with meta-iodine-benzyl-guanidine labeled by 123Iodine to evaluate adrenergic myocardial innervation. The findings revealed diminished tracer uptake in areas that typically later exhibit perfusion defects and wall motion abnormalities. This reduced uptake was observed even in individuals presenting with the indeterminate form of CD.[88,89] In fact, the presence and severity of ventricular arrhythmias in patients with CCM have been shown to correlate with regional sympathetic myocardial denervation even better than with fibrosis, another hallmark of this arrhythmogenic disease.[90,91]

These findings suggest that autonomic remodeling-related disturbances could serve as early arrhythmia triggers, even before the development of significant fibrosis, which is a more definitive mechanism for the onset of malignant ventricular arrhythmias but typically occurs in later stages of the disease. This hypothesis is supported by data from the Syrian hamster model of *T. cruzi* infection, showing that impaired ventricular wall motion is more closely dependent on histopathologic inflammatory changes, rather than on fibrotic replacement of the myocardial tissue.[92] Furthermore, recent studies focusing on the prognostic meaning of dysautonomic remodeling as detected using spectral analysis of heart rate variability reported on the association of the autonomic derangement involving both the parasympathetic and the adrenergic limbs, with an elevated RASSI score, a major prognostic factor in CCM.[93]

MICROVASCULAR REMODELING IN CCM

The immune-mediated inflammatory reaction to parasitic persistence in the cardiac tissue triggers a remodeling of the coronary vessels at the microscopic and macroscopic levels.[94] Histopathologic studies in autopsied humans with CCM demonstrated constriction of intramyocardial arterioles, intimal hyperproliferation, extensive capillary basement membrane thickening, focal myocytolysis—a form of cell death typically caused by repetitive ischemic injury—and reparative fibrosis.[95–97]

Additionally, in postmortem angiography of patients with CD, there is a striking reduction in the density of myocardial microvessels.[98]

A hallmark of CCM is the development of LV aneurysms, predominantly at the apex and the inferolateral regions, areas that represent watershed coronary territories.[99,100] These regions may present marked anatomic and functional microvascular remodeling that is responsible for abnormal patterns of vasodilation and vasoconstriction, causing transient myocardial ischemia of low intensity and short duration that ultimately leads to aneurysm formation.[101,102]

Studies of Microvascular Derangements in Experimental Models of *T. cruzi* Infection

Studies focusing on the acute phase of in vitro animal models of *T. cruzi* infection have demonstrated the occurrence of myocardial ischemia attributed to multiple factors that include excessive local stimulation by catecholamines, occlusive platelet thrombosis and spasm causing focal vasoconstriction, neuraminidase induced platelet aggregation, endothelial microvascular hyperproliferation, direct damage caused by the parasite interaction with immune effector cells, increased production of endothelin and thromboxane-A2, and inhibition of cAMP endothelial protective role.[103–108] In a hamster model of chronic *T. cruzi* infections, it was found that at 6 months, nearly 50% of the animals had extensive myocardial perfusion defects (MPDs) at rest on single-photon emission computed tomography imaging.[92,109] In addition, histology showed that MPD areas had a clear topographical association with regions of inflammatory changes rather than regional transmural fibrosis. Dipyridamole compared with placebo showed a significant reduction of resting MPD in viable myocardium.[110] However, this was neither associated with a reduction in myocardial inflammatory histological lesions nor with a reversal of LV systolic dysfunction. In contrast, experiments in mice and Syrian hamster models have shown improvement in perfusion derangements with the administration of dipyridamole and pentoxifylline, respectively.[110,111]

Evidence of Microvascular Remodeling Derangements from Clinical Studies

There is a paucity of evidence demonstrating abnormal endothelial and nonendothelial dysregulation of coronary flow at the epicardial level. However, significant evidence exists that establishes myocardial ischemia in patients with CCM even in the presence of angiographically normal coronary arteries.[88,112–114] In a recent prospective study from Brazil, it was found that 15% of patients referred for diagnostic coronary angiograms had CD, with most of them not having evidence of obstructive epicardial coronary artery disease.[115]

Several studies have demonstrated both reversible and fixed MPD at various stages of CCM.[116,117] Additionally, in patients with CCM and malignant ventricular arrhythmias, MPD regions have demonstrated local myocardial sympathetic denervation.[118] It has also been found that in patients with the indeterminate form of CD, there is a reduction in coronary vasodilator flow reserve as demonstrated by stress echocardiography, as well as rest and stress-induced MPD and wall motion abnormalities.[119,120] A longitudinal study of patients with CCM revealed that 68% of segments that showed reversibility on scintigraphy scans at baseline progressed to fixed perfusion abnormalities after a 5.6-year follow-up period.[114] However, it is believed that the early phases of microvascular remodeling may be reversible as dipyridamole and isosorbide dinitrate, 2 coronary vasodilators, have been associated with short- and long-term improvements in the systolic LV function, even in the absence of improvement in symptoms.[121,122] A preliminary study of aspirin plus verapamil in patients with CCM who had chest pain and evidence of MPD demonstrated a significant reduction of reversible perfusion defects and improvement of quality of life scores.[123] These results have prompted further investigation into the role of vasodilation in a patient population, with an ongoing randomized controlled trial testing sildenafil on MPD in patients with CCM with normal epicardial coronary arteries.[124]

CONTRACTILE REMODELING IN CCM

Mechanical remodeling at the cellular and whole heart levels has been shown in both experimental models of *T. cruzi* infection and humans with CCM. It comprises abnormalities in both the relaxation and the contractile properties of the working myocardium.

Impairment in Relaxation

The ventricular diastolic dysfunction of CCM was first demonstrated in studies of patients with the indeterminate form of CD, which revealed no systolic abnormalities, but a striking elevation of LV end-diastolic pressure.[113,125] The diastolic dysfunction identified by independent researchers through diverse echocardiographic techniques[126,127] is likely the result of inflammatory and fibrotic alterations observed in endomyocardial biopsies, autopsies, or cardiac magnetic resonance imaging, even in patients with the indeterminate form of CD.[128–130] The lusitropic dysfunction is also consistently described in models of CCM in infected mice, which is frequently associated with slower calcium transient decay, indicating a causal role for this phenomenon.[35,37,41] Impaired actin-myosin interaction may also play a role.

Impairment in Systolic Function

Importantly, while systolic dysfunction in CD is typically classified as dilated cardiomyopathy, mild regional wall

motion abnormalities often precede the deterioration of overall LV function. These abnormalities can be identified even in less common instances of asymptomatic individuals who have a normal ECG.[131] The segmental wall motion systolic dysfunction leading to the contractile remodeling can progress from hypokinesis to akinesis, or dyskinesia, causing the characteristic aneurysms that predominate in the LV apical or inferolateral regions of watershed coronary supply.[132]

Another hallmark of CCM is that contractile systolic impairment involves both ventricles, and, consequently, both systemic and pulmonary congestion can occur concomitantly at later stages of the disease.[127] Despite the fact that it is the severe global LV systolic impairment that connotes the worse prognosis in patients with CCM, it is relevant to emphasize that regional wall motion abnormalities are also an important predictor of death. A prospective study conducted in 1508 patients of the BENEFIT randomized trial (Benznidazole Evaluation for Interrupting Trypanosomiasis) showed that despite normal global LV systolic function, regional wall motion abnormalities identified patients at higher risk for a composite of hard adverse clinical outcomes, including death.[133]

Contractile Remodeling at the Cellular Level

Research using the Syrian hamster model to investigate chronic *T. cruzi* infections has shown that fibrosis is not necessarily the primary cause of LV wall motion abnormalities.[92] Rather, it appears that segmental dysfunction could initially arise from inflammatory alterations, which then lead to disruptions in microvascular perfusion. Moreover, serial studies in humans showed that LV wall motion abnormalities are preceded by regional myocardial sympathetic denervation, another typical feature of CCM that is also involved in provoking malignant arrhythmias.[89,92]

Murine models of CCM have reported reduction in the amount of Ca^{2+} released from SR, and this was attributed to diminution of the expression of the calcium ion pump SERCA2a (sarcoplasmic/endoplasmic reticulum Ca^{2+}-ATPase), responsible for Ca^{2+} reuptake from the sarcoplasm back into the SR.[35] Thus, reduced Ca^{2+} reuptake would lead to incomplete SR refilling, contributing to diminished cardiomyocyte contractile force, one of the hallmarks of CD. At the cellular level, appropriate organization of the excitation-contraction coupling is most likely to be altered in CCM, as already described in experimental models of the disease.[35]

Normal excitation-contraction coupling functionality relies on the anatomy of dyads, t-tubules, ryanodine receptors, and microtubules. Microtubule responses to stress (ie, excessive shear and long exposure to increased preload) result in increased ROS production in cardiomyocytes.[134,135] Stretch-dependent ROS production through activation of NOX2 leads to enhanced and synchronous calcium release from the SR, such as that observed during varying mechanical loads.[135] This mechanotransduction pathway contributes to contractile dysfunction, aberrant calcium signaling, and the generation of arrhythmias both when exacerbated or when impaired. There is also evidence that in CCM such structural remodeling occurs. In a murine model of CCM, an asynchronous calcium release from SR was already described.[35]

In another study using the NOX2$^{-/-}$ mice infected with *T. cruzi*, it was found that the absence of the enzyme, contrary to the initial hypothesis, led to impaired calcium dynamics and cardiomyocyte contraction in isolated cells, favoring the occurrence of arrhythmias in infected isolated cells compared with infected control mice.[37]

Table 3 summarizes the main insights related to autonomic, microvascular, and contractile remodeling processes in CCM.

LINKING THE EXPERIMENTAL/CELLULAR DATA TO THE ARRHYTHMOGENIC MANIFESTATIONS OF CCM: FROM BENCH TO BEDSIDE

The full understanding of disease pathogenesis ideally requires a comprehensive knowledge of the molecular changes at the cellular scale, which are responsible for the observed organ-scale remodeling and, ultimately, lead to clinical manifestations. Unfortunately, at this point, we can only propose some general cellular mechanisms potentially related to cardiac arrhythmias in humans. To date, this knowledge is mostly based on experimental models of CD or extrapolation of data from other arrhythmogenic cardiomyopathies.

After *T. cruzi* infection, CCM takes several years to develop and to express its overt clinical manifestations. The range of arrhythmogenic clinical manifestations varies widely but can be classified as conduction system abnormalities (ie, sinus node dysfunction and atrio-ventricular conduction derangements) and ventricular arrhythmias (ie, isolated premature ventricular contractions, bigeminy, couplets, nonsustained VT, and, finally, VT and ventricular fibrillation).

Myocardial fibrosis, a most striking and peculiar hallmark of CCM, results from multiple diverse mechanisms, including inflammation directly linked to the tissue parasite persistence and to immune-mediated injury, myocytolytic necrosis induced by ischemia due to microvascular disturbances and, less importantly, apoptosis.[136,137] Because it is multifactorial and diffuse, the essential triad of inflammation, cell death, and fibrosis described in experimental models of *T. cruzi* infection, as well as in human materials obtained from endomyocardial biopsy and autopsy studies, manifests initially as a

Table 3. Summary of Autonomic, Microvascular, and Contractile Remodelings in CCM

	Specific finding	Impact on CCM
Autonomic remodeling in CCM, its descriptions, and its impact on the disease		
Remodeling component		
Initial observation	Blunted chronotropic response to atropine, suggesting cardiac autonomic involvement in CCM.	Autonomic impairment could be a contributing factor to SCD in patients with CCM.
Pathological evidence	Intense neuronal depopulation mainly in the parasympathetic cardiac intramural ganglia due to necrosis caused by direct parasitism, periganglionic inflammation, and autoimmune reactions.	Indicates significant autonomic denervation, more prominent in CCM than in other cardiac diseases, contributing to the disease's pathogenesis.
Dysautonomia	Can be typically detected before the development of ventricular dysfunction and in all phases and forms of the disease, including the indeterminate and digestive forms.	Dysautonomia in CD is largely irreversible, differing from the reversible autonomic dysfunction seen in heart failure caused by neurohumoral activation and neural pathway desensitization.
Parasympathetic denervation	Loss of inhibitory action of the parasympathetic system on the sinus node, leading to a lack of rapid bradycardia or tachycardia response to changes in blood pressure and venous return.	Represents a natural model for studying autonomic heart remodeling, showing irreversible dysautonomia that affects heart functionality throughout all disease phases.
Sympathetic dysregulation	Disturbances in sympathetic innervation at the ventricular level shown by reduced uptake in SPECT myocardial scintigraphy are associated with serious ventricular arrhythmias.	Plays a crucial role in the development of ventricular arrhythmias, potentially acting as early arrhythmia triggers, with the sympathetic alterations having a significant impact on the severity and prognosis of CCM.
Microvascular remodeling in CCM and its findings and impact on the disease pathophysiology and progression		
Aspect		
Histopathologic changes	Constriction of intramyocardial arterioles, intimal hyperproliferation, capillary basement membrane thickening, focal myocytolysis, and reparative fibrosis. Reduction in myocardial microvessel density observed in postmortem angiography.	Contributes to the pathogenesis of CCM by impairing myocardial perfusion and leading to ischemic injury and fibrosis.
Left ventricular aneurysms	Development of left ventricular aneurysms, especially at the apex and inferolateral regions, due to abnormal microvascular vasodilation and vasoconstriction patterns leading to transient myocardial ischemia.	Aneurysms indicate severe microvascular remodeling and are associated with an increased risk of morbidity and mortality in CCM.
Experimental model findings	Acute phase studies in *T. cruzi*-infected animal models show myocardial ischemia due to various factors such as excessive catecholamine stimulation, occlusive thrombosis, endothelial hyperproliferation, and direct parasitic damage. Chronic infection animal models show extensive myocardial perfusion defects.	Highlights the multifactorial nature of microvascular disturbances in CCM and their role in disease progression.
Clinical study evidence	Evidence of myocardial ischemia in patients with CCM with angiographically normal coronary arteries. MPD was observed at various disease stages, with regions of sympathetic denervation and reduced coronary vasodilator flow reserve.	Demonstrates that microvascular remodeling can lead to significant cardiac dysfunction in CCM, despite the absence of epicardial coronary artery disease.
Therapeutic interventions	Use of coronary vasodilators such as dipyridamole and isosorbide dinitrate shows improvement in systolic LV function. Incipient trials of aspirin plus verapamil and of sildenafil showing reduction of MPD in patients with CCM may indicate promising potential for reversing microvascular remodeling.	Suggests that microvascular remodeling in CCM may be partially reversible with appropriate vasodilator therapy, offering potential targets for therapeutic intervention.
Contractile remodeling in CCM		
Remodeling component		
Diastolic dysfunction	Elevated LV end-diastolic pressure without systolic abnormalities.	Causes heart failure symptoms due to impaired relaxation.
Systolic dysfunction	Progression from regional wall motion abnormalities to global dysfunction.	Affects overall heart pumping efficiency, leading to heart failure and increased mortality.
Cellular remodeling	Reduced Ca^{2+} release from SR and altered excitation-contraction coupling.	Impairs cardiomyocyte contractility and contributes to arrhythmogenesis.
Fibrosis and microvascular changes	Fibrosis is not always the primary cause of LV impairment; may be linked to inflammation and microvascular disturbances.	Indicates a complex interplay of factors contributing to contractile dysfunction.

CCM indicates Chagas cardiomyopathy; CD, Chagas disease; LV, left ventricular; MPD, myocardial perfusion defect; SCD, sudden cardiac death; SPECT, single–photon emission computed tomography; SR, sarcoplasmic reticulum; and *T. cruzi*, *Trypanosoma cruzi*.

focal microscopic process that ultimately is coalescent and assumes the form of an organ-scale macroanatomic disorder.[138,139]

Among others, 2 major remodeling consequences of myocardial fibrosis in CCM result from early contractile mechanical dysfunction that affects both the diastolic

and the systolic ventricular performance[126,140,141] and, no less conspicuously, the electrical properties of the whole heart, thereby causing various types of arrhythmia. Moreover, extensive ventricular areas exhibit myocardial fibrosis intermingled with abnormally functioning ischemic but still viable fibers. Of note, contractile disturbances

have been reported using more sophisticated methods such as speckle-tracking echocardiography in humans with the indeterminate form of CD, even before a significant amount of coalescent fibrosis can be detected by the method of cardiac magnetic resonance.[142] Such heterogeneous environments of dispersed electrical
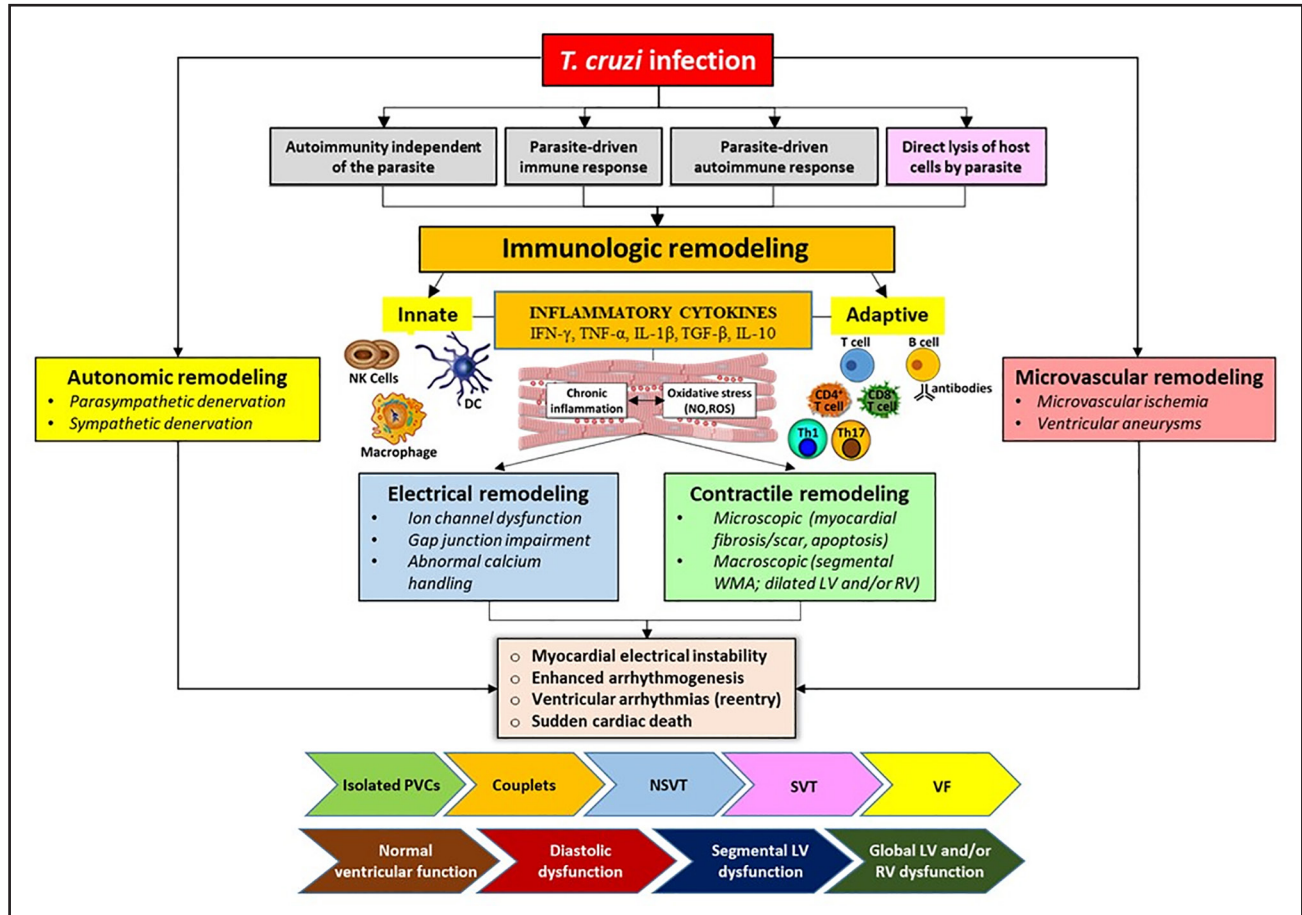
Figure 5. Multifaceted cardiac remodeling in Chagas cardiomyopathy (CCM).
The clinical course of CCM is characterized by a complex cascade of pathological remodeling processes that encompasses 5 distinct but interrelated phenomena: immunologic, electrical, structural, autonomic, and microvascular. The initial immune response to *Trypanosoma cruzi* (*T. cruzi*) infection is a combination of innate and adaptive mechanisms. Innate immunity involves dendritic cells (DCs), natural killer (NK) cells and macrophages, releasing a cascade of inflammatory cytokines such as IFN-γ (interferon gamma), TNF-α (tumor necrosis factor-alpha), IL (interleukin)-1β, TGF-β (transforming growth factor-beta), IL-12 and IL-10, while the adaptive immune response involves T cells and B cells. Although the immune response aims to control the infection, it also induces a state of persistent inflammation and oxidative stress, potentially leading to myocardial injury. Concurrently, the heart undergoes electrical remodeling. This is characterized by a disruption in ion channels' function and gap junction connectivity, along with aberrant calcium handling, culminating in electrical instability. The consequence is an increased susceptibility to various forms of arrhythmias, ranging from benign premature ventricular contractions (PVCs) to serious ventricular arrhythmias, which can precipitate sudden cardiac death. As the heart faces persistent inflammation and imbalanced immune responses, structural changes ensue. On a microscopic level, there is an accumulation of myocardial fibrosis, scarring, and apoptosis of cardiac cells. Macroscopically, these changes manifest as segmental wall motion abnormalities (WMA) and dilatation of the left ventricle (LV) and right ventricle (RV). The autonomic nervous system is equally affected, undergoing early functional remodeling. The cardiac autonomic innervation, pivotal in modulating heart rate and rhythm, is disrupted through parasympathetic and sympathetic denervation, increasing the propensity for arrhythmogenesis and exacerbating the progression of cardiac dysfunction. Finally, the microcirculations are not spared in this pathogenic odyssey. Microvascular remodeling is characterized by ischemia in watershed zones between the main coronary arteries, leading to the formation of the characteristic aneurysmatic lesions at 2 principal sites of the left ventricle: the apex and the inferolateral wall. In summary, this figure succinctly captures the intricate and interconnected nature of cardiac remodeling induced by CCM, emphasizing the sequential development of ventricular arrhythmias as a hallmark of the disease. Yet, it is critical to acknowledge that ventricular arrhythmias do not always follow a predictable pattern in relation to myocardial changes, indicating a need for nuanced understanding in clinical assessment and management. This multidimensional model underscores the critical points for potential therapeutic intervention and highlights the necessity of a comprehensive approach to mitigate the adverse outcomes associated with CCM. NSVT indicates nonsustained ventricular tachycardia; ROS, reactive oxygen species; SVT, sustained ventricular tachycardia; and VF, ventricular fibrillation.

conduction properties are key phenomena, leading to focally abnormal patterns of refractoriness that cause unidirectional blocks and reentry circuits, which are the basic substrates for VT and ventricular fibrillation.

Before the expansion of fibrotic tissue in the heart, the most common arrhythmic findings in patients are triggered activities, probably due to the occurrence of focal excitation and spiral waves. It is plausible that the progression of the electrical remodeling at the clinical setting, thereby causing nonsustained or sustained VT, either monomorphic or polymorphic, happens together with the scar accumulation in the heart, thus providing a substrate for not only functional but also anatomic reentrant circuits.[51,143] It is interesting to highlight that hyperactivation of CAMKII, together with increased diastolic calcium accumulation, may contribute to the activation of necrotic and apoptotic pathways in cardiomyocytes, leading to both reactive and reparative scar formation.[144]

In addition, with the progression of cardiomyocyte deaths, more inflammation occurs due to excessive production of pathogen-associated molecular patterns and damage-associated molecular patterns. This effect is particularly relevant because the intensity of inflammation is usually not proportional to the level of tissue parasitism, as found in experimental models of *T. cruzi* infection and in patients with CCM. From these studies, it is also apparent that additional mechanisms are involved in causing arrhythmias, such as microvascular derangements[110,145] and sympathetic innervation abnormalities, which accompany the progression of CCM, as described above.[89–91]

In contrast to what is more often observed in ischemic cardiomyopathy (ie, malignant arrhythmia occurrence only at more advanced stages of the disease and with higher scar burden), in CCM, patients may experience SCD before any clinically apparent scar formation or contractile dysfunction as assessed by more conventional methods. It has been speculated that some of these catastrophic events may be related to higher susceptibility to oxidative stress and to an enhanced response of the immune system to *T. cruzi* infection. This speculation has been advanced based on recent experimental evidence supporting the concept that polymorphism of key genes involved in the immune response, following *T. cruzi* infection, favors the development of CCM and may be responsible for arrhythmogenesis. For example, it was reported that mutation in the *RyR2* gene is associated with increased occurrence of polymorphic VT, particularly the catecholaminergic polymorphic VT.[146]

CONCLUSIONS

Despite some recent achievements in regard to the cellular and molecular basic mechanism of ventricular arrhythmias, the full understanding of the arrhythmogenic manifestations in patients with CCM is still incomplete.

There is a relative paucity of literature findings to provide direct evidence of causality between the abnormal oxidative inflammatory profile found in patients with CCM and the remodeling of cardiomyocyte machinery responsible for the electrical behavior of the diseased heart. Moreover, most of the evidence is based on experimental models of *T. cruzi* infection; hence, a direct correlation of data from cellular and molecular investigations with research findings in human patients remains elusive and awaits further clarification.

It should be acknowledged that the complex intrinsic pathophysiology of CCM entails remodeling effects acting simultaneously in the immune system, the cellular electrical conduction, the autonomic control, the coronary microvascular structure and function, and the contractile performance of the affected heart (Figure 5).

Treatment of patients with CCM remains challenging. Some of the new potential therapies for CCM lack information on its effects on the electrical function of cardiomyocytes, which makes it hard to optimize treatment guidelines, especially because CCM is a primarily arrhythmogenic pathological entity.[2] To accomplish the goal of improving the therapeutic control of such a complex disease, a more comprehensive and integrated understanding of functional remodeling of the cardiovascular system, as proposed in this review, is necessary.

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