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NEUROVASCULAR DYSFUNCTION AS A POTENTIAL PATHOGENIC AXIS IN TRYPANOSOMA CRUZI INFECTION: MECHANISMS, CLINICAL IMPLICATIONS AND THERAPEUTIC PERSPECTIVES

DISFUNÇÃO NEUROVASCULAR COMO UM POTENCIAL EIXO PATOGÊNICO NA INFECÇÃO POR TRYPANOSOMA CRUZI: MECANISMOS, IMPLICAÇÕES CLÍNICAS E PERSPECTIVAS TERAPÊUTICAS

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Daniella Evelyn Generoso Manhães[1]

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ABSTRACT

Chagas disease, caused by Trypanosoma cruzi, remains a major neglected tropical disease with increasing global relevance due to migration and geographic expansion. Although cardiac and gastrointestinal manifestations have been extensively investigated, growing experimental evidence indicates that microvascular and neurovascular alterations may play an important role in disease progression. However, these mechanisms are often interpreted as inflammatory consequences rather than potential central determinants of pathogenesis. This review examines experimental and clinical studies addressing endothelial dysfunction, nitric oxide imbalance, dysregulation of VEGF signaling, and blood–brain barrier alterations during T. cruzi infection. By integrating data from vascular biology, immunopathology, and host parasite interaction research, a unifying pathogenic framework is proposed, supporting the hypothesis that neurovascular dysfunction may represent a potential pathogenic axis in Chagas disease. Evidence from in vitro, in vivo, and clinical investigations suggests that parasite-induced endothelial activation, oxidative stress, and microcirculatory impairment contribute not only to cardiac pathology but also to cerebral microvascular damage, potentially underlying neurological manifestations observed in both acute and chronic phases of the disease. Rather than viewing vascular permeability alterations as secondary phenomena, this review highlights their potential role as active contributors to systemic microvascular injury. This conceptual integration may support the identification of novel adjunctive therapeutic strategies targeting endothelial integrity and vascular signaling pathways in Chagas disease.

KEYWORDS: Chagas disease. Trypanosoma cruzi. Endothelial dysfunction. Vascular permeability. Blood–brain barrier.

RESUMO

A doença de Chagas, causada por *Trypanosoma cruzi*, permanece como uma importante doença tropical negligenciada, com crescente relevância global devido à migração e à expansão geográfica. Embora as manifestações cardíacas e gastrointestinais tenham sido amplamente investigadas,

[1] Pharmacist, postgraduate in Clinical Analyses from Faculdade FaSouza (distance learning), Brazil, and in Clinical Pathology from Faculdade Uniminas (distance learning), Brazil. Holds specialization focused on the laboratory field, with interest in clinical diagnosis, interpretation of laboratory tests, and disease pathophysiology. Her work is centered on the application of scientific knowledge to support diagnosis and healthcare practice. Postgraduate in Clinical Analyses, Faculdade FaSouza (distance learning), Brazil. Postgraduate in Clinical Pathology, Faculdade Uniminas (distance learning), Brazil.

evidências experimentais crescentes indicam que alterações microvasculares e neurovasculares podem desempenhar um papel importante na progressão da doença. No entanto, esses mecanismos são frequentemente interpretados como consequências inflamatórias, em vez de potenciais determinantes centrais da patogênese. Esta revisão examina estudos experimentais e clínicos que abordam a disfunção endotelial, o desequilíbrio do óxido nítrico, a desregulação da sinalização de VEGF e as alterações da barreira hematoencefálica durante a infecção por *T. cruzi*. Ao integrar dados da biologia vascular, imunopatologia e pesquisas sobre a interação hospedeiro-parasita, propõe-se um modelo patogênico unificador, sustentando a hipótese de que a disfunção neurovascular pode representar um potencial eixo patogênico na doença de Chagas. Evidências provenientes de investigações *in vitro*, *in vivo* e clínicas sugerem que a ativação endotelial induzida pelo parasita, o estresse oxidativo e o comprometimento microcirculatório contribuem não apenas para a patologia cardíaca, mas também para o dano microvascular cerebral, potencialmente subjacente às manifestações neurológicas observadas tanto na fase aguda quanto na crônica da doença. Em vez de considerar as alterações na permeabilidade vascular como fenômenos secundários, esta revisão destaca seu possível papel como contribuintes ativos para a lesão microvascular sistêmica. Essa integração conceitual pode apoiar a identificação de novas estratégias terapêuticas adjuvantes voltadas à integridade endotelial e às vias de sinalização vascular na doença de Chagas.

PALAVRAS-CHAVE: Doença de Chagas. *Trypanosoma cruzi*. Disfunção endotelial. Barreira hematoencefálica.

RESUMEN

La enfermedad de Chagas, causada por Trypanosoma cruzi, continúa siendo una importante enfermedad tropical desatendida con creciente relevancia global debido a la migración y la expansión geográfica. Aunque las manifestaciones cardíacas y gastrointestinales han sido ampliamente investigadas, la creciente evidencia experimental indica que las alteraciones microvasculares y neurovasculares pueden desempeñar un papel importante en la progresión de la enfermedad. Sin embargo, estos mecanismos suelen interpretarse como consecuencias inflamatorias en lugar de posibles determinantes centrales de la patogénesis. Esta revisión examina estudios experimentales y clínicos que abordan la disfunción endotelial, el desequilibrio del óxido nítrico, la desregulación de la señalización de VEGF y las alteraciones de la barrera hematoencefálica durante la infección por T. cruzi. Al integrar datos de biología vascular, inmunopatología e investigación sobre la interacción hospedador-parásito, se propone un marco patogénico unificador que respalda la hipótesis de que la disfunción neurovascular puede representar un posible eje patogénico en la enfermedad de Chagas. La evidencia proveniente de estudios in vitro, in vivo y clínicos sugiere que la activación endotelial inducida por el parásito, el estrés oxidativo y el deterioro microcirculatorio contribuyen no solo a la patología cardíaca, sino también al daño microvascular cerebral, potencialmente subyacente a las manifestaciones neurológicas observadas tanto en la fase aguda como en la crónica de la enfermedad. En lugar de considerar los cambios en la permeabilidad vascular como fenómenos secundarios, esta revisión destaca su posible papel como contribuyentes activos a la lesión microvascular sistémica. Esta integración conceptual puede apoyar la identificación de nuevas estrategias terapéuticas adyuvantes dirigidas a la integridad endotelial y a las vías de señalización vascular en la enfermedad de Chagas.

PALABRAS CLAVE: Enfermedad de Chagas. Trypanosoma cruzi. Disfunción endotelial. Permeabilidad vascular. Barrera hematoencefálica.

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1. INTRODUCTION

Trypanosoma cruzi is the flagellated protozoan responsible for Chagas disease, also known as American trypanosomiasis. The disease affects more than 7 million people worldwide, primarily in Latin America (1). It was first described in rural areas of Brazil in 1909 by the Brazilian physician Carlos Chagas, who characterized both the parasite's life cycle and the clinical aspects of the disease (2). Chagas disease presents acute and chronic phases and is transmitted by insects of the family Reduviidae, subfamily *Triatominae* (3).

Different parasite strains distributed across distinct geographic regions exhibit variable tissue tropism, virulence, and clinical manifestations. The epidemiology of Chagas disease varies considerably across endemic regions, and although millions of individuals have been infected historically, only a proportion of infected individuals develop clinically significant disease (4). It has been estimated that approximately 10% to 30% of infected individuals will develop symptomatic forms of the disease during the chronic phase (4). Historical estimates from the 1990s suggested that approximately 17 million people were infected with the parasite, mainly in Central and South America (5).

However, due to advances in globalization and increasing migratory movements toward non-endemic areas, cases of Chagas disease have been increasingly reported in several regions worldwide. Even more than a century after its discovery, Chagas disease remains a major cause of morbidity and mortality among parasitic diseases, accounting for a substantial proportion of deaths associated with neglected tropical diseases (6) and resulting in more than 10,000 deaths annually worldwide (1). In the global context, *T. cruzi* infection has spread beyond endemic regions and is now recognized as an emerging public health concern in non-endemic countries (7). Due to socio-environmental changes and increased population mobility, many infected individuals currently reside in urban areas, and cases have been reported in more than 40 countries, including Canada, the United States, and several European countries, as well as regions in the Western Pacific, Africa, and the Eastern Mediterranean (1).

Despite advances in antiparasitic therapy, morbidity and mortality in Chagas disease remain strongly associated with progressive microvascular damage affecting multiple organs (3,7,20). Increasing evidence indicates that vascular and neurovascular alterations may represent an important component of disease pathophysiology (15,21).

In particular, parasite-mediated endothelial activation, imbalance of vasoactive mediators, and disruption of vascular barrier integrity have been increasingly associated with microvascular dysfunction affecting both cardiac and cerebral tissues (16,21,24).

Therefore, the present narrative integrative review aims to synthesize experimental and clinical evidence regarding endothelial dysfunction, nitric oxide imbalance, VEGF signaling, and blood–brain barrier alterations in *Trypanosoma cruzi* infection (3,15,21,24).

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By integrating evidence from vascular biology, immunopathology, and host–parasite interaction studies derived from experimental models, histopathological observations, and clinical investigations, this review proposes a conceptual framework for understanding the neurovascular mechanisms involved in the progression of Chagas disease (3,15,21).

1.1. Modes of transmission

The main vector of the protozoan is *Triatoma infestans*, also known as the kissing bug. After feeding on the host's blood, the triatomine transmits the infective form of the parasite to the vertebrate host through contaminated feces and urine, which infect the individual via mucosal surfaces or through skin lesions resulting from the insect bite (8). In addition to vector-borne transmission, other routes of *T. cruzi* infection include blood transfusion, ingestion of contaminated food, congenital transmission, organ transplantation, or accidental exposure through direct contact with the parasite (9).

1.2. Phases of the disease and clinical manifestations

The disease presents two clinical phases – acute and chronic. In most individuals infected with *T. cruzi*, the acute phase is asymptomatic. Patients who develop the clinical form of the disease typically present symptoms 8 to 10 days after infection, including fever, headache, pallor, myalgia, dyspnea, edema, and abdominal or chest pain (1).

Hepatosplenomegaly, lymphadenopathy, myocarditis, electrocardiographic abnormalities, and localized or generalized subcutaneous edema may also occur. These manifestations are directly associated with parasitemia in the infected individual (10). The main cause of death during the acute phase is heart failure; however, particularly in children and immunocompromised patients, neurological manifestations have also been observed (8).

Approximately, 2 to 3 months after the initial infection, the indeterminate form of chronic Chagas disease becomes prevalent among infected individuals. The remaining patients (30 to 40%) develop the clinical form 10 to 30 years later, characterized by minimal but persistent inflammation. This may manifest as the cardiac form (arrhythmias, thromboembolism, and heart failure), the digestive form (megacolon or megaesophagus), or a combination of both (3). Furthermore, the correlation between the chronic form of the disease and central nervous system alterations has been discussed, with reported cases of stroke or cognitive dysfunction (11).

2. METHODS

This study was conducted as a narrative integrative review aimed at synthesizing experimental and clinical evidence regarding neurovascular mechanisms associated with *Trypanosoma cruzi* infection. This approach was chosen to integrate findings from heterogeneous

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sources, including experimental models, clinical studies, and mechanistic investigations, allowing the construction of a conceptual framework for neurovascular alterations in Chagas disease.

Literature Search Strategy

A structured literature search was conducted using the PubMed/MEDLINE, Scopus, and Web of Science databases to identify studies investigating endothelial dysfunction, VEGF signaling, nitric oxide imbalance, blood–brain barrier disruption, and neurovascular mechanisms associated with *Trypanosoma cruzi* infection.

The literature search was performed between April and December 2025, including publications available up to December 2025. No temporal restrictions were applied to include both foundational mechanistic studies and more recent investigations relevant to the pathophysiology of Chagas disease.

The following keywords and Boolean combinations were used:
("*Trypanosoma cruzi*" OR "Chagas disease") AND ("endothelial dysfunction" OR "blood–brain barrier" OR "neurovascular" OR "vascular permeability").

These search terms were adapted when necessary according to the indexing system of each database. Additional relevant studies were identified through manual screening of the reference lists of selected articles.

Study Selection

The initial search retrieved a broad set of publications across the selected databases. After removal of duplicate records, titles and abstracts were screened to assess relevance to vascular and neurovascular mechanisms associated with *T. cruzi* infection.

Studies considered potentially relevant were subsequently evaluated through full-text analysis to determine eligibility for inclusion in the review.

Eligibility Criteria

Inclusion criteria comprised:

- experimental studies (*in vitro* and *in vivo*);
- clinical studies;
- peer-reviewed publications addressing vascular or endothelial mechanisms related to *T. cruzi* infection.

Exclusion criteria included:

- duplicate records;
- non–peer-reviewed publications;
- studies not directly related to vascular mechanisms associated with the infection.

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Data Extraction and Synthesis

For each eligible study, information regarding study design, experimental model, main vascular mechanisms investigated, and key findings related to endothelial dysfunction and neurovascular alterations was extracted.

Eligible studies were qualitatively analyzed to synthesize available experimental and clinical evidence and to support the construction of an integrative mechanistic framework focusing on endothelial dysfunction, nitric oxide imbalance, VEGF signaling, and neurovascular alterations in Chagas disease.

Given the heterogeneity of the available evidence, which includes experimental models, histopathological observations, and clinical data, a qualitative narrative synthesis was adopted rather than a systematic quantitative analysis.

Because the objective of this review was conceptual integration of mechanistic evidence rather than quantitative comparison of outcomes, formal risk-of-bias assessment tools were not applied.

Therefore, the purpose of this review was not to establish causal relationships but to integrate findings from different levels of evidence and to propose a conceptual pathophysiological model of neurovascular involvement in Chagas disease.

3. NEUROVASCULAR ALTERATIONS IN CHAGAS DISEASE

Although cardiac and digestive disorders represent the main pathogenic manifestations, cellular alterations induced by *T. cruzi* in cerebral microcirculation remain under investigation (4).

The central nervous system is considered an immune-privileged site, as it restricts the access of immune cells and macromolecules through the blood–brain barrier (24). However, under pathogenic conditions such as intracellular parasitic invasion, this cerebrovascular barrier becomes altered, initiating an inflammatory process characterized by leukocyte migration from the bloodstream into the target tissue through the vascular endothelium (12). Central nervous system (CNS) involvement during acute and chronic Chagas disease in humans has gained increasing recognition and has been widely reported. Meningoencephalitis is a frequent finding during acute infection, whereas in the chronic phase CNS involvement is associated with behavioral and cognitive changes (13).

Previous studies suggest a relationship between stroke, thromboembolic phenomena, and heart failure in patients with Chagas disease (7); however, 25.53% of stroke cases were classified as of indeterminate cause, without association with cardioembolism (4). Ischemic stroke was also observed in 38.4% of asymptomatic patients. Although the cause remains unclear, endothelial dysfunction may be associated with these findings (14).

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Nisimura et al. demonstrated, in a murine model of acute *Trypanosoma cruzi* infection, cerebral microcirculatory dysfunction, with significant reduction in arteriolar diameter and impaired nitric oxide bioavailability, suggesting an important role of endothelial dysfunction in the cerebral pathophysiology of the acute phase (15). Furthermore, protozoan infection induces systemic inflammation characterized by cytokine release and immune system activation (12,16). This inflammatory environment promotes imbalance in nitric oxide production and its relationship with vascular endothelial growth factor (VEGF) (17–19). Another study demonstrated increased VEGF expression in cardiac tissue infected by the parasite, associated with local inflammatory hypoxia and temporal parallelism between angiogenesis and cardiac remodeling; that is, angiogenesis does not occur in isolation but rather as part of an integrated inflammatory remodeling process (20).

Consequently, endothelial dysfunction may represent a central pathogenic axis, increasing vascular permeability and promoting microvascular damage (21–22). In the heart, these mechanisms contribute to ischemia, fibrosis, and progression of cardiomyopathy (7–8). In the central nervous system, disruption of the blood–brain barrier facilitates inflammatory infiltration and microvascular impairment, contributing to neurological manifestations (13,23–24).

These observations support the hypothesis that neurovascular dysfunction may represent an important component of the pathophysiological mechanisms underlying neurological complications in Chagas disease.

4. VEGF SIGNALING IN VASCULAR PERMEABILITY AND ANGIOGENESIS

In 1989, the purification and sequencing of a specific endothelial cell mitogen, termed vascular endothelial growth factor (VEGF), was reported (25). VEGF is a key angiogenic factor essential for vascular endothelial cells (26). In addition to inducing angiogenesis, it is a major regulator of vascular permeability. It belongs to a family of dimeric glycoproteins that includes VEGF-A, VEGF-B, VEGF-C, VEGF-D, and placental growth factor (PlGF). VEGF-A is the principal member of this family and, besides promoting vascular growth, exerts potent effects on vascular permeability, also being referred to as vascular permeability factor (VPF) (19). Moreover, in the infectious context, VEGF is responsible for loosening interendothelial junctions, increasing plasma extravasation, facilitating inflammatory cell infiltration, and contributing to edema and tissue damage (27).

VEGF induces angiogenesis by directly acting on endothelial cells through binding and activating membrane receptors belonging to the receptor tyrosine kinase (RTK) family: VEGFR-1 (Flt-1), VEGFR-2 (KDR in humans or Flk-1 in animals), and VEGFR-3 (Flt-4).

Receptor activation promotes a cascade of intracellular events that induce cellular proliferation, migration, and survival, making it a critical mediator of angiogenesis. VEGF-A primarily acts on VEGFR-2, promoting the formation of new vessels from pre-existing vasculature under both physiological and pathological conditions (28), whereas VEGF-C and VEGF-D exert predominantly

lymphangiogenic effects (17). In the context of *Trypanosoma cruzi* infection, experimental studies have demonstrated increased VEGF expression in infected cardiac tissue, associated with inflammatory hypoxia and tissue remodeling (20). These findings suggest that angiogenic signaling may contribute to microvascular remodeling and increased vascular permeability during the progression of Chagas disease.

Vascular growth may be induced by hypoxic or inflammatory stimuli. Hypoxia-inducible factor (HIF) plays a central role in the transcriptional activation of genes responsible for vascular growth. Low physiological oxygen levels lead to increased production and release of HIFs by endothelial cells, stimulating the expression of angiogenic growth factors (19). Cytoplasmic accumulation of HIF leads to its translocation to the nucleus, where it activates the expression of multiple genes, including VEGF and endothelial nitric oxide synthase (eNOS), which is responsible for nitric oxide production (29,30).

Activation of VEGF receptors begins with VEGF binding to the extracellular domain of the receptor. This interaction induces receptor dimerization, resulting in autophosphorylation of tyrosine residues within the intracellular domain, while the extracellular portion corresponds to the receptor itself, leading to activation of VEGF-induced signal transduction pathways. Phospholipase Cγ (PLCγ) degrades membrane phospholipids, leading to the production of diacylglycerol (DAG), which induces intracellular calcium (Ca^{2+}) release and activates protein kinase C (PKC). PKC subsequently stimulates the Raf/MAPK (mitogen-activated protein kinase) pathway, activating MEK and inducing ERK1/2 phosphorylation, thereby increasing cellular proliferation. Ca^{2+} mobilization and PKC activation are key components of VEGF-induced vascular permeability signaling through induction of endothelial nitric oxide synthesis and regulation of molecular passage across the endothelium via the junctional protein VE-cadherin (19,31–32) (Figure 1).

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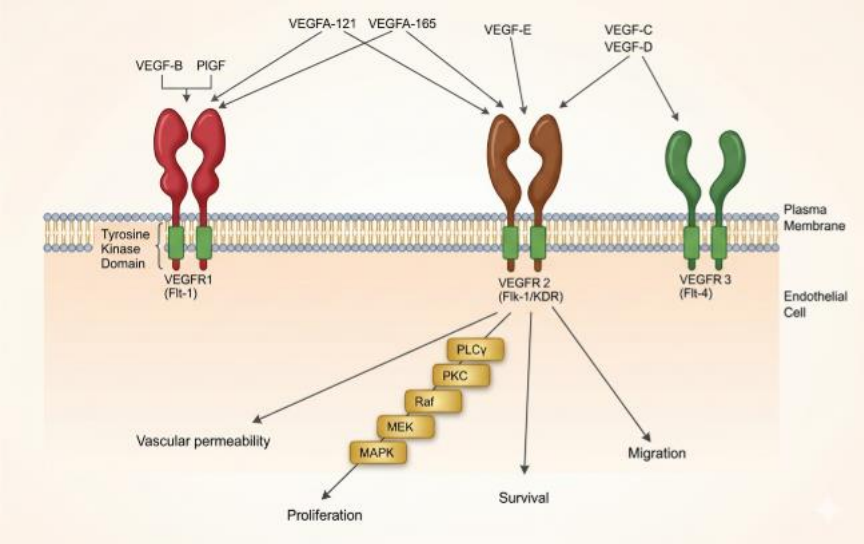
Figure 1. Schematic representation of VEGF binding to its receptors and activation of intracellular pathways involved in angiogenesis



Source: Adapted from Capp C et al. (19).

In 2022, experimental studies demonstrated that experimental *T. cruzi* infection induces increased VEGF-A expression and angiogenesis in cardiac tissue, in addition to diffuse inflammatory infiltration throughout the myocardium (20). Therefore, understanding how infection modulates vascular permeability pathways is important for elucidating mechanisms involved in the pathogenesis of Chagas disease and may contribute to the development of future therapeutic strategies.

5. NITRIC OXIDE IN CEREBRAL VASCULAR REGULATION DURING *TRYPANOSOMA CRUZI* INFECTION

Nitric oxide (NO) plays a central role in vascular homeostasis, and growing evidence suggests that its dysregulation contributes to microvascular alterations observed during *Trypanosoma cruzi* infection (16,36).

In 1980, it was first demonstrated that acetylcholine-induced vascular relaxation was dependent on the presence of the endothelium, and this effect was later attributed to the release of a substance subsequently identified as nitric oxide (33,34).

Nitric oxide is a free radical rapidly degraded by oxygen, and its oxidation generates nitrite (NO_2^-) and nitrate (NO_3^-) (35). In addition to its immunomodulatory properties, NO acts as a potent vasodilator on vascular smooth muscle. Its action on the endothelium depends on the cell type, site of action, and stimulus (36).

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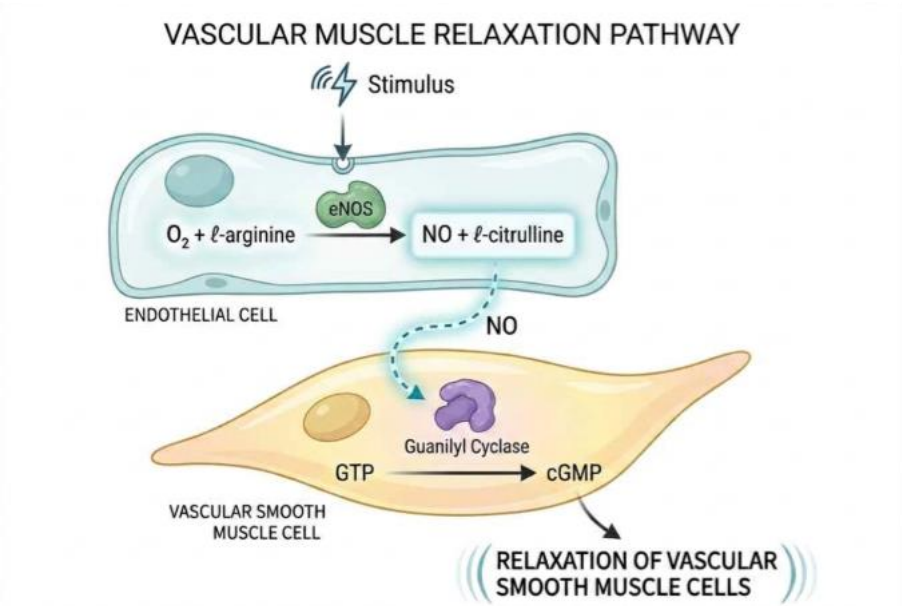
NO synthesis depends on the catalytic enzyme nitric oxide synthase (NOS), which is constitutively expressed in vascular endothelial cells (eNOS) and neurons (nNOS), or inducible (iNOS) by lipopolysaccharide (LPS) and bacterial endotoxins, acting in conjunction with released cytokines such as TNF-α and IL-1β (18).

In vascular endothelial cells, NO production occurs from the precursor L-arginine: the guanidino nitrogen terminal of L-arginine is converted into nitric oxide and L-citrulline in a process catalyzed by nitric oxide synthase (Figure 2). This mechanism is oxygen-dependent (35).

Figure 2. Representation of the vasodilation mechanism mediated by constitutive nitric oxide synthase (cNOS), also known as eNOS in endothelial cells and nNOS in neuronal cells



Source: Adapted from Cerqueira NF et al. (33).

The NO produced in this process diffuses from the endothelium to vascular smooth muscle and directly stimulates soluble guanylate cyclase (sGC), which converts guanosine triphosphate (GTP) into intracellular cyclic guanosine monophosphate (cGMP). Increased cGMP levels reduce calcium influx and enhance calcium uptake by the endoplasmic reticulum, promoting vascular smooth muscle relaxation (36).

In healthy individuals, basal NO production exerts a moderate and sustained vasodilatory effect, maintaining vascular homeostasis. If basal NO formation ceases, marked vasoconstriction may occur. Additionally, reduced NO formation, as observed in several vascular diseases, may impair tissue perfusion and favor thrombus formation (37). NO may also mediate vasodilation during physiological angiogenesis or pathological processes such as tumor development (38). However, in

the context of *Trypanosoma cruzi* infection, alterations in nitric oxide production have been associated with endothelial dysfunction and cerebral microcirculatory impairment.

Experimental studies demonstrate significant imbalance in nitric oxide bioavailability during infection, contributing to vascular dysregulation and inflammatory amplification (15,16). Experimental models of *T. cruzi* infection have also demonstrated intense vasoconstriction in cerebral microcirculation, indicating disruption of nitric oxide–mediated vascular regulation and endothelial dysfunction in the brain of infected animals (15).

Collectively, these findings indicate that *Trypanosoma cruzi* infection is associated with endothelial dysfunction and altered nitric oxide bioavailability, suggesting that modulation of basal NO levels may represent an important component of the vascular pathophysiology observed during infection.

6. VEGF–NITRIC OXIDE–VE-CADHERIN INTERACTIONS IN THE VASCULAR PATHOPHYSIOLOGY OF CHAGAS DISEASE

The heart is the most affected organ in individuals with chronic Chagas disease, and consequences include myocardial cell destruction, fibrosis, and ventricular wall thinning (8). Cardiomyopathy occurs in approximately 30% of seropositive individuals, potentially leading to arrhythmias, heart failure, thromboembolism, and sudden death (7).

Blood vessels are essential for the supply of oxygen and nutrients to tissues. During *Trypanosoma cruzi* infection, inflammatory processes and alterations in vascular homeostasis may impair tissue perfusion, triggering adaptive responses aimed at restoring blood flow. Among these mechanisms, the activation of angiogenic pathways mediated by vascular endothelial growth factor (VEGF) is particularly notable, as it represents a major regulator of angiogenesis and endothelial permeability (17).

Experimental studies have demonstrated increased VEGF expression and vascular remodeling in tissues infected by *T. cruzi,* suggesting the involvement of these pathways in the pathophysiology of Chagas disease (20). Furthermore, VEGF exerts pro-inflammatory effects by modulating adhesion molecule expression in endothelial cells (39).

The endothelium forms a semipermeable barrier that regulates bidirectional exchange between blood vessels and tissues. This function relies on the dynamic architecture of cell–cell junctions, particularly adherens junctions mediated by VE-cadherin, a key protein in maintaining endothelial barrier integrity. Alterations in VE-cadherin phosphorylation and stability promote increased vascular permeability (32).

Through nitric oxide release, the endothelium also induces vascular smooth muscle relaxation, modulates inflammatory responses, and inhibits platelet activation and aggregation,

contributing to an antithrombotic state. Reduced NO bioavailability is associated with endothelial dysfunction and increased thrombotic risk (22).

Increased expression of angiogenesis-related proteins may be detrimental, as observed in cancer development (31) and chronic inflammatory diseases, where dysregulated vascular growth contributes to enhanced inflammatory cell recruitment and sustained tissue damage (40). Under physiological conditions, angiogenesis may play beneficial roles by promoting tissue revascularization in ischemic conditions (41).

7. CEREBRAL MICROCIRCULATION AND ENDOTHELIAL INTEGRITY ALTERATIONS IN CHAGAS DISEASE

Central nervous system alterations are described during the acute phase, particularly in children and immunosuppressed patients (11,23). During acute *T. cruzi* infection, mice exhibit marked cerebral microcirculatory alterations, including reduced perfused capillary density, intense microvascular inflammation, vascular obstruction, and endothelial dysfunction (15). Parasites and intense inflammatory infiltrates have also been observed in human brain tissue (23).

Together, these findings suggest disruption of the blood–brain barrier, which normally restricts the entry of immune cells and macromolecules into the central nervous system (24).

Scientific evidence demonstrates that *Trypanosoma cruzi* infection profoundly alters vascular endothelium and mechanisms regulating vascular permeability (21).

Nitric oxide regulates vascular tone and endothelial integrity. During infection, excessive production (inflammatory response) or functional deficiency (endothelial dysfunction) may occur. Both conditions may contribute to alterations in vascular permeability and tissue perfusion (16).

Since cerebral manifestations may occur in both the acute (meningoencephalitis) and chronic phases of Chagas disease (13), understanding the mechanisms underlying microvascular alterations in the central nervous system is fundamental for elucidating the pathophysiology of infection-associated neurological complications.

8. INTEGRATIVE PATHOPHYSIOLOGICAL MODEL

T. cruzi infection induces systemic inflammation characterized by cytokine release and immune activation (8). This inflammatory microenvironment promotes imbalance in nitric oxide production (16) and increased VEGF expression (20), leading to disruption of VE-cadherin–mediated endothelial junctions (32).

As illustrated in Figure 3, the proposed integrative model suggests that parasite infection initiates a cascade of vascular events beginning with systemic inflammatory activation triggered by infection. This inflammatory state promotes endothelial activation and dysfunction, which in turn disrupts key regulatory mechanisms of vascular homeostasis.

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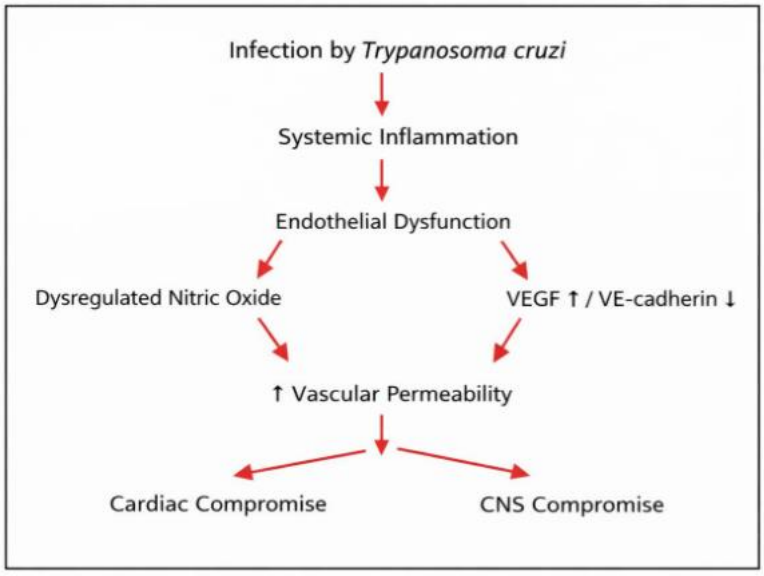
Within this context, dysregulation of nitric oxide production contributes to alterations in vascular tone and endothelial stability (16), while increased VEGF signaling promotes changes in endothelial junction integrity, particularly through modulation of VE-cadherin–mediated cell–cell adhesion (20,32). The combined effects of nitric oxide imbalance and VEGF-mediated signaling contribute to increased vascular permeability.

The resulting endothelial barrier disruption may lead to microvascular dysfunction and impaired tissue perfusion. As depicted in the model, these alterations may contribute to microvascular damage affecting critical target organs, particularly the heart and the central nervous system (15,21). In cardiac tissue, such processes are associated with ischemic injury, inflammatory amplification, and progressive cardiomyopathy (3,20), whereas in the central nervous system they may facilitate blood–brain barrier disruption and inflammatory infiltration (23,24).

Consequently, endothelial dysfunction may represent a key pathogenic component linking parasite-induced inflammation to vascular permeability alterations and subsequent organ damage (15,21), providing a conceptual framework for understanding the neurovascular component of Chagas disease pathophysiology.

Figure 3. Proposed integrative model of vascular permeability in Chagas disease. *Trypanosoma cruzi* infection induces systemic inflammation and endothelial dysfunction, leading to nitric oxide imbalance and increased VEGF signaling. These mechanisms disrupt endothelial junctions and increase vascular permeability, contributing to microvascular injury affecting the heart and central nervous system



However, it is important to recognize that the evidence supporting this framework originates from heterogeneous sources, including experimental animal models, histopathological observations, and clinical studies. Therefore, caution is required when extrapolating findings across different biological contexts, particularly between murine models and human disease or between the acute

and chronic phases of infection.

Furthermore, many of the proposed mechanisms derive from mechanistic associations rather than direct causal demonstration. As a result, the integrative model presented here should be interpreted as a conceptual synthesis of available evidence rather than as a definitively established pathogenic pathway.

9. CONCLUSION

This review integrates endothelial dysfunction, VEGF signaling, nitric oxide imbalance, and blood–brain barrier alterations into a unified pathophysiological framework for Chagas disease, highlighting vascular regulatory mechanisms as potential targets for therapeutic intervention.

Available evidence indicates that *Trypanosoma cruzi* infection is associated with complex vascular alterations involving inflammatory activation and endothelial dysfunction. These processes contribute to increased endothelial permeability and microvascular dysfunction, particularly affecting target organs such as the heart and the central nervous system (4,8).

Direct endothelial invasion by the parasite and subsequent immune activation promote the expression of adhesion molecules and leukocyte recruitment, compromising vascular barrier integrity (12,21). In the central nervous system, these alterations have been associated with blood–brain barrier disruption, inflammatory infiltration, neurological damage, thromboembolic phenomena, and stroke (4,14,23,24).

Nitric oxide dysregulation represents another important component of this process. Altered nitric oxide production during infection affects vascular tone, tissue perfusion, and endothelial stability. Both reduced bioavailability and excessive production may contribute to vasoconstriction, inflammatory activation, and increased vascular permeability (16,18,35–37).

Dysregulated angiogenesis also appears to play a relevant role. Increased expression of angiogenic mediators such as VEGF, frequently induced by hypoxia and inflammation, promotes vascular proliferation, permeability changes, and structural remodeling (25–27,29–31). In parallel, alterations in endothelial junction proteins, particularly VE-cadherin, weaken intercellular cohesion and facilitate the passage of inflammatory cells and macromolecules into the interstitium (32). These vascular alterations may affect critical target organs, particularly the heart and the central nervous system. In cardiac tissue, these mechanisms have been associated with ischemia, fibrosis, and the progression of Chagas cardiomyopathy (3,7,20). In the central nervous system, experimental and clinical observations demonstrate reduced capillary perfusion, microvascular obstruction, and local inflammatory responses, suggesting that endothelial dysfunction and altered vascular permeability may contribute to neurological involvement in the disease (13,15,23).

Taken together, these findings suggest that endothelial barrier dysfunction may represent an integrative link between parasitic infection, immune activation, and progressive organ damage

(21,22). In this context, vascular permeability alterations may not only reflect inflammatory responses but may also contribute to parasite dissemination, persistence of inflammation, and lesion progression.

However, the evidence currently available derives from heterogeneous sources, including experimental models, histopathological observations, and clinical studies, which requires caution when extrapolating findings across different biological contexts. Consequently, the neurovascular framework proposed here should be interpreted as an integrative conceptual model rather than a definitively established causal pathway.

Important knowledge gaps remain regarding the specific contribution of microvascular alterations to central nervous system involvement, particularly during the chronic phase of Chagas disease.

Further research integrating experimental, translational, and clinical approaches will be essential to clarify the mechanisms underlying neurovascular involvement in Chagas disease and to determine whether modulation of endothelial pathways may represent a viable therapeutic strategy.

In this context, a deeper understanding of the interactions between inflammation, endothelial dysfunction, and alterations in vascular permeability may open new perspectives for the development of therapeutic strategies aimed at microvascular protection and the reduction of systemic complications associated with Chagas disease.

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