

# Novel Insights into the Kallikrein–Kinin System in Fulminant Myocarditis: Physiological Basis and Potential Therapeutic Advances

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**Abstract:** Fulminant myocarditis (FM) is characterized by rapid cardiac deterioration often instigated by an inflammatory cytokine storm. The kallikrein–kinin system (KKS) is a metabolic cascade known for releasing vasoactive kinins, such as bradykinin-related peptides, possessing diverse pharmacological activities that include inflammation, regulation of vascular permeability, endothelial barrier dysfunction, and blood pressure modulation. The type 1 and type 2 bradykinin receptors (B1R and B2R), integral components of the KKS system, mediate the primary biological effects of kinin peptides. This review aims to offer a comprehensive overview of the primary mechanisms of the KKS in FM, including an examination of the structural components, regulatory activation, and downstream signaling pathways of the KKS. Furthermore, it explores the involvement of the tissue kallikrein/B1R/inducible nitric oxide synthase (TK/B1R/iNOS) pathway in myocyte dysfunction, modulation of the immune response, and preservation of endothelial barrier integrity. The potential therapeutic advances targeting the inhibition of the KKS in managing FM will be discussed, providing valuable insights for the development of clinical treatment strategies.

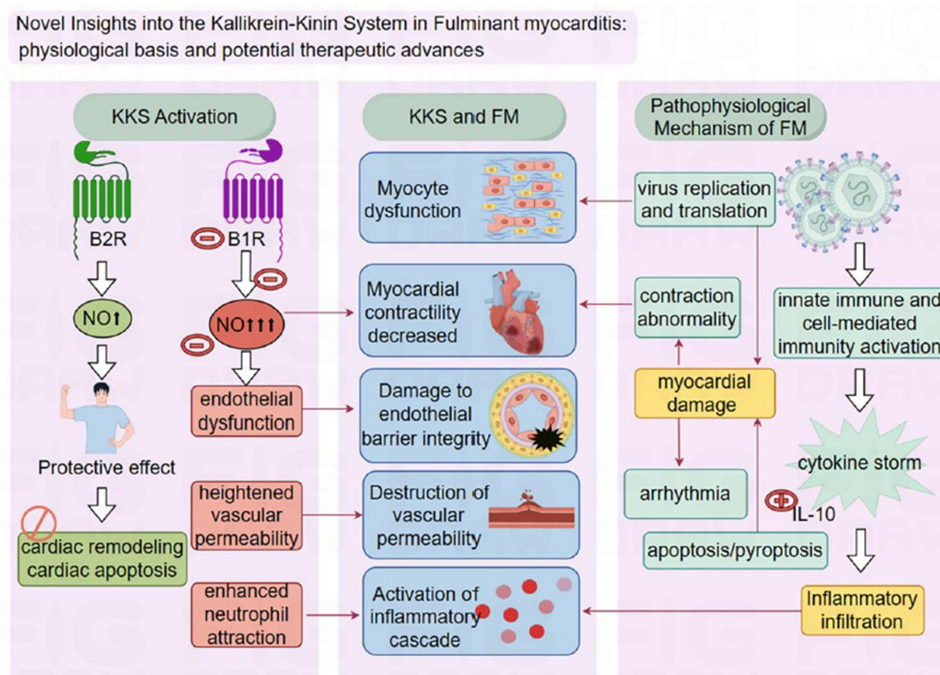
**Keywords:** fulminant myocarditis, Kallikrein–Kinin system, inducible nitric oxide synthase, nitric oxide, inflammatory

## Background

Fulminant myocarditis (FM) is a rare yet severe cardiac inflammatory disease characterized by inflammatory infiltration and myocardial damage. It is often triggered by infectious agents or autoimmune disorders, particularly viral infections.<sup>1–3</sup> This review focuses primarily on viral myocarditis. The detrimental effects of infectious pathogens can hyperactivate the immune response, accelerating disease progression.<sup>4</sup> This excessive immune activation can cause severe myocardial injury, leading to FM. Inflammatory infiltration and myocardial damage represent the primary pathogenic mechanisms of FM, with immunomodulatory therapy emerging as an effective and dependable treatment option.<sup>5–7</sup> Nonetheless, the limited understanding of the pathophysiological mechanisms underlying FM has impeded the development of comprehensive therapeutic strategies that could intervene effectively at various disease mediators.

The Kallikrein–Kinin System (KKS) is an enzymatic cascade of molecules intricately linked to the activation of the coagulation and renin-angiotensin-aldosterone system (RAAS) pathways, influencing vascular permeability and inflammation.<sup>8</sup> The KKS is an important endothelial autacoid system that exerts several beneficial protective actions on

## Graphical Abstract

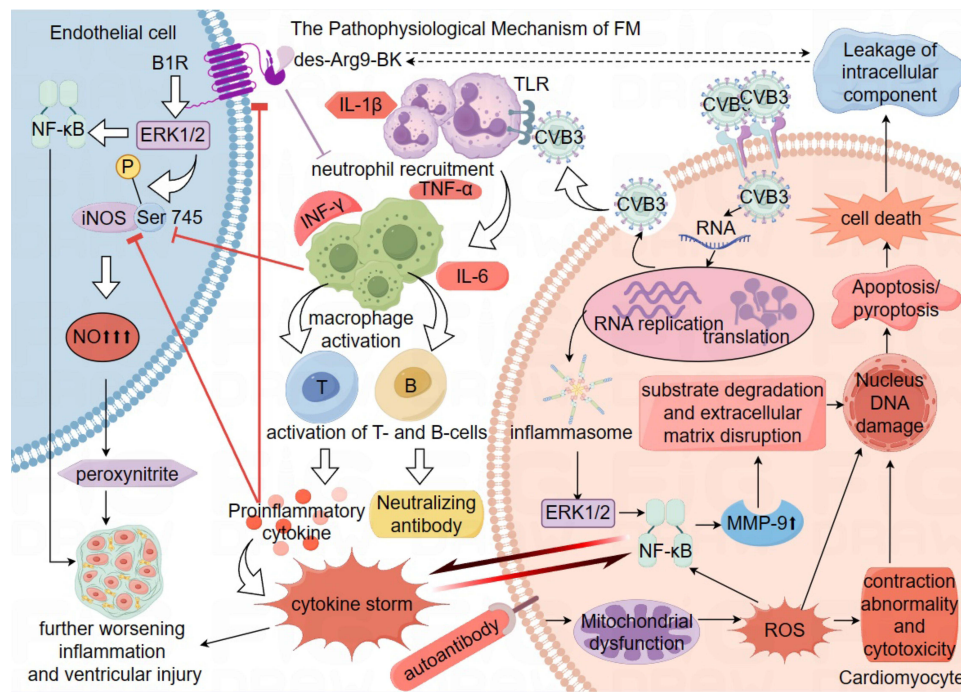


the endothelium, such as preventing the formation of thrombi and possibly the formation of atherosclerotic plaques.<sup>9</sup> Kinins exert their effects through two types of kinin receptors: the predominant type 2 bradykinin receptor (B2R) and the injury-induced type 1 bradykinin receptor (B1R). Bradykinin receptor (BKR) signaling within the KKS is associated with vasodilation, hypotension, increased vascular permeability, edema formation, angiogenesis, and pain, commonly observed during viral infections. Cell death from viral infection and activation of innate immune cells can trigger the release of KKS activators, leading to the production of vasoactive kinin peptides. Our research indicates that the B1R of the KKS can activate inducible nitric oxide synthase (iNOS) through the p21ras/rapidly accelerated fibrosarcoma protein kinase/mitogen-activated protein kinase/extracellular signal-regulated kinase/extracellular signal-regulated kinase/iNOS/nitric oxide (Ras/Raf/MEK/ERK/iNOS/NO) signaling pathway, eliciting robust and sustained responses that release significant amounts of NO, mediating inflammatory responses and enhancing vascular permeability.<sup>10</sup> iNOS, a key enzyme in NO production under pathological conditions,<sup>11</sup> is increasingly associated with progressive myocardial damage in myocarditis.<sup>12,13</sup> Upregulation of iNOS production plays a crucial role during cardiac stress, such as in myocarditis, bridging the gap between the pathophysiological changes in myocarditis and the molecular alterations of the KKS. Therefore, the tissue kallikrein (TK)/B1R/iNOS pathway is emerging as a significant route involved in inducing proinflammatory responses triggered by viruses.

The purpose of this review is to reveal the potential correlation between the inflammatory cascade in FM and the activation of the KKS. It is proposed that the activation of the TK/B1R/iNOS signaling pathway could play a crucial role in driving the inflammatory response in FM. Furthermore, the review discusses the therapeutic implications of targeting the B1R/iNOS signaling axis in the clinical management of FM.

## Pathophysiological Mechanism of FM

FM is primarily triggered by viral infections, which induce viral injury and evoke an immune response, contributing to its development.<sup>14</sup> Viral replication in cardiac myocytes directly results in tissue injury<sup>15</sup> (Figure 1). Initially, viral replication and transcription result in cardiomyocyte destruction, causing cellular damage and the release of intracellular components.<sup>16</sup> This activates the innate immune response through pattern recognition receptors such as toll-like receptors (TLRs) (Figure 1).



**Figure 1** Pathophysiological mechanism of fulminant myocarditis (FM) and the cytokine storm cascade. FM triggers an intense inflammatory response driven by various factors, notably infections. The process initiates with the activation of inflammatory pathways such as Toll-like receptors (TLRs), leading to the generation of pro-inflammatory cytokines like IL-1, IL-6, and TNF- $\alpha$ . This surge in cytokines amplifies inflammation, activating immune cells such as macrophages and neutrophils. Inflammation within cardiomyocytes results in mitochondrial dysfunction, accumulation of reactive oxygen species (ROS), and cell death, consequently affecting heart function and potentially leading to heart failure. Endothelial cells play a crucial role in this mechanism by producing nitric oxide (NO). The release of internal components due to cell death triggers a subsequent wave of cytokine release, exacerbating inflammation. Therapeutic approaches, such as the use of neutralizing antibodies targeting vital cytokines, are designed to mitigate the cytokine storm, reduce inflammation, and safeguard cardiac function.

For instance, Coxsackievirus B3 (CVB3) can stimulate neutrophils via TLR8, initiating nuclear factor kappa-B (NF- $\kappa$ B) activation<sup>17</sup> (Figure 1) and subsequent production of inflammatory cytokines, thus triggering an immune response.<sup>18</sup>

The innate immune system further activates the acquired immune response by initiating the activation and proliferation of T- and B-cells (Figure 1). Neutralizing antibodies play a vital role in inhibiting viral replication in the heart and other organs. Concurrently, autoantibodies, particularly those targeting mitochondrial and contractile proteins, are produced by activated B cells to assist in viral clearance. Nevertheless, autoantibodies can detrimentally affect myocyte function.<sup>19</sup> Proinflammatory cytokines and infiltration of antigen-specific T lymphocytes additionally aggravate myocardial inflammation and necrosis, ultimately leading to ventricular dysfunction<sup>20</sup> (Figure 1). In cases of persistent viral replication, a continuous cycle of cell-mediated immunity activation attracts a variety of immune cells to the site of injury. The excessive production of inflammatory cytokines, along with antibodies targeting viral and cardiac proteins, worsens cardiac damage and impairs systolic function.

Besides cytokines, NO plays a significant role in FM pathogenesis, particularly in immunocompromised individuals. Excessive NO production, facilitated by iNOS, can exacerbate the severity of myocarditis (Figure 1).<sup>21</sup> Interventions targeting iNOS activity have displayed promise in preserving contractile function during ischemic conditions, underscoring the intricate interplay of factors in myocarditis pathophysiology. Extensive research has shed light on the mechanisms involved in FM; however, the in-depth comprehension of the pathophysiological processes associated with FM remains limited and warrants further investigation. The significant contribution of iNOS/NO to the pathogenesis of FM emphasizes the crucial need to comprehend and target this mechanism to improve clinical management strategies.

## Immune Response and Inflammatory Cytokines in FM

In FM, inflammatory infiltration and myocardial damage are significant pathogenic mechanisms influenced by various inflammatory cytokines. Cytokines and chemokines act as essential mediators in the inflammatory response by quickly

responding to infection. Elevated levels of proinflammatory cytokines like tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), Interleukin-1 $\beta$  (IL-1 $\beta$ ), and Interleukin-6 (IL-6) are found in FM patients, present in the myocardium during infection.<sup>22</sup> Initially triggering a protective and healing process, prolonged expression of these cytokines, along with immune cell infiltration, can have harmful effects.

The term “cytokine storm” describes the disrupted immune balance in FM, impacting myocardial contraction and function<sup>4</sup> (Figure 1). Cytokines such as IL-1, IL-2, TNF- $\alpha$ , and Interferon- $\gamma$  (IFN- $\gamma$ ) negatively affect heart function by reducing muscle contractility and promoting cell death.<sup>23</sup> Inflammatory activation is common in various types of myocardial damage,<sup>24</sup> with evidence of immune cell infiltration in necrotic areas.<sup>4</sup>

The severity of myocardial damage and distribution of inflammatory cells in FM are closely linked, suggesting that extensive myocyte damage from inflammation contributes to the rapid progression of myocarditis. Inflammatory markers, erythrocyte sedimentation rate (ESR) and high-sensitive c-reactive protein (hs-CRP), played the most important role in diagnosing myocarditis in the Diagnosis of Acute Myocarditis in Emergency (DAME) score,<sup>25</sup> which corroborates our viewpoint. Overstimulation of the immune response by infectious agents accelerates disease progression, resulting in sustained inflammation, endothelial dysfunction, tissue damage, and heart remodeling.<sup>26</sup> Our recent research has shown that the TK/BIR/iNOS pathway plays a significant role in cardiac inflammation and endothelial dysfunction following reperfusion injury, potentially exacerbating inflammation and endothelial permeability.<sup>10</sup> It is hypothesized that the upregulation of proinflammatory mediators in FM may trigger this pathway, resulting in increased NO production, further worsening inflammation and ventricular injury. Subsequently, the activation of downstream signaling cascades may amplify the release of proinflammatory factors, establishing a feedback loop that contributes to cytokine storms, worsening myocardial injury, and hastening the progression of FM (Figure 1).

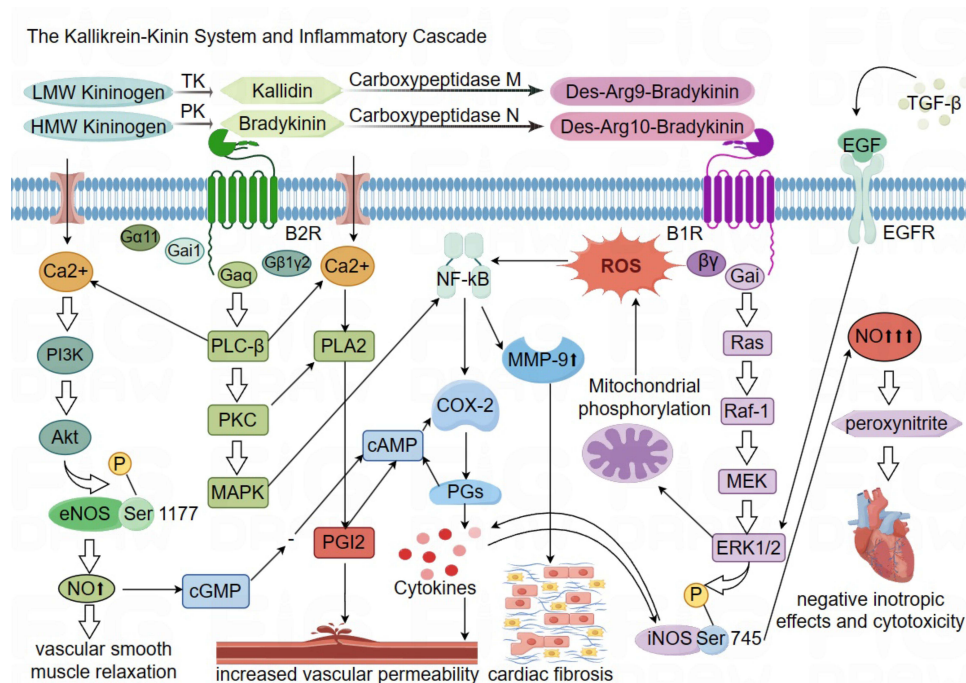
## Role of the KKS in Inflammation and Cardiovascular System

The KKS is a part of the humoral defense system that participate in the inflammatory response. In mild, acute insults, kallikreins and kinins play a salutary role recruiting to the extravascular milieu proteases, acute phase proteins, and neutrophils. In severe inflammation, however, the same system amplifies the inflammatory cascade, and contributes to tissue destruction and chronic inflammation.

The KKS involves a series of enzymatic reactions that generate bioactive kinin peptides.<sup>27</sup> When activated, the KKS releases kinin peptides from low/high-molecular-weight kininogen, which are further processed by kallikreins to generate BK and Lys-BK in response to factors like infection, tissue trauma, or inflammation. Kininase I (carboxypeptidase N, CPN) and carboxypeptidase M(CPM) remove arginine from the carboxyl terminus of BK and kallidin, producing des-Arg9-bradykinin(des-Arg9-BK) and des-Arg10-kallidin, respectively<sup>27</sup> (Figure 2). These derivatives exhibit affinity for receptors such as B1R, whereas BK predominantly binds to B2R. Both receptor types, B1R and B2R, are G-protein coupled receptors that play BK crucial roles in inflammation, vascular function, blood pressure regulation, and pain response.

B2R is widely distributed and exerts a crucial function in various physiological processes by activating diverse signaling pathways, including the synthesis of NO and prostaglandins(PGs).<sup>27</sup> Upon binding with BK, B2R interacts with multiple G proteins, such as G $\alpha$ <sub>q</sub>s, G $\alpha$ <sub>q</sub>/G $\alpha$ <sub>11</sub>, G $\alpha$ <sub>i1</sub>, and G $\beta$ 1 $\gamma$ 2, leading to the activation of G $\alpha$ <sub>q</sub> and G $\alpha$ <sub>i</sub> proteins (Figure 2). This interaction triggers a series of events involving the activation of molecules like phospholipases, protein kinase C (PKC), and phosphoinositide 3-kinase/ protein kinase B (PI3K/AKT), as well as the release of secondary messengers such as inositol-1,4,5-trisphosphate and diacylglycerol.<sup>28,29</sup> These pathways can activate endothelial NO synthase (eNOS) through Akt phosphorylation at Ser1177<sup>30</sup> (Figure 2) and induce the expression of NF- $\kappa$ B and Cyclooxygenase-2 (COX-2) through the cyclic adenosine monophosphate (cAMP) response element and the Ras/Raf-1/ERK pathway. The BK-B2R signaling pathway plays a vital role in protecting the heart from ischemic damage, as evidenced by the cardioprotective effects of TK or kinin infusion against cardiac remodeling, apoptosis, and fibrosis mediated by B2R-NO. However, it is crucial to note that BK can also stimulate the production of inflammatory mediators through NF- $\kappa$ B and cAMP response element-induced COX-2, leading to potentially adverse outcomes (Figure 2). These signaling pathways are implicated in the inflammatory side effects associated with B2R signaling. Moreover, B2R can undergo temporary desensitization through phosphorylation, which induces endocytosis followed by receptor recycling.





**Figure 2** The Kallikrein-Kinin System (KKS) and the Inflammatory Cascade. The figure primarily elucidates the KKS and its associated signaling pathways that regulate inflammation, with a specific focus on the B1R/iNOS pathway in fulminant myocarditis. The pathways controlled by B1R and iNOS are emphasized, demonstrating their roles in modulating crucial inflammatory processes. B1R activation triggers the production of reactive oxygen species (ROS) and subsequent mitochondrial phosphorylation, thus contributing to the inflammatory response. The signaling cascade involves Gai, MAPK, and ERK1/2, culminating in iNOS expression and the formation of peroxynitrite, which exerts negative inotropic effects and enhances cytotoxicity. Furthermore, interactions with pathways regulated by EGF and TGF-β are indicated, elucidating the intricate network of interactions within the KKS system responsible for modulating myocardial inflammation. Additionally, the figure underscores the significance of related signaling pathways and molecules like B2R, PI3K, eNOS, PLC, PLA2, cAMP, COX-2, PGE2, and MMP-9 in processes such as vascular relaxation, permeability, cytokine release, and cardiac fibrosis.

In contrast, B1R lacks this desensitization mechanism, as it is not susceptible to phosphorylation, potentially resulting in prolonged signaling duration.<sup>31</sup>

B1Rs are typically sparse or absent in normal tissues, but exhibit heightened responsiveness and rapid upregulation following exposure to inflammatory stimuli, infections, trauma, or agents like lipopolysaccharide endotoxin.<sup>32</sup> These receptors mainly modulate vasodilation and endothelial permeability. Studies employing specific agonists and antagonists have shown that B1R activation induces vascular leakage in diverse peripheral organs.<sup>33,34</sup> An important role of B1R is its contribution to the recruitment of inflammatory cells. Recent investigations, conducted both *in vivo* and *in vitro*, indicate that stimulating B1R in neutrophils during inflammation promotes their attachment and movement to nearby tissues. The interaction of des-Arg9-BK with B1R leads to heightened vascular permeability,<sup>35</sup> enhanced neutrophil attraction, and triggers broncho- and vasoconstriction, sparking inflammation.<sup>36</sup>

BK is acknowledged for its critical involvement in specific cardiovascular disorders.<sup>37</sup> It has been implicated in the pathogenesis of septic shock syndrome due to its elevated production following infection and its established effects in inducing hypotension and plasma extravasation.

The excessive presence of BK can induce vasodilation, heightened vascular permeability, and hypotension, ultimately culminating in severe manifestations such as lung edema and cardiovascular dysfunction. Consequently, BK is believed to primarily impact the cardiovascular system through vasodilation and plasma leakage, actively contributing to the inflammatory cascade. Collectively, the KKS serves as a pivotal regulator of inflammatory pathways and is influenced by innate immune response elements.<sup>35</sup> Previous research has highlighted the pivotal role of an inflammatory cytokine storm in the pathogenesis of FM.<sup>4</sup> Elevated levels of BK have been consistently associated with heightened inflammation, oxidative stress, endothelial dysfunction, and fibrosis, all of which are prominent clinical features of FM.

## Inflammatory Cascade and KKS Activation in FM

The initiation of the inflammatory cascade in FM involves the activation of the inflammasome within the innate immune response, induced by diverse pathogens or stimuli. This activation facilitates the transmission of signals from pathogen-associated molecular patterns and external stimuli into the cell, where they are amplified through the MAPK pathway.<sup>38</sup> ERK, a crucial member of MAPK family, has been implicated in the development of inflammatory diseases, including cardiac injury. Studies have shown that the proteolytic cleavage of Ras GTPase-activating protein RasGAP by CVB3 leads to the activation of the MAPK ERK-1/2 pathway via a Raf-1/MEK-1-dependent mechanism<sup>39</sup> (Figures 1 and 2). Additionally, ERK has been observed to phosphorylate NF- $\kappa$ B, resulting in the transcription of various inflammatory molecules. Inhibition of ERK1/2 has been shown to block virus replication, highlighting its significance in the inflammatory response.<sup>40</sup>

Furthermore, the production of reactive oxygen species (ROS), predominantly derived from mitochondrial oxidative phosphorylation, additionally stimulates NF- $\kappa$ B, sustaining the inflammatory cascade<sup>41</sup> (Figure 2). Another important protein kinase involved in cell survival and cellular balance is Akt, which is activated in cardiomyocytes during CVB3 infection through a specific pathway involving PI3K and integrin-linked kinase. This activation of Akt has been studied for its role in the regulation of downstream effectors in the PI3K/Akt pathway.<sup>42</sup>

Interestingly, these signaling pathways intersect significantly with the KKS, where BK-induced activation of MAPKs contributes to the upregulation of various cytokines.<sup>43,44</sup> This suggests a pivotal role for BK in the activation of inflammatory responses. The KKS can be activated on endothelial cell surfaces, along with the coagulation cascade, with the B1R showing pro-inflammatory characteristics that promote inflammation by increasing cytokine production and immune cell migration, as well as inducing vascular permeability (Figure 2). Transcription factors like NF- $\kappa$ B and activator protein 1 (AP-1), along with the TGF- $\beta$ 1/MAPKs signaling pathway, regulate the expression of the B1R during inflammatory processes.<sup>45</sup> Research has shown that inhibitors targeting different MAPKs and NF- $\kappa$ B can reduce the overexpression of B1Rs<sup>46,47</sup> (Table 1).<sup>10–12,22,35,47–51</sup> Various stimuli, including inflammatory cytokines, innate immune system activators, growth factors, and phorbol esters activator of PKC, can trigger an increase in B1R expression in vascular cells.<sup>52</sup> Activation of the B1R has been linked to oxidative stress through nicotinamide adenine dinucleotide phosphate hydrogen (NADPH) oxidase activation in the vasculature.<sup>50</sup> Notably, B1R knockout has been shown to provide protection against hypotension, pain sensitivity, and injury in different experimental models.<sup>53</sup> It can also lead to the post-translational activation of iNOS through specific intracellular pathways, suggesting a significant role in myocardial inflammation and other biological effects mediated by kinins (Figure 2).

## NO Production and iNOS Activation in Myocarditis

Myocarditis, a condition characterized by myocardial inflammation, is associated with the upregulation of proinflammatory cytokines that contribute to tissue damage and modulation of immune responses. NO functions as a pivotal mediator in this pathophysiological cascade, serving as a signaling molecule in the host's antiviral defense mechanisms.

The vasodilatory and antioxidant properties of NO have been demonstrated to mitigate mitochondrial oxidant damage in adult rat cardiomyocytes.<sup>54</sup> Furthermore, NO can inhibit the production of neutrophil superoxide anions by directly acting on the membrane components of NADPH oxidase and the assembly of dihydronicotinamide adenine dinucleotide (NADH)/NADPH oxidase subunits.<sup>55</sup> It also mediates the effects of TK in improving cardiac function and limiting post-infarction remodeling by inhibiting inflammation.<sup>56</sup> Activation of the B2R/eNOS pathway leads to a transient release of NO, contributing to improved cardiac function.<sup>9</sup>

Conversely, activation of the B1R/iNOS signaling pathway in response to acute inflammation leads to persistent generation of high levels of NO, resulting in edema, inflammation, pain, and excessive ROS production. The presence of activated macrophages and neutrophils in inflammatory and autoimmune lesions can exacerbate NO production, further damaging tissues<sup>57</sup> (Figure 1). Recent animal studies have underscored the detrimental effects of increased NO production, driven by proinflammatory cytokines, on heart muscle function, leading to reduced contractility and impaired coronary autoregulation and oxygen utilization.<sup>58–60</sup>

**Table I** The BIR/iNOS Pathway of KKS in the Pathogenesis of Inflammation and Cardiovascular Diseases

Model	Intervention/Target	Conclusion/Outcome	Ref
Ventricular myocytes isolated from adult rat	Measurement of myocyte contractile function.	Increased NO produced may contribute to the contractile dysfunction characteristic of advanced systemic sepsis and some cardiomyopathies, the effect was reversed by specific inhibitors of NO synthase.	[48]
Rat	Injection of porcine cardiac myosin	Excess amounts of NO produced by iNOS appear to contribute to the progression of myocardial damage in myocarditis. AG may prove to be useful in the treatment of myocarditis	[12]
Mice [CD-1 and C3H.He] (C3H)]	Inoculation with 10 <sup>5</sup> pfu of CVB3	Mice infected with CVB3 show increased expression of proinflammatory cytokines as well as iNOS associated with reduced contractile performance.	[22]
Rat	LPS vs Tyr <sup>8</sup> -BK+LPS, LPS+des-Arg <sup>9</sup> -BK vs LPS+ACEI	Kinin B1 receptor up-regulation after LPS administration may involve the production of pro-inflammatory cytokines such as TNF- $\alpha$ and IL-1 $\beta$	[47]
Human endothelial cells or HEK293 cells	HEK293 cells were co-transfected with iNOS and BIR cDNA plasmids	ERK and phospho-ERK (after BIR activation) were co-localized with iNOS as determined by confocal fluorescence microscopy. ERK co-immunoprecipitated with iNOS	[49]
Rat	Selective BIR antagonist (SSR240612)	Prolonged blockade of BIR restored cardiovascular, sensory and metabolic abnormalities by reducing oxidative stress and BIR gene expression	[50]
Male Balb/c mice	DL-Propargylglycine (PAG) and NaHS, inoculated intraperitoneally with CVB3.	H2S can inhibit iNOS overexpression and induce HO-1 expression, both of which contribute to the cardioprotection of H2S in CVB3-induced mice myocarditis	[11]
Rat and patient plasma sample	Kinin receptor antagonists and C1-inhibitor	Blockade of the KKS can reduce complement activation and thereby the inflammatory response on the endothelium.	[51]
Mice model of FM	Anti-Cxcl2 antibody and anti-Cxcl3 antibodies targeting the Cxcl2/Cxcl3-Cxcr2 axis	Neutrophils play a key role in early cardiac functional collapse and early blockage of neutrophil migration from the peripheral blood significantly reduces mortality in mice with FM	[35]
CABG patients plasma samples and a model of cardiac IRI in mice	Ulinastatin (anti-inflammatory and cytoprotective)	B1 receptors are a critical target in the treatment of reperfusion-induced injury	[10]

**Abbreviations:** LPS, Lipopolysaccharide; ACEI, Angiotensin-converting enzyme inhibitor; IRI, Ischaemia-reperfusion injury; AG, aminoguanidine.

iNOS is primarily regulated at the expression level, induced in response to inflammatory mediators such as lipopolysaccharide (LPS) or cytokines like IL-1 $\beta$ , IL-6, and IFN- $\gamma$ .<sup>61</sup> Activation of iNOS through BIR mediated MAPK ERK signaling significantly increases NO production, indicating an alternative regulatory mechanism beyond conventional modes of regulation<sup>49</sup> (Figure 2).

Various mechanisms regulate iNOS activity, including post-translational modifications.<sup>61</sup> S-nitrosylation can inhibit iNOS activity,<sup>62</sup> while interaction with heat shock protein 90 (hsp90) can enhance it.<sup>63</sup> Once iNOS is expressed, it continuously produces NO until undergoing degradation.<sup>61</sup> This unregulated production of NO by iNOS can have cytotoxic effects, particularly in the context of the host defense response.

## Role of BIR/iNOS Pathway in FM

Recent research has shed light on the connection between iNOS and the KKS in FM pathophysiology. Studies indicate that inhibiting iNOS can reduce autophagy, apoptosis, and oxidative stress while promoting cell proliferation in cardiomyocytes infected with CVB3. Additionally, it has been found that reducing iNOS activity leads to a decrease in oxidative stress and improvement in cardiac function affected by cytokines.<sup>48</sup> Moreover, research indicates that overproduction of NO due to iNOS expression can hinder mitochondrial function and contribute to reduced mechanical performance during prolonged cytokine exposure<sup>58</sup> (Figures 1 and 2). In agreement with this, mutant mice lacking iNOS were resistant to LPS-induced mortality.<sup>64</sup> Furthermore, studies have revealed that the integrity of the blood-

brain barrier (BBB) can be influenced by the TK via B1R/iNOS signaling pathway, which can impact various cellular processes.<sup>65</sup>

Activation of B1R has been linked to the induction of Matrix metalloproteinase 9 (MMP-9) through the ERK MAP kinase pathway<sup>66</sup> (Figures 1 and 2), which plays a crucial role in neurovascular damage and BBB disruption. Excessive MMP-9 expression can lead to BBB injury and inflammation by promoting inflammatory cell migration. It has been suggested that ERK/NF- $\kappa$ B/MMP-9 pathway may be downstream of the B1R signal in FM pathogenesis.<sup>67,68</sup>

Nevertheless, some studies have presented conflicting results, low to moderate doses of iNOS inhibitors restore myocardial contractility in hearts exposed to proinflammatory cytokines, whereas at higher doses, the effect reverses itself. This finding may indicate that small amounts of NO produced by iNOS may be necessary to maintain contractility.<sup>58,69</sup> NO donors may reduce inflammation by limiting cytokine-induced endothelial activation, leukocyte adherence, and microvascular permeability alterations<sup>70</sup> (Figure 2). The effect caused by iNOS may depend on the amount of NO produced. Collectively, recent studies have deepened our understanding of how the B1R/iNOS pathway contributes to inflammation in FM. These findings suggest that B1R-induced leukocyte recruitment and increased NO production are key factors in inflammatory cardiovascular diseases. The continuous self-amplification of this pathway after the initial inflammatory trigger may sustain and aggravate the inflammatory response.

## Therapeutic Implications of Targeting KKS in FM

Kinins have long been recognized for inducing various features of acute inflammation, including microvascular permeability, leukocyte migration, and apoptosis<sup>71</sup> (Table 2).<sup>67,72–77</sup> This leads to a wide range of potential therapeutic targets, such as hypertension<sup>9,78</sup> ischemic diseases, diabetic complications, hereditary or acquired inflammatory diseases,<sup>79</sup> and brain diseases.<sup>75</sup> Hara et al demonstrated that selective, orally active, nonpeptide B1R antagonist SSR240612 significantly reduced intestinal tissue damage and neutrophil influx in a mouse model of colitis.<sup>77</sup> Moreover, a selective B2R agonist showed cardioprotective effects in post-acute myocardial infarction.<sup>80</sup> Although the clinical development of these drugs is in the early stages and limited human clinical studies have been reported so far.

Kinins, as inflammatory mediators implicated in vascular responses, play a crucial role in inflammation as observed in FM. The dual effects of kinin receptors, particularly B1R, raise an unsettled issue on the therapeutic value of B1R agonists versus antagonists in cardiovascular diseases. Targeting kinin receptors, especially the B1R, presents a promising therapeutic approach for FM (Figure 3). By blocking the B1R/iNOS pathway and regulating NO production, it may be possible to alleviate cardiac inflammation and endothelial dysfunction associated with FM. In addition to B1R antagonists, inhibiting CPM to reduce B1R agonists generation could serve as a novel therapeutic strategy (Figure 3). This approach may enhance the cardioprotective and anti-diabetic effects of the B2R by preventing the cleavage of certain kinins. Developing kininase 1 inhibitors could also be beneficial for pharmacotherapy in FM<sup>9</sup> (Figure 3). Research indicates that inhibiting MAPK-associated pathways and reducing iNOS expression or activity could help in reducing fibrosis and improving cardiac inflammation. Strengthening the effects of the B2R, which may protect against heart disorders from oxidative stress and reduce ROS, while simultaneously inhibiting the B1R, could be advantageous for managing cardiovascular diseases.<sup>81,82</sup>

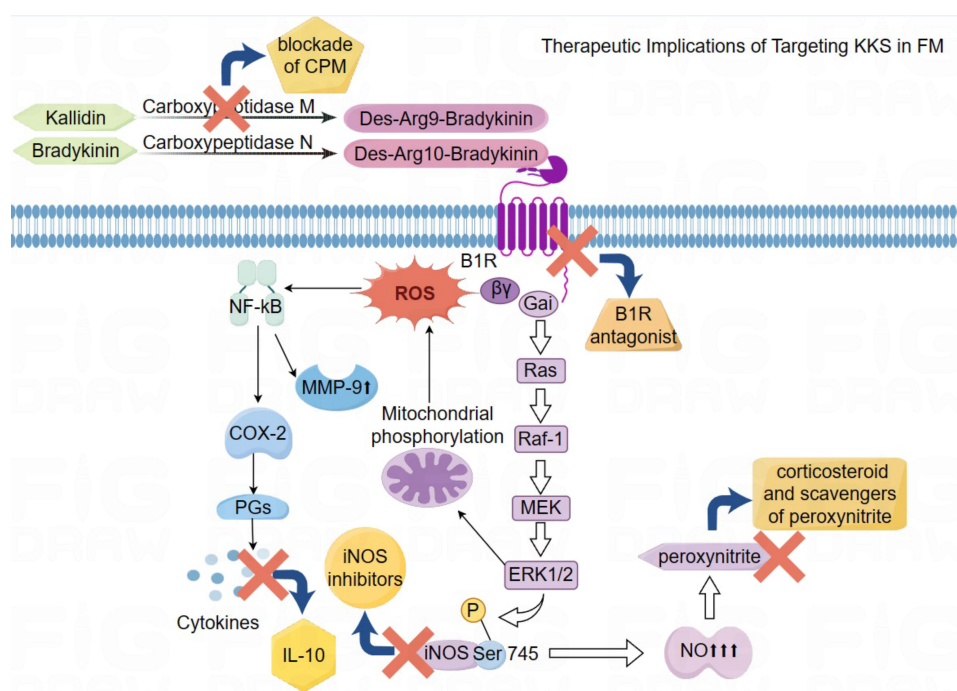
To safeguard the positive impacts of the KKS while minimizing adverse effects, selective iNOS inhibitors like aminoguanidine could provide protection against the harmful effects of NO and PGs production.<sup>83</sup> Additionally, the use of corticosteroids and NO scavengers may be beneficial in reducing cardiac damage resulting from cytokine exposure in FM patients. It is worth to note that elevated cytokine levels, including IL-10, in FM patients present opportunities for cytokine-targeted treatments. IL-10 has shown to regulate iNOS mRNA production, preventing ongoing myocardial injury. Studies suggest that IL-10 plays a protective role in myocarditis and can modulate macrophage activities to limit cardiomyocyte destruction.<sup>84</sup> Further exploration into the therapeutic implications of IL-10 in inflammatory cardiomyopathy, including administration methods and potential side effects, is warranted.<sup>85</sup>



**Table 2** Summary of Therapeutic Effects of Pharmacological B1 or B2 Receptor Agonists and Antagonists in Inflammation and Cardiovascular Diseases

Ligands		Pharmacological	Model	Preclinical	Clinical
<b>Agonists</b> B2R	Labradimil <sup>72</sup> (Arg-Pro-Hyp-Gly-Thi-Ser-ProTyr(Me)-psi (CH <sub>2</sub> NH)-Arg) FR190997 <sup>73</sup>	Increase the permeability of the BBB  The kinin mimic FR190997 might maintain low sodium levels in the smooth muscle cells through increased urinary sodium excretion	RG2 rat model of glioma  Young spontaneously hypertensive rats	Facilitating the entry of chemotherapeutics  FR190997, may be useful for inhibiting or preventing hypertension	Icatibant is registered for the treatment of acute attacks of the hereditary BK-mediated AE Less risk of brain swelling and cerebral edema. A bradykinin antagonist may play a neuroprotective role in severe brain injury.
	B1R  R-838 <sup>74</sup> (Sar-[D-Phe <sup>8</sup> ]des-Arg <sup>9</sup> -BK)	Enhanced collateral vascular growth in ischemic skeletal muscle, accelerated the rate of perfusion recovery, and improved limb salvage.	A murine model of limb ischemia	B1R is crucial in defending against ischemic injury and could be a valuable target for treating ischemic vascular disease	
<b>Antagonists</b> B2R	Icatibant <sup>75</sup>  Deltibant, CP-1027 <sup>76</sup>	Antagonize bradykinin-induced edema	Patients with TBI  Severely brain injured patient	Antagonists of B2R are promising therapeutics for relieving symptoms of inflammation, pain, and diabetes	
	B1R  B6929/ des-(Arg <sup>10</sup> ,Leu <sup>9</sup> )-kallidin <sup>67</sup>  B1R knockout mice <sup>77</sup>	B1R Activation Increased MMP-9 Expression Through ERK1/2/NF-κB Pathway After I/R in Diabetic Rats  NO might alter TNBS-induced colitis via kinin B1 receptor upregulation.	A rat model of cerebral I/R with type I diabetes A mouse model of colitis	Withstand HT after ischemic stroke in diabetic patients  New and important approaches towards the possible use of selective B1 receptor antagonists for the treatment of human IBD	

**Abbreviations:** BBB, blood brain barrier; HT, Hemorrhagic transformation; AE, angioedema; TBI, traumatic brain injury; I/R, ischemia/reperfusion; ERK1/2, extracellular signal-regulated kinases 1 and 2; MMP-9, matrix metalloproteinase-9; TNBS, 2,4,6-trinitrobenzene sulphonic acid; iNOS, inducible nitric oxide synthase; IBD, inflammatory bowel disease.



**Figure 3** Therapeutic Strategies Targeting Kallikrein–Kinin System (KKS) in Fulminant Myocarditis (FM). The figure illustrates key treatments for FM targeting the KKS, focusing on B1 receptor (B1R) and inducible nitric oxide synthase (iNOS) signaling. The use of B1R antagonists and selective iNOS blockers is crucial for regulating the KKS and reducing nitric oxide production, which are essential for addressing inflammation and oxidative stress in FM. Moreover, carboxypeptidase enzymes aid in decreasing inflammation levels by breaking down kinins. The combination of corticosteroids and peroxynitrite scavengers, which counteract harmful peroxynitrite effects, helps reduce inflammation and maintain cardiac function in FM cases. Additionally, the inclusion of interleukin-10 (IL-10) assists in resolving inflammation linked to FM. A comprehensive therapeutic approach centered on B1R inhibition is critical for minimizing reactive oxygen species (ROS) generation and modulating downstream signaling pathways, such as the Ras-Raf-MEK-ERK1/2 axis, in FM.

## Conclusion and Prospect

The upregulation of iNOS is a critical factor in the pathogenesis of FM, affecting myocardial function and contributing to inflammation and compromised endothelial barrier integrity. The KKS was considered to participate in the inflammatory cascade of FM by activating the B1R/iNOS signaling pathway. Activation of the B1R-dependent iNOS results in excessive NO production. This pathway is influenced by inflammatory signals triggered by the host's response to viral infection, modulating the release of inflammatory molecules and balancing anti-inflammatory responses against myocardial damage. Future investigations could explore the complex molecular mechanisms and pathways related to B1R/iNOS in FM, potentially yielding novel insights into diagnostic and therapeutic strategies for improving FM management.

## Abbreviations

FM, Fulminant myocarditis; KKS, kallikrein–kinin system; TK, tissue kallikrein; BK, bradykinin; BKR, bradykinin receptor; B1R, type 1 bradykinin receptor; B2R, type 2 bradykinin receptor; iNOS, inducible nitric oxide synthase; RAAS, renin-angiotensin-aldosterone system; Ras, p21ras; Raf, rapidly accelerated fibrosarcoma protein kinase; MAPK, mitogen-activated protein kinase; ERK, extracellular signal-regulated kinase; MEK, MAPK ERK kinase; NO, nitric oxide; TLRs, toll-like receptors; CVB3, Cocksackievirus B3; CPN, carboxypeptidase N; CPM, carboxypeptidase M; PGs, prostaglandins; eNOS, endothelial NO synthase; PKC, protein kinase C; PI3K/Akt, Phosphatidylinositol 3-kinase/protein kinase B; MAPK, mitogen-activated protein kinase; ERKs, extracellular signal-regulated kinases; ROS, reactive oxygen species; AP-1, activator protein 1; NADPH, nicotinamide adenine dinucleotide phosphate hydrogen; NADH, dihydro-nicotinamide adenine dinucleotide; hsp90, heat shock protein 90; TNF, tumor necrosis factor; IFN- $\gamma$ , Interferon- $\gamma$ ; ESR, erythrocyte sedimentation rate; hs-CRP, high-sensitive c-reactive protein; DAME score, the Diagnosis of Acute Myocarditis in Emergency score; PAF, platelet-activating factor; BBB, Blood–Brain Barrier; NF-kb, nuclear factor

kappa-B; MMP-9, Matrix metalloproteinase 9; LPS, Lipopolysaccharide; IL, Interleukin; GTP, Guanosine triphosphate; mRNA, messenger Ribonucleic Acid; cAMP, Cyclic adenosine monophosphate; COX-2, Cyclooxygenase-2; TGF- $\beta$ 1, transforming growth factor- $\beta$ 1.

## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

## Funding

This study was supported by funding from National Natural Science Foundation of China (82271358) and Natural Science Foundation of Hubei Province (2024AFB642).

## Disclosure

The authors declare no conflicts of interest in this work.

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