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Review

The role of anti-inflammatory drugs and nanoparticle-based drug delivery models in the management of ischemia-induced heart failure

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ABSTRACT

Ongoing advancements in the treatment of acute myocardial infarction (MI) have significantly decreased MI related mortality. Consequently, the number of patients experiencing post-MI heart failure (HF) has continued to rise. Infarction size and the extent of left ventricular (LV) remodeling are largely determined by the extent of ischemia at the time of myocardial injury. In the setting of MI or acute phase of post-MI LV remodeling, anti-inflammatory drugs including intravenous immunoglobulin (IVIG) and Pentoxifylline have shown potential efficacy in preventing post-MI remodeling in-vitro and in some clinical trials. However, systemic administration of anti-inflammatory drugs are not without their off-target side effects. Herein, we explore the clinical feasibility of targeted myocardial delivery of anti-inflammatory drugs via biodegradable polymers, liposomes, hydrogels, and nano-particle based drug delivery models (NDDM) based on existing pre-clinical and clinical models. We summarize the barriers to clinical application of targeted anti-inflammatory delivery post-MI, including challenges in achieving sufficient retention and distribution, as well as the potential need for multiple dosing. Collectively, we suggest that localized delivery of anti-inflammatory agents to the myocardium using NDDM is a promising approach for successful treatment of ischemic HF. Future studies will be instrumental in determining the most effective target and delivery modalities for orchestrating NDDM-mediated treatment of HF.

1. Introduction

Ischemic heart disease (IHD) is the leading cause of morbidity and mortality worldwide [1]. Ischemia-induced myocardial loss initiates an irreversible process through which cardiac function begins to deteriorate [2,3]. Negative left ventricular (LV) remodeling leads to reduced ejection fraction (EF) and left ventricular heart failure (LVHF) [3]. Despite the clinical challenges that arise with LVHF, modern advances in the treatment of IHD and its complications have decreased mortality attributable to myocardial infarction (MI) [4,5]. However, with an increasing number of patients surviving MI and living with IHD, the prevalence of heart failure (HF) continues to soar [6,7]. Successful management of patients with progressive HF is dependent on the prevention or reversal of myocardial remodeling [8,9]. While revascularization of the occluded vessel can be performed in the setting of IHD, reversal of myocardial remodeling has not been achieved in clinical practice to-date. This is attributable to an incomplete understanding of the underlying mechanisms driving ischemia-induced myocardial remodeling in HF.

Our knowledge of the pathophysiological mechanisms underlying HF has evolved significantly over the past decade [10–12]. The pathophysiology underlying heart failure is quite complex, owing to the

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various contributing etiologies such as ischemic heart disease, hypertension, diabetes and other cardiomyopathies such as valvular heart disease and cardiotoxic drugs. At the onset of the heart failure, compensatory mechanisms including increased cardiac output, increased ventricular volume and increased ventricular wall thickness result from ventricular remodeling to maintain heart function. At a molecular level, local injury to cardiomyocytes initiates numerous stress-response signaling cascades which result in both localized and systemic inflammatory response. As a hallmark of ventricular remodeling, ventricular hypertrophy is a strong risk factor for cardiovascular morbidity and remains a primary target for therapeutic intervention.

Importantly, the role of the G protein-coupled receptor (GPCR) apelin has been described in cardiac hypertrophy [11]. The apelin receptor is widely distributed throughout the body. Ligand-binding of the apelin receptor is known to initiate vasoconstriction, vasodilation, angiogenesis and increased heart muscle contractility [13]. Concerning ischemia in the setting of myocardial infarction, Wang et al. were the first to demonstrate reduced myocardial apelin levels in patients with ischemic heart failure [14]. The authors found that the loss of apelin was associated with increased mortality related to MI, increased infarct size and increased inflammation [14]. Later, Masoud et al. observed in their in-vitro study that the apelin mediated autocrine growth resulted in sustained vascular repair and prevented the immune-mediated injury, thus identifying apelin as a potential therapeutic target for preventing the immune-mediated injury of coronary vasculature [15].

The role of myocardin acetylation through long noncoding RNA transcripts has also been emphasized in myocardial hypertrophy [10, 12]. Myocardin plays an integral role in the development of cardiac myocytes and vascular smooth muscle cells. As a co-activator of serum response factor (SRF), myocardin expression is altered in human and animal models of atherosclerosis, in which it is believed to play a primary role [16]. Recently, myocardin has emerged as a mediator of vascular inflammation [17]. With respect to the role of myocardin in mediating immune response in the context of post-MI ischemia, Jiang et al. demonstrated that the interferon regulatory factor 9 (IRF9) - a well-established transcriptional regulator of the immune system competes with p300 for binding of the transcriptional activation domain of myocardin, thereby inhibiting the development of cardiac hypertrophy [18]. Furthermore, an imbalanced innate [19–21] and adaptive immune response [22,23] has also been implicated in chronic ischemia-induced heart failure and cardiac remodeling. The inflammatory response which persists beyond the window of myocardial infarction can contribute to ventricular remodeling and subsequent development of HF [24–26].

A recent in-vivo study in Foxp3-diphtheria toxin receptor transgenic mice indicated that pro-inflammatory T-lymphocytes play an important role in cardiac remodeling in the setting of ischemic cardiomyopathy [23]. The authors observed that selective ablation of T regulatory cells resulted in the reversal of LV remodeling and LV dysfunction, which minimized hypertrophy and fibrosis [23]. Moreover, circulating $CD4^+$ T cells and systemic inflammation were suppressed in the model, with concomitant evidence of enhanced tissue neovascularization [23].

As a family of pattern-recognition receptors, toll-like receptors (TLRs) have also been implicated in the pathophysiology of HF [27,28]. Specifically, TLR2, TLR3, and TLR4 [28] have been recognized as inflammatory enhancers in the setting of chronic MI [27]. Shushido et al. demonstrated both increased survival and attenuated myocardial fibrosis post-MI in a TLR2-knockout mice model, further demonstrating the role of TLR2 in cardiac remodeling [29]. Relative to all TLRs, TLR4 levels are highest in the heart [30]. Interestingly, in a model of doxorubicin-induced cardiomyopathy, Ma et al. highlight the specific role of TLR4 in driving post-MI inflammation [31]. The authors showed that inhibition of TLR4 increased fibrosis and further impaired cardiac function via increased inflammation and suppressed autophagy, with TLR4 blockade resulting in increased levels of monocyte chemoattractant protein-1 (MCP-1), interleukin (IL)-13 -IL-13 and transforming growth factor beta-1 (TGF-β1) [31].

Several HF treatments have evolved based on an understanding of the inflammation-driven cardiac remodeling that occurs post-MI. The Celacade system is a device-based non-specific immunomodulatory treatment (Vasogen Inc, Canada) which was developed to target inflammation as a primary driver of heart failure. As a potential treatment option for patients with chronic heart failure [32,33], the underlying principle of the Celacade system is based on re-infusion of autologous blood exposed to oxidative stress ex-vivo, as a trigger for an immune response in-vivo. The concept of autologous re-administration of blood exposed to heat, ultraviolet ration, and controlled oxidative ozone was developed based on benefits observed from utilizing the VasoCare approach in individuals with vascular diseases [34]. It has been hypothesized that VasoCare therapy on whole blood using the Celacade system has the potential to reduce the transforming growth factor beta-1 (TGF-β1) expression [33] and modulate immune response to heat shock proteins in mononuclear cells [34]. Although the primary endpoint of a reduction in time to death was not met, the results of the Advanced Chronic Heart Failure Clinical Assessment of Immune Modulation (ACCLAIM) trial showed a risk reduction of up to 39% for death or cardiovascular hospitalization in patients with New York Heart Association (NYHA) class II, and a 26% reduction in patients with NYHA II, III, and IV with no previous history of MI or ischemic cardiomyopathy [35]. While Celacade is approved and currently marketed in the European Union and Latin America, the FDA has mandated a confirmatory study prior to considering its approval in the US [32].

The association of immunological response with cardiac remodeling in HF provides new hope for the development of pharmaceutical interventions for this increasingly prevalent condition. Although stem cell therapy is less pertinent to this review, several interesting associations between stem cell therapy and immune-mediated responses have emerged in ventricular remodeling studies. Vagnozzi et al. recently assessed the mechanistic basis of stem cell therapy in a mouse model of ischemia-reperfusion injury [36]. The authors observed an improvement in cardiac function driven by an immune response as opposed to regeneration of the damaged cardiac tissue [36]. These findings warrant further investigation of stem cell combinations in the reduction and reversal of cardiac remodeling post-MI. The overarching goal of this review is to elucidate the critical role that anti-inflammatory drugs and nano-particle based systems can play in thwarting the onset of ventricular modeling in the context of ischemia-induced heart failure.

2. Anti-inflammatory medications in the management of heart failure

As multiple inflammatory mechanisms are known to drive cardiac remodeling post-MI, inflammatory biomarkers now play an increasingly important role in the diagnosis of heart failure [37,38]. From an inflammatory perspective, heart failure is classified into an acute inflammatory phase, a reparative phase and a chronic inflammatory phase which occurs 14 days post-MI [39]. The early inflammatory phase is triggered by necrosis of cardiomyocytes and ischemia in the surrounding tissue. Generation of reactive oxygen species (ROS) and IL-1 results in stimulation of pro-inflammatory fibroblasts which in turn secrete chemokines and cytokines [40]. Transition to the reparative phase is marked by increased IL-10 and TGF-β, which is driven by neutrophil-mediated recruitment of monocytes [39]. Interestingly, Sager et al. showed that targeting cell adhesion molecules (CAMs) resulted in inhibition of leukocyte recruitment to the infarcted myocardium, which significantly reduced cardiac remodeling [41]. Through RNAi targeting of CAMs, the authors demonstrate a monocyte-mediated pro-inflammatory microenvironment that is sustained in post-MI remodeling [41]. These findings are consistent with findings by Maekawa et al. wherein blood monocyte count was shown to be predictive of reduced ejection fraction (EF) [42]. Collectively, our understanding of the molecular mediators of the inflammatory response post-MI have proven invaluable in forming diagnoses and developing

treatment strategies post-MI.

The use of anti-inflammatory drugs in the management of cardiovascular disease has been widely addressed in the literature [43–45]. Indeed, a growing number of clinical trials have targeted inflammatory agents for the treatment of HF [26,32,35,37,46–52]. As summarized in Table 1, these trials have employed anti-inflammatory agents including HMG CoA reductase inhibitors [46–48], anti-TNF-α (etanercept and infliximab) [49,53], Pentoxifylline [52,54–56], and intravenous immunoglobulin (IVIG) [57,58]. While this review is intended to assess the progress made in localized NDDM delivery of anti-inflammatory drugs, it is important to acknowledge the off-target side effects experienced in systemic administration of anti-inflammatory drugs. Metabolic effects of the long-term use of glucocorticoids as anti-inflammatory agents include osteoporosis, hypertension, dyslipidemia and diabetes mellitus, all of which are significant co-morbidities in the background of post-MI ischemia [59]. In investigating the effects of a monoclonal antibody targeting interleukin-1β in patients with a history of HF, the Canakinumab Anti-Inflammatory Thrombosis Outcomes Study (CANTOS) was a landmark trial which conclusively found anti-inflammatory drugs to be protective in HF [60]. However, systemic (subcutaneous) administration of Canakinumab was associated with significantly higher incidence of fatal infection and sepsis relative to the placebo control [60]. Given the variable and diverse off-site effects documented as a result of systemic administration of anti-inflammatory drugs, the argument for the design of localized NDDM in the setting of heart failure is especially strong.

2.1. The role of HMG-CoA inhibitors

Pre-clinical studies investigating the effects of anti-inflammatory drug delivery post-MI have assessed agents including prostaglandin E1 (PGE1), Pitavastatin, glucocorticoids, and chemokine receptor type 2 (CCR2) siRNA [61–67]. Pitavastatin, a HMG-CoA reductase inhibitor was found to reduce cardiomyocyte apoptosis [62], inhibit monocyte recruitment [63], and decrease inflammation post-MI [64]; whereas glucocorticoids primarily decreased macrophage content post-MI [65,66]. The outcomes of each of the aforementioned studies are detailed in Table 2.

With respect to clinical trials, primary endpoints were not met for the majority of studies testing HMG-CoA reductase inhibitors and anti-tumor necrosis factor-α (anti-TNF-α) as potential anti-inflammatory drugs for the treatment of HF. Clinical trials investigating the use of HMG CoA reductase inhibitors demonstrated no significant changes in echocardiographic parameters of HF or in inflammatory biomarkers [46–48]. It has been postulated that the highly effective treatment for congestive heart failure (CHF) may negate any potential benefits of HMG CoA reductase inhibitors [47]. Another proposed explanation for the negligible beneficial effects observed with HMG CoA reductase inhibitors is owing to the fact that reduced coenzyme Q10 levels have been correlated with the severity of cardiomyopathy [68], and Rosuvastatin—an established HMG CoA reductase inhibitor—is known to reduce coenzyme Q10 [46]. Ultimately, the authors indicated that they were unsure as to why Rosuvastatin did not reduce the primary outcome. However, they hypothesized that either patients were not followed for a sufficiently long interval to observe a beneficial effect of treatment with Rosuvastatin, or that Rosuvastatin had pleiotropic effects, whereby myocardial ischemia was reduced by improving endothelial function [42]. Given that most patients enrolled were also treated with beta blockers, ACE inhibitors and aldosterone antagonists, the protective effect of these added drugs may have posed an additional challenge in elucidating the protective effects of Rosuvastatin with regards to a change in the primary outcome of sudden death.

2.2. The utility of anti-TNF therapy

To-date, the results of two clinical trials utilizing anti-TNF-alpha (α) agents, infliximab and etanercept have been published [49,53]. Infliximab - a chimeric monoclonal antibody for TNF, was first investigated in the 'Anti-TNF Therapy Against Congestive Heart failure (ATTACH)' trial. The ATTACH trial demonstrated no significant benefit in clinical status following short term (6 weeks) administration of infliximab; and documented deterioration of outcome in the high-dose (10 mg/kg)

Table 1
Anti-inflammatory agents used in clinical trials for HF patients.

Anti-Inflammatory agent	Target	Primary endpoint	Outcome	Reference
Rosuvastatin	HMG CoA reductase	Serum LDL; LVEF; Echocardiographic parameters; inflammatory markers	46:Patients in Rosuvastatin group had decreased low density lipoprotein cholesterol and CRP($p < 0.001$). Primary outcome occurred in 692 pt in Rovsuvastatin grp vs 732 in placebo (not significant). 47: Compared to placebo, ROS pts had a decrease in low density lipoprotein cholesterol ($p < 0.001$). Did not alter parameters of LV remodeling. 48: Endpoint of death – not significant for placebo v. Rosuvastatin.	[46–48]
Pentoxifylline	Phosphodiesterase inhibitor; anti TNF-α	LVEF, functional symptoms, and serum inflammatory biomarkers	**52:** Pentoxifylline group had significant improvement in NYHA functional class v. placebo. LVEF change was not significant. **54:** LVEF v. placebo, not significant. 55: Pentoxifyline group showed reducedTNF-alpha and Fas/Apo-1 concentrations, and increased EF after 1mo ($p < 0.05$). **56:**Pentoxifylline group showed improved NYHA functional class, increased systolic BP and LVEF ($p < 0.05$)	[52, 54–56]
Etanercept	Anti TNF-α	Death or hospitalization due to HF	**49:** Trial terminated early due to lack of benefit	[49]
Infliximab	TNF-α antagonism	Death or hospitalization due to HF	**53:**Neither dose of infliximab improved clinical status (primary endpoint). No significant change in inflammatory markers & EF	[53]
Intravenous Immunoglobulin (IVIG)	B-cells; T-cells; macrophages; complement; cytokines; cellular adhesion molecules	LVEF; functional symptom; inflammatory biomarkers	57: IVIG: significantly increased LVEF ($p < 0.01$); N-term pro-ANP decreased significantly in IVIG group, IVIG group showed increase in plasma IL-10, IL-1R, TNF 58: No significant change in LVEF between placebo and IVIG group	[57,58]

LDL: Low-density lipoprotein cholesterol; HMG CoA: 3-hydroxy-3-methyl-glutaryl-CoA; LVEF: Left ventricular ejection fraction; TNF: Tumor necrosis factor; HF: Heart failure; IVIG: Intravenous immunoglobulin; TGF: Transforming growth factor; HSP: Heat shock protein. IL: interleukin

Table 2
Summary of pre-clinical studies using anti-inflammatory agents in HF.

Anti-inflammatory agent	Mechanism of action	Delivery method	Outcome	Reference
PGE1	Dilates smooth muscle via cAMP signaling	Liposome / bolus admin	- Reduced infarct size - Inhibition of neutrophils	[61]
Pitavastatin	Inhibits HMG-CoA reductase	Poly(lactic-co-glycolic acid) / IV injection of nanoparticles (NP)	- Reduced cardiomyocyte (CM) apoptosis - Inhibited inflammation - Reduced MI size 24 h post reperfusion	[62]
		Poly(lactic-co-glycolic acid) / IV injection of NP	- Inhibited plaque rupture - Inhibited monocyte recruitment	[63]
		Reconstituted HDL / IV injection	- Decreased plaque macrophage density - Decreased inflammation	[64]
Dexamethasone	Glucocorticoid	Poly(lactic-co-glycolic acid) biogel	- Decrease in plaque macrophage content	[65]
Prednisone phosphate		Liposomes / IV injection	- Decrease in plaque macrophage content	[66]
Chemokine receptor type 2 siRNA	siRNA	Lipid nanoparticle / IV injection	- Reduced monocyte and macrophage number	[67]

infliximab treatment group [53]. While the authors acknowledged that increased TNF antagonism may have contributed to worsening heart failure as reflected by the results of the study, they also highlighted other explanations for the study findings including potential complement fixation or the effects of TNF rebound [17]. Etanercept - a dimeric fusion protein that fuses the TNF receptor is another anti-TNF agent that has been assessed for efficacy in the treatment of HF. The Randomized EtaNErcept Worldwide evALuation (RENEWAL) trial ruled out any clinical benefit resulting from etanercept with respect to HF-related death or hospitalization [49]. While the authors were unsure as to why no benefit was observed with etanercept treatment, they hypothesized that the doses used may have been insufficient to elicit a response whereby circulating levels of TNF were neutralized [54]. Alternatively, the authors suggested that the targeted methodology used may not have been sufficient to disrupt the full network of inflammatory mediators that are activated in HF. These are important discussion points insofar as they may inform study design and dosing in future trials. It would be beneficial to measure TNF bioactivity and circulating levels of inflammatory cytokines in future studies.

2.3. Methylxanthine phosphodiesterase inhibitors as immunomodulatory agents

Pentoxifylline, a non-selective methylxanthine phosphodiesterase inhibitor which has both anti-inflammatory and immunomodulatory effects has been one of the most promising immunomodulatory agents for MI to-date. As the first drug to be approved for the treatment of intermittent claudication, Pentoxifylline decreases blood viscosity and consequently improves blood flow [69]. Pentoxifylline is also known to decrease serum Tumor Necrosis Factor (TNF) and inhibit T helper 1 lymphocyte activity [69]. Fernandes et al. demonstrated the immunomodulatory effects of pentoxifylline on inflammatory response in patients with coronary artery disease (CAD), who showed a significant increase in anti-inflammatory cytokines (TGF-beta 1, IL-10) and a concomitant decrease in proinflammatory markers (CRP, IL-6, IL-12, IFN-gamma, TNF-alpha) [70].

The use of pentoxifylline as an immunomodulatory agent with pump-improving function in mild-to-moderate HF has been investigated in several other clinical trials as well [52,54–56]. With the exception of a neutral outcome in one trial [54], the addition of pentoxifylline to the conventional treatment of HF (digoxin, angiotensin-converting enzyme inhibitors, and a beta blocker) has improved LVEF, functional outcome, and plasma inflammatory markers in patients with idiopathic dilated [52,55] and ischemic [56] cardiomyopathy.

2.4. Intravenous immunoglobulins in the management of chronic heart failure

Intravenous immunoglobulin (IVIG) has also been assessed for therapeutic efficacy in the treatment of patients with chronic HF and dilated cardiomyopathy due to its immunomodulatory effects [57,58]. Although treatment with IVIG resulted in an anti-inflammatory effect in congestive HF and was directly correlated with LVEF improvement [57], no additional benefit was observed in patients with recent onset dilated cardiomyopathy [58]. These findings highlight the importance of selecting the appropriate patient population for indication of treatment with IVIG. As IVIG is an immunomodulatory agent, it relies on the proposed inflammatory pathophysiology for ischemic HF.

Collectively, the anti-inflammatory agents reviewed herein are justified potential treatments for post-MI cardiac remodeling given the well-documented role of inflammation in driving left ventricular remodeling. However, careful review of the findings of each study documented in Table 1 reveal pentoxifylline and IVIG to be the only anti-inflammatory agents with any promising clinical effect. While there was no clinical benefit observed by treating HF with HMG CoA reductase inhibitors or anti-TNF antibodies, the respective hypotheses as to why these studies demonstrated no clinical benefit suggests that further studies may be warranted.

3. Methods for delivering anti-inflammatory drugs to the myocardium

In considering the feasibility of delivering anti-inflammatory drugs to the myocardium post-MI, it is first important to review the underlying state of inflammation in infarcted myocardium in post-MI remodeling phase. Following infarction, necrosis of cardiomyocytes elicits both local and systemic inflammatory responses mediated by pro-inflammatory cytokines, leukocytes, macrophages and lymphocytes [44]. Sager et al. suggested that extensive loss of contractile myocardium following infarct can result in mechanical stress that drives macrophage proliferation and subsequent development of a fibrotic microenvironment [21]. Frangogiannis et al. further suggested that poor containment of the infarct border zone perpetuates inflammatory infiltration into the remaining viable segments of the myocardium [71].

Rationale for targeting post-MI inflammation is substantial. Containing inflammation in the early post-ischemic phase may inhibit leukocyte-mediated injury of cardiomyocytes in the infarct border zone [44]. Localized delivery of anti-inflammatory drugs may also inhibit delayed activation of pro-inflammatory signaling which could prevent apoptosis of cardiomyocytes in the remodeling zone [44]. Inhibiting protease activation by limiting inflammation may prevent dysregulated

remodeling and promote scar healing. As previously mentioned, extensive fibrosis can be avoided by suppressing fibrotic signaling driven by inflammation. Finally, localized administration of anti-inflammatory drugs may exert anti-arrhythmic effects and may prevent future plaque rupture [44].

3.1. Localised delivery of non-steroidal anti-inflammatory drugs encapsulated in biodegradable polymers

Localized delivery of non-steroidal anti-inflammatory drugs (NSAIDs) encapsulated in drug delivery vehicles such as hydrogels and biodegradable polymers has been achieved in numerous disease settings including osteoarthritis and periodontal disease [72,73]. Hydrogel-mediated drug delivery offers the advantage of both spatial and temporal control over the release of small molecule drugs and in some cases, cells. Though not specific to delivery of anti-inflammatory drugs, Paul et al. described the development of an injectable and biocompatible hydrogel for the delivery of graphene oxide and vascular endothelial growth factor (VEGF) gene therapy for ischemic heart disease [74]. A low modulus methacrylated gelatin (GelMA) hydrogel was determined to be efficacious for transfecting localized gene therapy directly to the myocardium without inducing cytotoxic effects [74]. Recently, Yi et al. demonstrated successful implementation of an injectable filamentous hydrogel depot (FM-depot) designed for sustained release of low-dosage anti-inflammatory nanoparticles [75]. Although the FM-depot had been extensively characterized previously, the hydrogels had not been previously utilized or tested for their ability to deliver micelles transporting bioactive or therapeutic molecules. The authors successfully demonstrated subcutaneous injection and subsequent controlled release of the micelles for several months following injection, thus highlighting the hydrogel depots as a potential future avenue for delivery and release of low-dose anti-inflammatory drugs in the post-MI setting [75].

3.2. Multimodal drug delivery systems accentuate the utility of targeted drug delivery

The majority of clinical trials investigating the efficacy of delivering anti-inflammatory agents to the myocardium have utilized systemic delivery approaches including intravenous injection or oral administration [32,35,47–49,51,54,58,76]. With the development of multimodal drug delivery systems, the concept of targeted drug delivery holds considerable promise in cardiovascular medicine [77–79]. Multimodal drug delivery system eliminates the disadvantages associated with systemic drug administration, such as suboptimal drug-target binding and drug-drug interaction. Additionally, multimodal drug delivery system offers the advantage of enhanced penetration into the target tissue, enabling delivery of optimal therapeutic drug concentrations in the target's microenvironment.

3.3. Nanoparticle-based drug delivery model (NDDM) for localized delivery of anti-inflammatory agents in the treatment of ischemia-induced heart failure

Incorporation of the nanoparticle-based drug delivery model (NDDM) has grown exponentially in cancer treatment in recent years [77,80,81]. NDDM enables accurate delivery of small-molecule inhibitors, proteins, and RNA to the target tissue [82]. NDDM consists of both active and passive targeting capabilities [83]. Through active targeting, NDDM uses antibodies and other target-seeking peptides to recognize and actively bind receptors for the biomarkers of interest [84]. Passive targeting is achieved through enhanced leakage and retention which increases local drug concentration [85].

Enhanced permeability and retention (EPR) is a physiological principle that was originally identified in tumor microvasculature, which enabled improved and sustained lipid-based drug delivery [85]. In short, clearance of macromolecules and lipids is significantly impaired, causing the lipids to remain in the tumor interstitium for a long time, which ultimately improves lipid-based drug delivery. In the setting of injury to the myocardium, it is well known that tissue vasculature becomes increasingly permeable immediately following injury [86]. While the increased vasculature allows for improved delivery of therapeutics to the damaged myocardium, retention remains a concern. In an inflammatory state, such as in the post-MI remodeling phase, clearance of lipids and macromolecules proceeds rapidly via the lymphatic system unlike tumor microvasculature where retention is prolonged. Interestingly, both Paulis et al. and Chang et al. have demonstrated that nanoparticle size is directly correlated to retention in the infarcted myocardium [87,88]. Chang et al. injected insulin-like growth factor (IGF)-1-complexed poly (D,L-lactide-co-glycolide) (PLGA) particles (PLGA-IGF-1) of varying sizes (60 nm, 200 nm, 1 μm) post-MI in a mouse model and found that compared to the 200 nm and the 1 μm particle groups, 60 nm PLGA-IGF-1 carried more IGF-1. Furthermore, PLGA-IGF-1 nanoparticle treatment prevented the thinning of the ventricular wall and subsequent dilation post-MI in-vivo, as opposed to the control and IGF-1 treatment alone [87]. Paulis et al. compared the accumulation pattern of differently sized lipid particles (15 nm and 100 nm) in a mouse model of MI [88]. The authors observed that the 15 nm micelles permeated the entire infarct area, whereas 100 nm particles accumulated in a smaller infarct area [88].

NDDM allows for accurate targeting, modulation of pharmacokinetics, and controlled biodistribution of the drug payload [89]. Additionally, NDDM has the advantage of penetrating deep into the tissue owing to its physiochemical characteristics, unlike systemically administered drugs, which are unable to accumulate at a sufficient dosage [84,90]. NDDM also allows for time-controlled release of the payload through internal (pH of microenvironment and oxidation status) and external stimuli (temperature, ultrasound, or light) [91]. The advantages and disadvantages of NDDM are listed in Table 3.

There are numerous ongoing clinical trials which are using nanoparticle systems to treat patients with cardiovascular disease. LDL-like nanoparticles containing either Methotrexate or Paclitaxel are being trialed as a treatment for patients with stable coronary disease at the University of Sao Paulo General Hospital [92]. Additionally, Paclitaxel loaded nanoparticles have been assessed in a clinical trial for the prevention of in-stent restenosis [93]. The Plasmonic Nanophotothermal Therapy of Atherosclerosis (NANOM-FIM) trial is also testing nanoparticle-mediated treatment of atherosclerosis, in which plasmonic nano-photothermal therapy is used to ablate atherosclerotic plaques [94]. Collectively, these trials will be important in highlighting the

Table 3
The advantages and disadvantages of NDDM compared to the conventional modalities.

Advantages	Disadvantages
High stability and carrier capacity[72]	Their ability to cross the blood brain barrier might culminate in brain toxicity [75]
Are suitable for the delivery of both hydrophobic and hydrophilic substances[75]	NDDM can induce reactive oxygen species in a myriad of organs, thereby inducing oxidative stress[96]
NDDM can afford the controlled release of drugs from the matrix[79]	While they reduce drug clearance and increase the accumulation of drugs in diseased tissues, certain retained products of drug metabolisms can be toxic[102]
Compatible with various modalities of drug administration, including oral and inhalation pathways[79]	Their high surface area to volume ratio can render nanoparticles exceedingly catalytic[102]
NDDM increase the drug bioavailability and reduce the off-target adverse effects of the drugs[101]	The agglomeration of nanoparticles can be toxic to non-diseased tissues. This is especially true of inhaled drugs that can often lodge within the pulmonary system[96]

feasibility of introducing anti-inflammatory drugs via nanoparticles to prevent cardiac remodeling post-MI. Fig. 1 shows the proposed model for localized delivery of anti-inflammatories to the heart to prevent negative remodeling.

3.4. Liposomes as potential NDDM carriers

The use of liposomes as potential NDDM carriers has increased considerably over the past decade [95,96]. Modified liposomes have stimuli-responding capacity, optimized circulation time, and allow for covalent drug-lipid interaction which ensures effective drug release at the target site [95]. Modified liposomes can be delivered via nebulizer, oral administration, or in topical agents [95]. Liposome-loaded ATP and CoQ10-L have successfully attained high intracellular accumulation in experimental models of ischemic heart disease [97,98]. Multifunctional micelles have also been tested in NDDM as modular particles containing a targeting component, fluorophore, and a therapeutic agent [99]. Similar to NDDM-based liposomes, polymeric micelles can be loaded with therapeutic agents for local delivery to the myocardium [80,84,99].

3.5. The utility of hydrogels in localized drug delivery

Hydrogels are yet another nanostructure which can be harnessed for localized delivery of pharmaceutical agents to a target tissue. Using a rat model of infarcted myocardium, Roche et al. compared saline injections, injectable hydrogels (alginate and chitosan/β-glycerophosphate), and epicardial patches (alginate and collagen) as delivery carriers for stem cells [100]. Epicardial patches were attached to the myocardium with a single suture with the cell-seeded side adjacent to the epicardium, at the infarct border zone [100]. In-vivo, hearts that were injected with DiD-GFP-hMSCs delivered via alginate and chitosan/ β-glycerophosphate gels demonstrated 8 and 14 fold increases in fluorescent signal compared to saline injected hearts [100]. For the collagen and alginate patches, 47 and 59 fold increases were observed respectively [100]. All biomaterials tested demonstrated superior delivery and acute

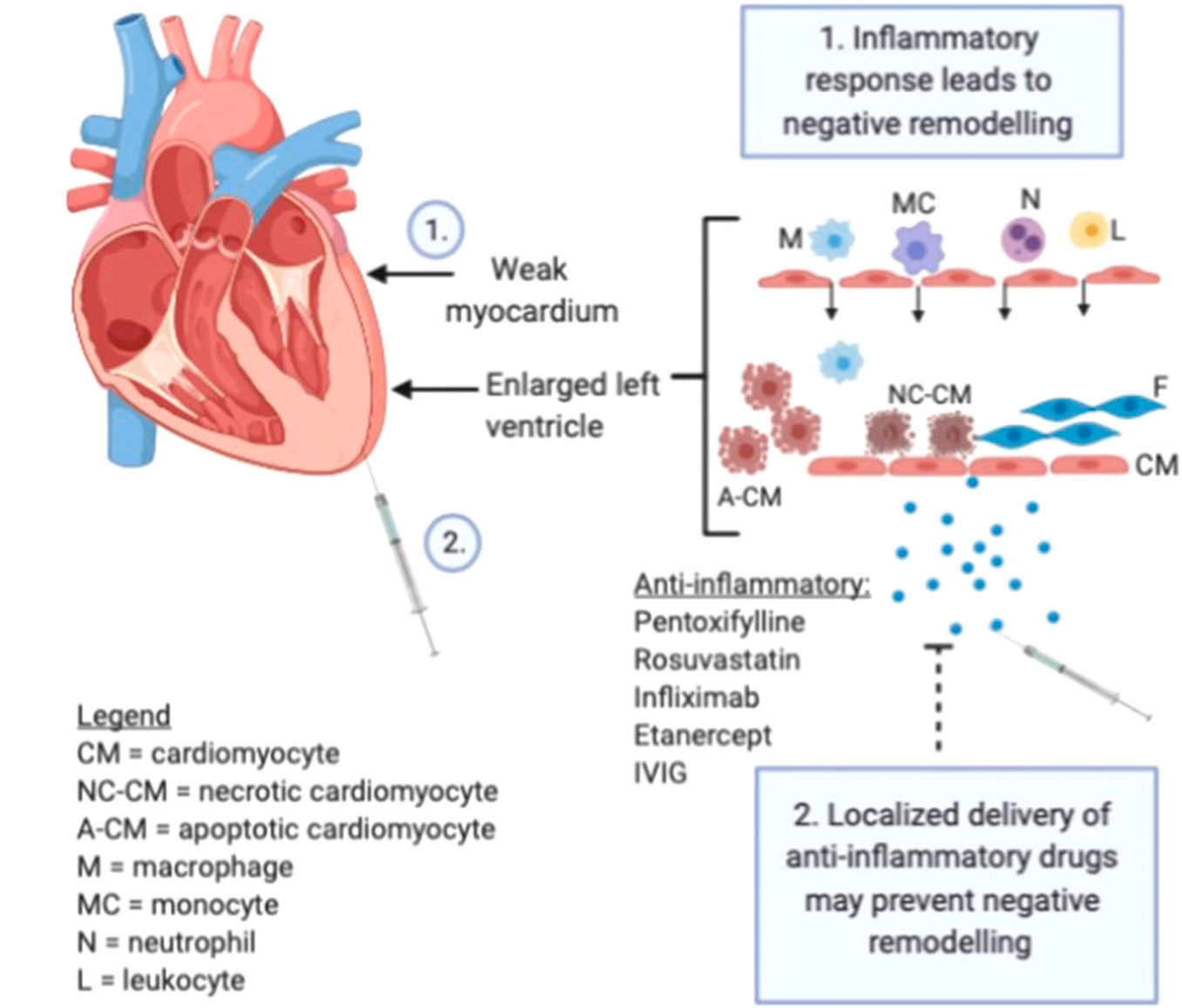

Fig. 1. Proposed model for localized delivery of anti-inflammatories to the heart to prevent negative remodeling: Post-MI, localized delivery of anti-inflammatory drugs such as IVIG, Rosuvastatin, Infliximab, Etanercept or Pentoxifylline via epicardial injection may mediate negative remodeling via direct inhibition of inflammatory mediators (monocytes, macrophages, neutrophils, leukocytes) which are recruited in response to necrotic cardiomyocytes. Inhibition of inflammatory signaling cascades may limit the fibrotic growth or scar tissue which contributes to cardiac remodeling post-MI.

retention of stem cells when compared to a saline injection control in rat model of MI. Both natural and synthetic hydrogels have been tested as vehicles for the delivery of cell-based treatment in mouse and rat models of MI. Naturally derived hydrogels resemble fibrin, hyaluronic acid, alginate, chitosan, and agarose in the extracellular matrix [79,101], whereas synthetic hydrogels offer the advantage of physicochemical modifiability which can be engineered to improve the delivery of the therapeutic agents [79,102].

Importantly, in 2019, Ventrix - a company established by researchers at the University of California San Diego conducted their first Phase I clinical trial of injectable extracellular matrix (ECM) hydrogels (VentriGel) in humans, with the aim of repairing injured myocardium and restoring cardiac function in heart failure patients with a history of MI [103]. The trial demonstrated that ECM based hydrogels can be safely and effectively injected via catheter into patients who had experienced MI in the past 2–36 months time. Each patient received up to 18 injections of the hydrogel to the damaged myocardium via catheter. The hydrogel, VentriGel, is composed of cardiac connective tissue derived from pigs which has been stripped of cardiomyocytes, then freeze-dried and later liquified into an injectable fluid [103]. Although the trial only assessed for safety and feasibility of the transendocardial injections, moderate clinical improvement was observed with no significant adverse events, warranting progression to a Phase II clinical trial.

The merits and demerits of the various drug delivery models discussed above are delineated in Table 4.

3.6. Potential hurdles in clinical utilization of NDDM in the treatment of ischemia-induced heart failure

Local delivery of anti-inflammatory agents to the infarcted myocardium holds great promise for the treatment of HF due to accurate targeting, fewer off-target effects and proven maintenance of optimal drug concentration at a local level even when administered at reduced dosages. However, there is still much progress to be made in order for delivery of anti-inflammatory drugs via NDDMs to be translated to a clinical setting.

The efficacy of anti-inflammatory agents in chronic HF has not yet been demonstrated to an extent where the model has been incorporated into clinical practice [104]. Given the small sample sizes employed in published clinical trials, there remains a need to further study the effects of NDDM of anti-inflammatory drugs before transitioning to clinical practice [32,35,46,47,51]. Moreover, our knowledge of the role of inflammation in HF and ventricular remodeling is still evolving [37,104]. As ongoing studies continue to identify new surface markers of the infarcted myocardium [23,26,50,80,95,104], multifunctional cargos need to be developed and scrutinized in order to optimize NDDMs.

As previously discussed, to-date, pentoxifylline has shown the most potential as a therapeutic anti-inflammatory in the setting of post-MI ischemia. Given its low bioavailability and short half-life, pentoxifylline is a natural candidate for nanoparticle mediated delivery. With respect to the feasibility of nanoparticle-mediated delivery of pentoxifylline, in-vivo studies have shown that pentoxifylline delivery via solid lipid nanoparticles (SLNs) increased the oral bioavailability of pentoxifylline beyond the standard 20% that occurs in the first pass metabolism [105]. In investigating the efficacy of nanoparticle delivery of pentoxifylline in the setting of cardiac hypertrophy, Dhiman et al. found that PEGylated SLNs for pentoxifylline demonstrated increased half-life and inhibit cardiac hypertrophy to a greater extent than the pentoxifylline control, suggesting its suitability to be transferred to a clinical setting [106]. Shuwaili et al. further investigated utilization of optimized elastic transferosomes formulations for transdermal delivery [107]. The authors found that transdermal transferosomes resulted in prolonged pentoxifylline release, with drug permeation through the skin increased by more than 9 fold relative to control [107]. The authors concluded that their optimized elastic transferosome formulation has notable potential for sustained release, increased bioavailability and further

Table 4
A tabulation of the merits and demerits of the various drug delivery models.

Modality	Merit	Demerit	References
Anti-inflammatory drugs encapsulated in biodegradable polymers	The core drug material contained within is largely guarded from variations in the external environment, thereby increasing bioavailability. The adverse effects consequent to undesired degradation before reaching the target site can be circumvented.	Despite the increased drug bioavailability, polymer instability remains a challenge. Selection of a suitable material for encapsulation poses several challenges, such as the biocompatibility and biomimetic properties of degradable polymers.	[73]
Systemic delivery through intravenous injection or oral administration	Suboptimal drug-target binding and drug-drug interaction can be circumvented, increasing the bioavailability of the desired agent. Enhanced penetration into the target tissue, enabling delivery of optimal therapeutic drug concentrations in the target microenvironment.	Drugs administered orally are subject to the hepatic first-pass effect, meaning that their concentration is significantly reduced by the time they reach the target site. There is an increased risk of arterial and/or venous damage when administering drugs intravenously. Additionally, the risk of infection and overdose is amplified.	[32,48,51,58]
Nanoparticle-based delivery models (NDDM)	Following injury to the myocardium, the vasculature becomes more permeable. NDDM can afford increased drug penetration in these circumstances. NDDM can allow for the delivery of a vast range of therapeutic agents, including both hydrophilic and hydrophobic compounds. NDDM confer increased flexibility in terms of the route of administration, which can take the shape of oral administration and inhalation amongst others. NDDM have high stability and carrier capacity, which means that the agent dosage can be manipulated.	Retention of the therapeutic agent delivered to the myocardium, in the context of myocardial injury, remains a concern.	[85,86]
Liposomes as NDDM carriers	Localised drug delivery can be achieved, thus avoiding the morbidity associated with systemic drug side effects that are frequently encountered.	Liposome-based models have an exorbitantly high production cost and a disproportionately short half-life. Solubility of such models is also unsatisfactory.	[93–96]
Hydrogels in localised drug delivery	Hydrogels offer the added benefit of localised sustained drug release. Additionally, they are	There are no guidance cues that can help direct hydrogel-based delivery, which can ultimately culminate	[79,98,100]

(continued on next page)

Table 4 (*continued*)

Modality	Merit	Demerit	References
	noted to boast high reactivity and biorthogonality. Membrane sealing is pragmatic with hydrogel-based delivery models.	in haphazard release of the desired therapeutic agent.	

avoidance of drug metabolism [107].

Although some anti-inflammatory drugs have shown promise in the treatment of cardiac remodeling in both pre-clinical and clinical settings, it is important to acknowledge that not all medications can be packaged into a nanomedicine-deliverable compounds owing to their physicochemical characteristics. Additionally, delivery of anti-inflammatory agents to the myocardium via NDDM can bear some challenges as the integrity of NDDM in-vivo and the functionality of anti-inflammatory compounds within the NDDM needs to be continuously monitored. Other obstacles to using NDDM to treat post-MI ischemia include difficulties achieving sufficient retention of anti-inflammatory agents within the myocardium to enable prolonged exposure. Furthermore, the potential requirement for multiple dosing would warrant multiple surgical catheterization procedures. Recent advances in the development of in-situ devices to continuously replenish therapeutic agents could be a promising solution to this obstacle [108]. Fig. 2 shows potential routes of anti-inflammatory drug delivery to the heart.

Finally, it is important to acknowledge that the potential incorporation of NDDM-based anti-inflammatory drugs can be costly for patients owing to drug pricing frameworks in the pharmaceutical industry.

3.7. Future Directions for NDDM

Repurposing of already available drugs and their localized delivery to the heart is an area of active research in cardiovascular space [77, 109]. Various drugs administered systemically have shown benefits in clinical trials to relieve the symptoms of heart failure, for example, diuretic therapy for fluid overload. However, they are not without their off-target side effects [110]. Furthermore, given the economic burden associated with the management of heart failure patients, achieving reversal or prevention of left ventricular remodeling leading to heart failure is still an area of unmet clinical need. Hence, we think that focus should be on developing localized drug delivery platforms, whereby possibility of off-target complications of a drug can be eliminated.

The extensive vasculature and enhanced permeability of the post-MI myocardium renders it an especially well-suited target for nanoparticle mediated drug delivery. As our understanding of the efficacy and limitations of NDDM evolves, future applications of NDDM in a post-MI setting will likely entail changes which improve distribution and retention, as well as enhance the specificity of nanoparticles targeted to ischemic myocardium. This will both reduce off-target toxicity and improve clinical response. For example, cell-specific targeting with peptides or aptamers may advance surface functionalization of nanoparticles, enabling increased specificity in cell-specific targeting [111]. Increased specificity may enable improved nanoparticle internalization which would improve cardiomyocyte retention. Most recently Lomis N et al. encapsulated an inotropic drug, milrinone, in albumin-angiotensin II nanoparticles and observed an improved retention time of milrinone in a rat MI model [112].

Furthermore, there is a potential of NDDM to be used in the management of other types of heart failure, for example, Heart Failure with preserved Ejection Fraction (HFpEF). The multifactorial origin of HFpEF leads to left ventricular remodeling. It is characterised by impaired ventricular relaxation and elevated left ventricular end-diastolic pressure (LVEDP). This elevated LVEDP over a period of time may retrogradely cause left atrial remodeling and secondary pulmonary hypertension. Various drugs have been tested, however, most of the clinical trials have had neutral results. With rising prevalence, this is an area of active reserach [113]. While nanoparticle delivery has yet to be optimized through direct injection or transcatheter endocardial delivery system, it could be facilitated through evolving methods such as paramagnetic NP delivery [111]. Furthermore, development and optimization of the devices that may help in replenishing the drug and its sustained delivery to the heart may expedite the clinical translation and wider acceptance of NDDM for localized delivery of drugs and proteins to the cardiovascular system.

4. Conclusion

Collectively, anti-inflammatory drugs are gaining attention in the treatment of cardiovascular disease, especially in the setting of acute MI and early stage ischemic HF. While precise biomarkers for infarcted myocardium have yet to be elucidated, localized delivery of anti-inflammatory agents to the myocardium using NDDM is a promising approach for successful treatment of ischemic HF. Future studies will be instrumental in determining the most effective target and delivery modalities for orchestrating NDDM-mediated treatment of HF. Ultimately, localized delivery of anti-inflammatory agents will reduce off-site complications and may limit or even reverse post-MI cardiac remodeling.

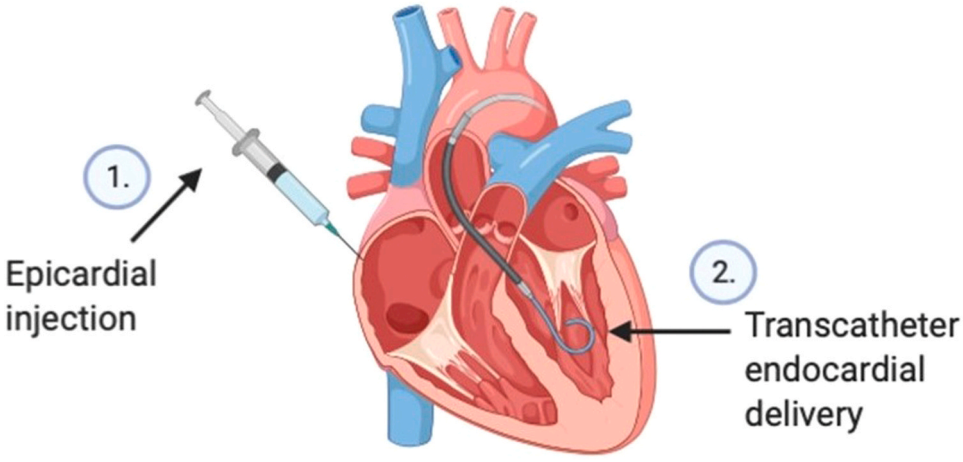

Fig. 2. Possible access routes for localized delivery of anti-inflammatory drugs to the heart. Access routes for nanoparticle injection include either epicardial injection or transcatheter endocardial delivery.

Ethics approval

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

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Kathryn E. Haley: Writing – original draft, Writing – review & editing, Visualization. **Talal Almas:** Writing – original draft, Writing – review & editing. **Saeed Shoar:** Writing – original draft. **Shan Shaikh:** Writing – original draft. **Maimoona Azhar:** Visualization, Writing – review & editing. **Faisal Habib Cheema:** Methodology, Supervision. **Aamir Hameed:** Conceptualization, Methodology, Supervision.

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