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Factors Influencing Retention of Injected Biomaterials to Treat Myocardial Infarction

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Biomaterials that are commonly used for the attenuation of adverse remodeling or as regenerative treatment for myocardial infarction (MI), often have the capacity to release drugs in a sustained manner, providing strength and stability to the infarcted area, or mimic the extracellular matrix. Retention and redistribution of the injected biomaterials is a factor often overlooked, but plays a significant role in the effectiveness of the treatment. Wash-out of therapeutics from the cardiac area can lead to unwanted side-effects and can therefore add insult to injury. Here, the authors seek a deeper understanding on the mechanisms that play an important role in the retention of injected therapeutics, being: materials, drugs, or a combination thereof. Several factors influencing the therapeutic quantity retained at the target site are discussed; being the timing of injection after MI, cardiac pulsation, and injectate properties such as volume, mechanical properties, and tissue affinity. The importance of understanding is highlighted and these different parameters are taken into. More insight in these parameters can lead to an increase in therapeutic effectiveness, in addition to examination of indirect off-target effects.

1. Introduction

Myocardial infarction (MI) is one of the highest leading causes of death worldwide induced mainly by atherosclerosis, causing a reduction or obstruction of blood flow in the coronary circulation. A significant infarction leads to adverse remodeling of the heart, in which fibrosis formation decreases contractile function leading to heart failure.

Current treatments are mostly palliative, focusing on improvement of life quality. New possible drug therapies, for example, proteins, growth factors, and ribonucleic acid interference (RNAi) drugs, are proposed to stimulate cardiac regeneration. These therapies are often injected in or at the border zone of the myocardial infarcted area. However, these injected drugs are rapidly washed away from the pulsatile heart without a delivery system. A wide variety of studies focus on the injection of drugs encapsulated in biomaterials, which can increase the efficacy of encapsulated drugs and improve cardiac function.

There are several drug delivery systems that focus on cardiac repair. Nano- and microparticles are a class of materials used for targeted therapies aiming to repair the cardiac muscle, in which therapeutics can be encapsulated. Other microparticles aim to mimic cellular-like systems, the so-called cell-mimicking microparticles. Poly(lactic glycolic acid) (PLGA)-based microparticles, carrying similar secreted proteins as cardiac stem cells (CSCs), were injected to examine their potential to preserve viable myocardium. Microparticles are also being used in the field of theranostics, providing localization in vivo after injection, as well as delivering therapeutics to the site of injection.

Other type of microparticles, such as hydrogel microparticles, are used in biomedical applications to deliver cells, drugs, or initiate aggregation at the site of injection to form a micro-porous scaffold. A high number of studies focus on injectable hydrogels on which the focus will lie mainly in this review, which offer the possibility to deliver cells, drugs, and mechanical support to the target site.

To maximize the targeted effect of the drugs encapsulated in hydrogel, the retention at the target site is of high importance. The efficacy of biomaterials (in combination with drugs) is often determined by examining indirect parameters such as the scar thickness, ejection fraction (EF), end-diastolic dimension (EDD), and fractional shortening (FS). In contrast, only a limited amount of studies focus on the retention of the biomaterial in the heart. It is important to establish a relation between the drug delivery system and attenuation of adverse remodeling or cardiac regeneration, which can give more insight into the amount-depending effectiveness of the delivery system. Additionally, examining and possibly increasing the retention of the therapeutic biomaterial at the target site could reduce possible off-target effects.
In this review, we specify key parameters which can affect the retention of the delivery system in the cardiac infarcted area, focusing mainly on injectable hydrogels. First, heart inherent characteristics will be described with the focus on injection timing post-MI and cardiac pulsation, followed by characteristics of the hydrogel system such as mechanical properties and tissue affinity (Figure 2). Finally, we speculate on the impact of these key parameters on hydrogel retention and focus on the off-target effects that can be induced in case of limited retention. The aim of this review is to obtain a deeper understanding on main factors influencing the retention of injectable hydrogels for cardiac repair, which will aid toward improved cardiac therapies.

2. Cardiac Features Influencing Therapeutic Retention

There is a high demand for cardiac regenerative therapies or therapies that attenuate the adverse cardiac remodeling, due to the incapacity of the heart to regenerate itself post-MI after severe deterioration.[29] One of the major challenges of cardiac disease is improving the efficacy of injected therapeutic agents, with a majority being washed away from the target site due to the continuous movement of the heart.[30] Often, a swift wash-out from the myocardium can be observed due to cardiac pulsation after intramyocardial cellular injection, for example, via the venous drainage, or the injectate being squeezed out of the myocardium.[31] Repeated administrations are often necessary to obtain and sustain effective drug levels, which can cause severe side effects depending on the type of drug.[32] Improving retention and drug efficacy at the target site will limit the amount of injections necessary for a therapeutic effect. Combinations of hydrogel and therapeutics, as well as the hydrogel alone, which can be injected at the target site, have shown to improve the functional cardiac output when injected post-MI. In this section key parameters known to influence the therapeutic retention by inherent cardiac traits will be discussed, being time of injection and cardiac contraction.

**A. Cardiac properties**

- Tissue density
- Space in the heart
- Optimum injection time
- Cardiac contraction
- CONTRACTION, RELAXATION

**B. Material properties**

- Hydrogel stiffness
- Degradation
- Viscosity
- Injection volume
- Affinity with tissue
- Bioactive compound
- Hydrogel

![Figure 1](https://www.advancedsciencenews.com)
**Figure 1.** Different therapeutic delivery methods are shown in which wash-out of the injected drugs lead to unwanted off-target effects. Drug-containing cargo delivery can increase the effectiveness of the drugs by retaining the drug at the target site.

![Figure 2](https://www.advancedsciencenews.com)
**Figure 2.** The different factors influencing retention of delivery systems; A) inherent cardiac properties such as the timing of injection and cardiac contraction, B) material properties such as the hydrogel stiffness, degradation, viscosity, injection volume, and affinity with tissue.
2.1. Timing of Injection Therapy

Severe MI leads to a cascade of cellular processes and remodeling events, that result in scar tissue formation to compensate for the loss of cardiomyocytes. The difference between healthy myocardial tissue and myocardial tissue post-infarction is significant, with an extensively higher collagen depletion post-MI.[34] Three main phases post-MI occur; the inflammatory phase, the proliferative phase, and the maturation phase (Figure 3).[35] Due to the fast remodeling and progressive pathophysiological process after a cardiac infarct occurs, the timing of therapeutic injection is most likely to have a significant effect on the cardiac outcome.[36] After an infarct occurs, the therapy can be injected early post-MI (during the inflammatory phase), late post-MI (during proliferative phase), or very late post-MI (during or after the healing phase). A greater expression of chemo-attractants and adhesion molecules was hypothesized to be present during the inflammatory phase, which can promote cellular retention after injection.[37,38] However, other studies indicate the harsh conditions of the microenvironment to hamper the cellular viability.[10] When reperfusion in the ischemic myocardium occurs during the first 3 h after MI, the infarct size was limited significantly and a high number of myocytes were salvaged.[10] An early response directly after MI can therefore lead to a limited remodeling process, but in practice this is challenging to accomplish. Collagenase and gelatinase activity is upregulated during the inflammatory phase, leading to disruption of the collagen network.[41] This can result in an increase of hydrogel degradation during this phase, lowering therapeutic effectiveness. The myocardial interstitium direct post-MI is still preserved, which slowly changes during the inflammatory phase.[42] When hydrogel therapy is directly injected post-MI, this forces the hydrogel between fibrillar bundles of the interstices, possibly giving the hydrogel a less bulky character and providing less mechanical support.

Some studies indicate the increased effectiveness in therapy when injected during the proliferating phase, during which the inflammation is resolved and fibroblasts proliferation initiates the formation of collagen-rich scar tissue. Injection during this phase can limit the extracellular matrix (ECM) remodeling and stimulate infarct repair.[43,44] Furthermore, a reduced inflammatory response during this phase can result in lower hydrogel degradation. Subsequently, a higher retention of the injected hydrogel due to limited degradation can be obtained, with a large bulk amount of the hydrogel providing myocardial support at the site of injection.

During the healing phase, the scar tissue undergoes a maturation process where the ECM becomes cross-linked and reparative cells are deactivated or go into apoptosis. Myofibroblasts remain, producing collagen and ensuring the ECM remodeling.[43] This process is highly dependent on the size of the infarcted area, with large infarcts inducing this adverse remodeling process.[45] The scar tissue can influence the injectability of the therapeutic carrier, with the stiffness of the collagen...
changing steadily over time as shown by Fomovsky et al.[46] Myocardial wall thinning can be observed after the healing period,[47] due to the increase of ventricular wall stress over time that can dilate the cavity.[48] This wall thinning, which is species independent,[49] can lead to a difficulty of injection at the target site, with thin and dense tissue being problematic for injection beyond the healing phase.[45] Furthermore, the delivery of growth factors or other therapeutics can be sub-optimal in efficacy during the healing phase, when the scar maturation is already in a developed stage, limiting regeneration with therapeutics.[19]

Several studies showed the importance of injection timing considering cellular injectates in the infarcted area.[50–55] For hydrogel injection, this timing is also highly important, as shown by Landa et al. who injected a calcium-crosslinked alginate solution in an infarcted rat heart 7 days and 60 days post-MI, corresponding to the proliferation and beyond the healing phase, respectively.[56] The cardiac function was examined 60 days after hydrogel injection, with the 7 days post-MI injection showing an increased scar thickness and a reduced left ventricular systolic and diastolic dilation, as well as cardiomyocyte migration to the infarcted area. The 60 days post-MI injection showed beneficial effects as well, but to a lower extent, with an increased scar thickness and improved systolic and diastolic function observed 60 days post-injection. Kadner et al. examined this timing effect after inducing MI in rat heart models, with injection of a poly(ethylene glycol) (PEG)-based hydrogel crosslinked with an enzymatically degradable peptide sequence that was injected immediately and 7 days post-MI.[57] Immediate injection after MI led to no observable improvements, while the delayed delivery led to significant increases in scar thickness, fractional shortening, and reduction in end-systolic diameter against saline controls, examined 2 and 4 weeks post-injection.

The timing effect of a thermo-responsive hydrogel was examined by Yoshizumi et al., injecting the biodegradable hydrogel poly(NIPAAm-co-HEMA-co-MAPLA) (NIPAAm: N-isopropylacrylamide methacrylate, HEMA: (hydroxyethyl)methacrylate, MAPLA: methacrylate-polyactic acid) in an infarcted rat heart.[58] Three different injection time-points were examined, being immediately after MI, 3 days after MI (3D), and 2 weeks after MI (2W). 10 weeks post-MI, the 3D and 2W groups showed a beneficial effect over the non-treatment MI control group. The left ventricle wall was thicker, with the 3D showing the most beneficial effect. Furthermore, the infarction size of the 3D group was smaller in comparison to the control and the 2W group. The hydrogel injection immediately post-MI did not show improved therapeutic effects.

The timing effect of an injectable hydrogel based on collagen (from rat tail) was examined in an infarcted mouse heart, being injected at 3 h, 7 days, and 14 days post-MI.[59] The 3 day post-MI injection showed the most beneficial results 4 weeks after therapeutic injection, with the highest left ventricular EF (LVEF) in comparison to the 7 days, 14 days, and control experiments. This indicated an optimal effect when injecting during the inflammatory phase, whereas a beneficial effect was observed when injected during the proliferation phase (7 days), but to a lower extent. In a follow-up study from the same group, hydrogels based on collagen type III were injected in an infarcted mouse heart at single and multiple time points.[60] The single treatment (3 h post-MI) showed the highest improvement in LVEF over time compared to the saline controls, which was examined up to 6 weeks after therapeutic injection. A slight improvement was shown in cardiac function when injecting at three time-points (3 h, 7 days, and 14 days post-MI), whereas the multiple time point injections at 7 days and 14 days showed a reduction in cardiac function (LVEF) compared to the saline control.

What should be noted is that all of these studies are performed on rodent models, which show differences in cardiac remodeling time of the infarcted area in comparison to humans, with the healing phase in a rat infarction being complete after approximately 3 weeks,[61] whereas in humans duration of the healing phase can last around 5 to 6 weeks or more.[45] The inflammatory phase of a rat lasts typically around ≈0–5 days post-MI, whereas the proliferation phase occurs after ≈5–14 days post-MI.[43] Optimal injection times for rodent models are therefore not directly translatable for human application. An interesting aspect which these studies suggest, is the difference in optimal therapeutic timing between non-bioactive hydrogels (PEG-based and poly(NIPAAm)-based) and bioactive hydrogels (collagen-based). The non-bioactive hydrogels show a trend toward an optimal effect when injected during the proliferation phase, whereas the bioactive hydrogels show a trend toward an optimal effect when injected during the inflammation phase. While the non-bioactive hydrogels are injected to provide mechanical support and therefore stress release to the infarcted tissue, as hypothesized by several studies, injection during the inflammatory phase can possibly lead to a high extent of matrix metalloproteinases (MMPs) and ECM-degrading activity, degrading the non-bioactive hydrogels.[65] During the proliferation phase, these MMPs and ECM-degrading molecules are present in a lower content, slowing down the degradation and not limiting the local gelation. Degradation products of bioactive hydrogels can, in contrast, stimulate signaling cascades leading to cellular adhesion, migration, and survival.[62] However, more studies are necessary to truly confirm this effect, as well as the translation toward large animal studies.

While all of these outcomes indicate beneficial cardiac outcomes, to our knowledge the long-term effects of these studies are unknown, with monitoring times not exceeding 3 months.

### 2.2. Cardiac Contraction

In healthy humans, the heart pumps approximately 60–100 times per min with a constant pressure on the ventricles and atria, the force not changing at higher pumping frequencies.[63] A high number of contractile cells are lost post-MI, subsequently leading to lower contractile forces.[64] Injectates are likely to be “washed away” from this area without any retention, with the pumping function of the heart pushing the injectate out of the target area, for example, via venous drainage, or squeezed out of the myocardium.[65] The effect of cardiac contraction on injected therapeutics will briefly be described in this section.

The influence of an arrested heart in comparison with a contracting heart is a subject only few studies focus on. A study that does examine this was performed by Terrovitis et al., in which cardiac-derived stem cells were labeled with
fluorodeoxyglucose-18 for quantification purpose, and injected in a beating and non-beating MI rat model. Retention of the stem cells in an arrested heart showed to be significantly higher in comparison to the contracting heart, being 75% and 17%, respectively. This indicates that a prominent reason of the cells being washed out of the myocardium of a rat is due to the cardiac contractile function. We hypothesize that hydrogels will respond in a similar manner to the contractile function, but having a lower wash-out from the injectate site due to an increased viscosity and lower flow. To our knowledge, no study has thus far examined the retention of injectable hydrogels in a beating as well as an arrested heart. An increased cellular retention has been observed when encapsulated in an injectable hydrogel. Furthermore, many studies have observed an enhanced therapeutic effect when combining the cells with a carrier material. Hydrogels themselves are also observed to show a functional therapeutic outcome when injected, having mechanical support and therefore elevating wall stress caused by the loss of cardiomyocytes, or mimicking the natural myocardial structure. When hydrogels exhibit rapid gelation, an increase in retention can be obtained, with the gel exhibiting lower flow properties and therefore less wash-out. The contraction can influence the shape of the injected hydrogel, changing its morphology. Self-healing hydrogels are interesting candidates for cardiac delivery, being a hydrogel that has the ability to reversibly repair the damages to itself and recover its functions. For examining the properties of hydrogels, fatigue resistant experiments are often performed on hydrogels, examining the rheological properties of the hydrogel and the ability of the hydrogel to respond to stimuli. In the subsection “Mechanical biomaterial properties”, the mechanical properties of these biomaterials will be discussed more extensively.

3. Biomaterial Properties Influencing Therapeutic Efficacy

A high number of natural or synthetic hydrogels, sometimes in combination with therapeutic agents have been used for cardiac therapies (Figure 4). Natural, more bioactive hydrogels (such as decellularized ECM) often induce physiological and chemical signaling mechanisms, or improve cell survival and cell motility into the surrounding tissue. Bioinert hydrogels (such as alginate-based hydrogels) are hypothesized to reduce the mean wall stress by the bulking of wall thickness upon hydrogel according to Laplace’s law, or, as presumed by more recent studies, diminishing the stress of cardiomyocytes surrounding the hydrogel on a more cellular level. Other parameters, such as injection volume, mechanical properties, and injectate retention are of influence on the therapeutic efficacy. These factors will be discussed here.

3.1. Injection Volume

A high number of the cardiomyocytes are lost during an MI, and therefore a number of studies attempted to increase the amount of cells at the infarcted area by injecting viable cells. Different amounts of cells and volumes are often injected, varying with each study and model. In human trials, bone marrow-derived stem cells were injected post-infarction, with the total injection volume varying from 10–26 mL. This indicates no “golden standard” for the injection volumes, considering these results. An increase in cellular injection volume can furthermore cause an adverse effect on the cardiac output.
For injectable hydrogels, to our knowledge, few studies have focused on the volume optimization of hydrogel injectate in the infarcted myocardium. However, finite model-based studies were performed, in which the optimal volume of the injectate for cardiac therapy was determined. Here, we describe the few studies that did volume optimization experiments, as performed by Wise et al., who developed a finite model of a rat heart and showed the therapeutic benefit between the injection volume of a stiff PEG-based hydrogel and the infarct size. With an infarcted area of 10% of the ventricle wall, 50% volume injection showed to have the largest benefits in comparison to the 25% and 75% volume injection. It was concluded that the injected volume relative to the infarcted area is of influence, and the effectiveness of the injected gel depends on this ratio. Injecting an excessive hydrogel volume could even further decrease the cardiac function. Therefore, the amount of volume injected is of high importance and more caution should be taken on the extensiveness of the infarcted area and the ratio to the injected hydrogel volume.

The effect of alginate hydrogel injection in a MI swine model was examined during a 60-day follow-up. Three different injection volumes were used, 1, 2, and 4 mL of hydrogel in total. The hydrogel was injected by intracoronary injection, 3 to 4 days post-MI. Favorable effects on the LV remodeling were observed when 2 and 4 mL of hydrogel were injected in the infarcted site, in comparison to 1 mL hydrogel. Mild favorable effects were observed for the animals treated with 1 mL hydrogel, preventing little left ventricle diastolic and systolic dilation compared with the control MI model. Hydrogel injections of 2 and 4 mL showed an increase in left ventricle mass, and reversed left ventricle diastolic and systolic dilation.

A study by Wang et al. showed the different functional outcomes with finite element models, in which 150 and 300 µL hydrogels with varying stiffness were injected. 150 µL hydrogel injection with a stiffness of 25 kPa reduced the myofibrillar stress by 18.9% at the epicardium, while 300 µL injection reduced the stress by 31%. Furthermore, 150 µL hydrogel injection with a stiffness of 100 kPa led to myofiber stress reduction of 39.2% at the epicardium, whilst 300 µL injection of the same hydrogel showed a stress reduction of 56.8%. The end diastolic volume decreased more extensively when 300 µL was used compared to the 150 µL injection volume. A finite element model of an ovine left ventricle was exploited by Wall et al., who examined the short-term effects of material injection, comparing a single injection, and multiple injections with changing volumes. Here, decreasing fiber stresses were also observed with increasing volume fraction (examined from 0.5–1.5 mL), in which stiffer materials furthermore improved this reduction. Additionally, the EF and stroke-volume/end-diastolic volume were improved. However, no significant changes were observed in the multiple injection group, in comparison to the infarct control. Another finite element model examined different factors which are of influence on hydrogel efficacy, being injection volume, hydrogel stiffness, and timing injection. The hydrogel injection overall showed to reduce the myocardial strain under physiological loading. Three volumes were modeled, being 15, 50, and 170 µL (1.5–17% of the total region volume), of which the local strain was decreased when the hydrogel volume was increased. Furthermore, increasing hydrogel stiffness showed further reduction in myocardial strain, with optimal moduli between 1–25 kPa. Recent studies suggest that bioinert hydrogels can reduce the stress on the myocytes by stimulating fibrotic encapsulation around the surface of the hydrogel, constraining the myocytes to the surface. This can prevent left ventricular dilation, and therefore decreases the stress of the surrounding myocytes. Several recent studies have been summarized in a table, with the volume, model, time of administration, delivery method, end-point time after treatment, and functional outcome presented (Table 1).

### 3.2. Mechanical Properties of Hydrogels

Injectable hydrogels are of great interest for cardiac applications, due to the minimally invasive manner in which they can be delivered to the target area. Stimuli-responsive hydrogels are often used in the cardiac therapy field, with their ability to adapt and gelate in situ based on responses to physical changes such as temperature, and pH. Furthermore, non-inert hydrogels such as fibrin and ECM-derived hydrogels show beneficial results for the treatment of MI. Often, these hydrogels show a low stiffness (<100 Pa), and their function is mostly dependent on the inherent bioactive compounds inducing a combination of physiological and chemical signaling mechanisms. Therefore, the focus in this subsection lies mostly on inert tunable injectable hydrogels, and their mechanical properties when regarding the therapeutic efficacy.

#### 3.2.1. Hydrogel Stiffness

The hydrogel stiffness indicates the rigidity of the hydrogel, and to which extent the hydrogel is able to resist deformation under force. The stiffness of a hydrogel can often be tuned by varying the concentration or cross-linking density. When injected into the myocardium after an infarct, the deformation under the cardiac force is, therefore, an important parameter to examine. These mechanical properties of hydrogels, with the focus on moduli, were examined by Iakovits et al., who injected hyaluronic acid-based hydrogels with differing moduli (~8 and 43 kPa), adapted by a change in the number of reactive methacrylate groups. The hydrogels were injected in an infarcted ovine heart 30 min post-MI (20 injections of 0.3 mL), and 8 weeks post-MI the functional output was examined.
Table 1. Studies using hydrogel delivery for targeting MI since 2017.

| Hydrogel material (and cell/therapeutic molecules) | Model | Injected volume | Time of administration post-MI | Type of ischemic injury | Delivery method | End-point after treatment | Functional outcome compared to infarct control | Reference |
|---------------------------------------------------|-------|----------------|-------------------------------|------------------------|-----------------|--------------------------|---------------------------------------------|-----------|
| Hyaluronic acid-based hydrogel with cholesterol-modified miR 302 | Mice | 10 µL (with 2 injections) | Directly post-MI | Ligation of the LAD | Epicardial injection | 28 days posttherapy | Improved cardiomyocyte proliferation, improved EF and FS, and reduced LVESV, decrease in infarct size | Wang et al. [9] |
| Laponite and gelatin type A hydrogel containing secretome of human adipose-derived stem cells | Rat | 100 µL (with 5 injections) | Directly post-MI | Ligation of the LAD | Epicardial injection | 21 days posttherapy | Improved EF and FS, decrease in infarct size increase capillary formation | Waters et al. [94] |
| Enzymatically degradable PEG-based hydrogel containing heparin and MSC in different cell densities | Rat | 100 µL (with 3/4 injections) | 30 min post-MI | Ligation of the LAD | Epicardial injection | 30 days posttherapy | Improved FS and EF, prevented increase EDD and ESD, prevention anterior wall thinning, reduced scar area | Ciuffreda et al. [96] |
| Triblock copolymers (PArg-PEG-PArg) and PMNT-PEG-PMNT coupled with poly(acrylic acid) | Mice | 50 µL | Directly post-MI | Ligation of the LAD | Epicardial injection | 28 days posttherapy | Improved thickness myocardial tissue Improved EF and FS, smaller infarction size | Vong et al. [91] |
| A Mix of mesoporous silica nanoparticles/miR-21 complex combined with aqueous solution of α-cyclodextrin and aldehyde-capped PEG | Pigs | 600 µL (with 6 injections) | Directly post-MI | Ligation of the first two obtuse marginal arteries of the left circumflex | Epicardial injection | 28 days posttherapy | Increase in EF, preserved myocardial wall thickness, small infarct size Enhanced vascularization | Li et al. [92] |
| Liposomes based on phosphatidylcholine and cholesterol containing VEGF, loaded into a hyaluronic acid-based hydrogel | Rats | 100 µL | Directly post-MI | Ligation of the LAD | Epicardial injection | 28 days posttherapy | Increased capillary density, lowest LVDD and LVSD values. Improved EF an FS, thicker ventricle wall | Zhang et al. [93] |
| N,N-methyleenbis(acylamide) + acrylic acid + core-shell poly(NIPAM) microgels loaded with tissue plasminogen activator (tPA) and small molecule | Rats | 50 µL | Directly post-MI | I/R injury, 30 min ligation of the LAD | Injection in the ventricular cavity with temporary aortic occlusion | 28 days posttherapy | Improved EF and FS, decreased scar size, decreased fibrotic markers | Mihalko et al. [94] |
| Poly(NIPAAm-co-HEMA-co-MAPLA) hydrogel | Rats and pigs | Rat: 100 µL (with 5 injections) Pig: 4 mL (with 20 injections) | Rat: 3 days post-MI, Pig: 2 weeks post-MI | Ligation of the LAD for both animal models | Epicardial injection for both models | 8 weeks posttherapy for both models | Rats: maintained stiffness of LV, Porcine: preserved ESV, improved EF, fractional area change, and Cardiac index, smaller infarct size, thicker LV wall. Smaller scar size, increased EF and FS, reduction in LV hypertrophy | Matsumura et al. [23] |
| Basic fibroblast growth factor-loaded PVA-TSPBA crosslinked hydrogel | Rats | 7.6 mg kg⁻¹ (estimated ~100 µL) | 30 min post-MI | I/R injury (specifics not stated) | Pericardial cavity injection | 28 days posttherapy | Increase in EF, lower pressures at end diastole, reduction of myofiber strains in hydrogel vicinity | Li et al. [39] |
| Alginate hydrogel | Swine | 3.6–4.2 mL (with 12–14 injections) | 8 weeks post-MI | Ligation of the obtuse marginal arteries of the left circumflex | Epicardial injection | 8 weeks posttherapy | Increase in EF, lower pressures at end diastole, reduction of myofiber strains in hydrogel vicinity | Sack et al. [24] |
| Hydrogel material (and cell/therapeutic molecules) | Model | Injected volume | Time of administration post-MI | Type of ischemic injury | Delivery method | End-point after treatment | Functional outcome compared to infarct control | Reference |
|---------------------------------------------------|-------|-----------------|-------------------------------|------------------------|-----------------|--------------------------|-----------------------------------------------|-----------|
| PEG functionalized with UPy-moiety based hydrogel containing VEGF | Mice | 20 µL (with 2 injections) | Directly post-MI | I/R injury (with 30 epicardial injection min of ligation) | Epicardial injection | 22 days post-therapy | Improved EF and LVESV, improved regional myocardial strain, reduced fibrosis. | Van den Boomen et al.[100] |
| Alginate hydrogel | Swine | 3.6–4.2 mL (with 12–14 injections) | 8 weeks post-MI | Occlusion of the obtuse marginal arteries of the left circumflex. Arterial occlusion, followed by 3-min reperusions, followed by permanent occlusion | Epicardial injection | 8 weeks post-therapy | Improved stroke volume, EF, wall thickness, LVESV, reduced myofiber stress | Choy et al.[101] |
| Extracellular matrix hydrogel | Humans | 5.4 mL (maximum amount, varied per person, 0.3 mL injections) | 60 days and 3 years post-MI | Patients treated by percutaneous coronary intervention within the past 60 days to 3 years and had an LVEF between 25% and 45% by baseline screening echocardiogram | Percutaneous transendocardial injections | 6 months posttherapy | Improvements were showed in the 6-min walk test, no echocardiographic significant differences | Traverse et al.[102] |
| Hyaluronic acid hydrogel containing rTIMP-3 protein | Pigs | 900 µL (with 9 injections) | Directly post-MI | Occlusion of the first two obtuse marginal arteries of the left circumflex. Arterial occlusion, followed by 3-min reperusions, followed by permanent occlusion | Epicardial injection | 28 days posttherapy | Improved EF, lower LVEDV and LVESV, reduced LV filling pressure, Reduced fibrillar collagen content. | Purcell et al.[103] |
| Recombinant human collagen type 1 and type 3. | Mice | 50 µL (with 5 injections) | 1 week post-MI | Ligation of the LAD | Epicardial injection | 28 days post-therapy | Improved EF. Reduced EDV, McLaughlin et al.[104] |
| Hyaluronic acid hydrogel containing extracellular vesicles | Rats | 100 µL (with 5 injections) | Directly postMI | Ligation of the LAD | Epicardial injection | 28 days posttherapy | Improved EF, increased systolic and diastolic pressure, increased vascular density, increased scar thickness | Chen et al.[105] |
| Gelatin coadministered with hyaluronic acid hydrogel | Rats | 100 µL | Directly postMI | Ligation of the LAD | Epicardial infarction | 28 days posttherapy | Increased EF and FS, decreased LVED, LVES, ESV, small infarct size and thicker left ventricle walls | Wu et al.[106] |
| Citrate-containing polyester hydrogel encapsulated Mydgf growth factor | Rats | 120 µL (with 3 injections) | Directly post-MI | Ligation of the LAD | Epicardial injection | 28 days post-therapy | Improved EF and FS, Decrease LVDD and LVSD, increased scar thickness and decreased fibrosis. | Yuan et al.[21] |
| Glutathione-modified collagen hydrogel, functionalized with a basic fibroblast growth factor combined with an MMP-2/9 cleavable peptide | Rats | 100 µL (with 5 injections) | Directly post-MI | Ligation of the LAD | Epicardial injection | 30 days post-therapy | Improved EF and FS, Decrease LVDD and LVSD, an increase in wall thickness, a decrease in collagen content | Fan et al.[27] |
findings showed less infarct expansion and reduced LV dilation in the higher modulus group, in comparison to the lower modulus group. An increase in myocardial stabilization was hypothesized, with the high modulus gel reducing the wall stresses in an increased extend in comparison to the low modulus gel. However, only a trend toward functional cardiac improvements was shown in the stiffer hydrogel group, with no significant changes.

These mechanical properties of hyaluronic acid-based hydrogels were further examined by Rodell et al., using a tandem crosslinking approach with the injection of hyaluronic acid hydrogel (<1 kPa), followed after a second injection which stiffened the hydrogel network in situ due to dual-crosslinking (~41 kPa).[114] Infarcted ovine models were used, in which the hydrogels were injected 30 min post-MI (16 injections of 0.3 mL). The functional output was examined 8 weeks post-MI. The dual-crosslinked hydrogel showed to have an optimal effect compared to the MI control, with a significant stress reduction, maintaining wall thickness, and improved EF. Some improvements were observed with the lower modulus hydrogel, but less significant as for the dual-crosslinked hydrogel.

The mechanical properties were further explored by finite element models, in which changes of stiffness were varied as well as volumes to examine the therapeutic effect on the cardiac function.[92,93] Both these models show that an increase in material stiffness led to a decrease in myofiber stresses around the injectate site, while lower stiffness hydrogel showed no significant stress reduction. The stiffness effect showed to recede around 50 kPa.[92] These results indicate the impact of the hydrogel stiffness, having a significant effect on the therapeutic outcome. This was suggested to be mainly due to the fibril stresses around the infarct area being levitated, as well as an improved wall thickness of the infarcted area.

### 3.2.2. Degradation

The degradation of a material after implantation or injection is an important parameter, which theoretically should match the attenuation or reverse remodeling process. The degradation products should be non-toxic and able to be metabolized and cleared from the body.[115] Hydrogel degradation is an important factor when considered for cardiac therapy, as shown by Dobner et al. who examined the efficacy of a non-degradable hydrogel based on PEG post-MI.[27] The hydrogel was injected with a volume of 100 µL directly after MI, with 2 to 3 injections. Wall thinning was prevented and LVED increase was reduced upon injection of the PEG hydrogel, in comparison to the saline control. However, this effect was lost after 13 weeks, with the ESD and EDD being equivalent for the saline as well as the hydrogel injection. An explanation given for these observations is the delayed buildup of cardiomyocyte stresses, with the PEG hydrogel acting as a buffer initially, but insufficient in reducing the stresses in the myocardium over a longer time span. An ongoing macrophage-based foreign body response was hypothesized to stall this improvement over time. Implementation of peptides which can be degraded by cell-driven enzymatic cleavage were introduced to the PEG-based hydrogel in a follow-up study to examine the degradable variant of this hydrogel.[57] This article was briefly mentioned in the “time of injection” section, in which two time-points were compared, being directly post-MI and one-week post-MI after infarction in a rat model. Swift degradation of the hydrogel was observed directly post-MI, with no hydrogel being present four weeks post-injection. The one-week post-MI injection showed little difference in remnants after one and four weeks post-injection, indicating lower degradation rates. The one week post-MI injection showed increases in scar thickness, fractional shortening, and decreases in end-systolic dimensions, but later time-points were not taken into account (as their previous study examined the functional effect of the non-degradable PEG hydrogel 13 weeks post-MI). Whilst these results show beneficial effects of the slowly degradable hydrogel injected one-week post-MI, this study does not elucidate further on the retention and functional outcome of the hydrogel therapy over longer time spans.

Hydrogel degradability and the effect on the functional cardiac output in infarcted ovine models was examined by adaption of hyaluronic acid hydrogels, which were tuned to degrade by enzymatic and hydrolytic degradation.[25] Low (~7 kPa) and high (~35–40 kPa) hydrogel moduli were examined, with both degrading and non-degrading hydrogels being analyzed. All hydrogel groups showed improved cardiac output in comparison to the infarcted control, but no significant differences between the hydrogel groups were observed. For the

| Hydrogel material (and cell)/therapeutic molecules | Model | Injected volume | Time of administration post-MI | Type of ischemic injury | Delivery method | End-point after treatment | Functional outcome compared to infarct control | Reference |
|--------------------------------------------------|-------|----------------|-------------------------------|------------------------|-----------------|--------------------------|---------------------------------------------|----------|
| P(NIPAM-co-AA) hydrogel in which human cardiac stem cells were encapsulated | Mice and pigs | Mice: 50 µL Pigs: not stated | Mice and pigs: directly post-MI | Ligation of the LAD for both animal models | Epicardial infarction | Mice: 3 weeks post-therapy Pigs: 4 weeks posttherapy | Increased EF, viable myocardium, and infarct thickness were observed for the gel and gel + cells group, with the gel + cell group displaying the highest functional outcome. | Tang et al.[67] |
| LAD = left anterior descending, EF = ejection fraction, FS = fractional shortening, LVEDV = left ventricle end-diastolic volume, LVESV = left ventricle end-systolic volume, EDD = end-diastolic dimension, ESD = end-systolic dimension, LVDD = left ventricle diastolic diameter, LVSD = left ventricle systolic diameter, ESV = end systolic volume, LVESV = left ventricle end systolic volume, LVEDV = left ventricle end diastolic volume. |
high hydrogel modulus, the non-degradable variant showed to reduce the LV volume more effectively at 8 weeks post-MI, indicating the importance of wall stabilization over a longer time period.

Natural hydrogels, such as ECM-derived hydrogels, can be modified with an MMP inhibitor such as doxycycline, as shown by Wassenaar et al. The in vivo degradation was examined in rats on healthy myocardial tissue, in which the retention was examined by a fluorescent label attached to the hydrogels 2 weeks post-injection. This showed a significant increase in fluorescence of the doxycycline-modified hydrogels, indicating a lower degradation rate. A prolonged degradation was also observed in similar ECM-based hydrogels which were tuned with genipin, a crosslinking agent extracted from gardenia fruit, reducing the degradation rate in vitro over time. However, this was not tested on an in vivo infarction model.

While all of these studies show that the degradation of the injectable hydrogels can be tuned, so far it is unclear what the optimal degradation rate of the hydrogel should be to reach the optimal functional cardiac output. While non-degradative hydrogels can lead to an adverse in vivo effect over longer timespans, more research needs to be performed to tune the degradation rate with the attenuation or reverse cardiac remodeling process.

### 3.2.3. Viscosity

One of the key mechanical features when regarding injectable hydrogels is the viscosity, of which the injectability is highly dependent. Determination of the viscosity as a function of shear rate can give insight in the injectability of the hydrogel. For shear-thinning hydrogels, the viscosity decreases with increasing shear stress. In some cases, crosslinks of the hydrogels are broken upon increasing shear, whereas they are reformed once the shear stress has been lifted. Furthermore, to inject a hydrogel in a non-invasive manner through a catheter, the Hagen-Poiseuille equation needs to be regarded, which can determine the injectability of a hydrogel (Equation 1):

$$\Delta p = \frac{8 \mu Q L}{\pi R^4}$$

Where $\Delta p$ is the pressure drop through a cylindrical pipe (syringe needle), $\mu$ is the dynamic viscosity, $L$ is the length of the pipe, $Q$ is volumetric flow rate, and $R$ is pipe radius. This equation shows the force necessary for injection, dependent on the volumetric flow rate, dynamic viscosity, needle length, needle bore diameter, and syringe plunger area. Higher needle length and dynamic viscosities lead to higher forces necessary for injection, which can limit the injectability of a hydrogel.

Furthermore, the viscosity and gelation time is of importance regarding the in vivo retention after injection. Low viscous solutions, with slow sol-gel transition times, can be easily washed away from the site of injection, which is why swift sol-gel transitions are optimal for proper retention.

For cellular or therapeutic delivery, the mechanical properties of the hydrogel influences the uniform suspension of cells or therapeutics when encapsulated. A problem often occurring when cells or therapeutics are mixed in gels is sedimentation, leading to a concentration gradient of cells or therapeutics. Often, uniform mixes are obtained by vigorous mixing before injection. The sedimentation is dependent on the molecular mass of the therapeutic compound, as well as the frictional coefficient. The viscosity of the hydrogel precursor plays a significant role in this sedimentation process, with an increase of viscosity decreasing the displacement of the cells. Na et al. improved the cell suspension of a gelatin-methacrylate-based bioink by increasing the viscosity of the solution upon addition of biocompatible silk fibroin particles. They observed the lowest sedimentation values upon addition of 1 w/v% silk fibroin particles, with a viscosity of ~60 Pa.s. While these viscosities were applicable for 3D-bioprinting, these high viscous solutions can be troublesome to inject, depending on the type of syringe, gauge needle, and applied force. Still, for minimally invasive injection methods, as well as cell and therapeutic delivery, the viscosity is an important parameter to take into account.

### 3.3. Biomaterial Affinity with the Surrounding Tissue

The choice of material plays a significant role in how the surrounding tissue responds to this foreign material. Natural biomaterials often show biocompatibility, bioactivity, assist in cellular activities such as cell-cell communication, and potential tissue regenerative properties. Synthetic biomaterials are easily adaptable to obtain high mechanical strength, degradability, and gelation rates. An improved retention can be obtained by introduction of adhesive components to increase the tissue-adhesion between the hydrogel and surrounding tissue at the injectate site.

Increasing the hydrogel adhesion can be realized by introduction of catechol-functionalities, which are known to adhere under wet conditions inspired by the mussel foot proteins. This was shown by Wu et al., who co-administered a hyaluronic acid hydrogel intramyocardial, whilst a gelatin-dopamine and dopamine-modified poly(ethylene glycol) was coated on the myocardium surface. The combined therapy showed beneficial effects on the functional output of the heart, displaying the highest wall thickness and lowest infarct size. Furthermore, the combined therapy showed to have beneficial effects on the cardiac output, with an increased EF and fractional shortening in comparison to the MI control.

The arginine-glycine-aspartic acid (RGD) peptide is a natural ligand peptide, which can interact with integrin receptors to provide cell-cell and cell-ECM interactions. Introduction of the RGD peptide to biomaterials can increase the cell density, cell adhesion, and cell migration. Sondermeijer et al. modified an alginate scaffold with cyclic RGD-peptide to enhance cellular recruitment in vivo. Moreover, scaffolds were seeded with human mesenchymal precursor cells (1 × 10^6 and 3 × 10^6 cells) and patched to the epicardial surface of an infarcted myocardium. Scaffolds with 1 × 10^6 cells showed optimal vascularization, while 3 × 10^6 cells showed a decrease in vascularization, possibly due to “crowding” of the cells. Scaffolds modified with...
only cyclic RGD were furthermore placed in the abdominal area (abdominal rectus muscles) as a control, which showed robust cellularization and vascularization in comparison to the patches containing no cyclic RGD. This displays that materials could be further modified with for example RGD-sequences to further increase cellular retention, cellular recruitment, and proliferation.

To increase the cellular adhesion of CSCs, platelet nanovesicles were used to decorate CSCs that increased adhesion properties of the cells.[133] Intraconoray injection of these CSCs with platelet nanovesicles in an infarcted porcine heart showed an increase in cellular retention after 24 h, in comparison to no platelet nanovesicle decoration.

These studies show that addition or modification of hydrogels with small molecules or peptides can lead to significant increases of adhesion to the surrounding tissue and cellular recruitment. This can furthermore increase the therapeutic effectiveness.

4. Off-Target Effects

Possible off-target effects of injected materials are a parameter often overlooked. Multiple types of hydrogel systems contain drug cargos, which can be released from the hydrogel in a sustained manner to target the surrounding area. Possible redistribution and complementary side-effects of the injectate material, the cargo, or both are often neglected.

Few studies focused on the redistribution of cells when injected in the myocardial infarcted area. Bone marrow cells labeled with 99mTc showed a retention of approximately 17% at the infarct site of rats 24 h after injection.[130] Most cells injected were found in the liver (>20%), and less abundantly in the spleen (~8%), and kidneys (~6%). Furthermore, intravenously injected endothelial progenitor cells labeled radioactively with 111indium oxine showed a retention of approximately 1% in a rat heart 96 h after injection. Most redistributed cells were found in the spleen and liver (~70%).

A combination of human mesenchymal stem cells and fibrin hydrogel was injected intramyocardial in an infarction model and examined 90 min post-injection.[132] The cellular retention was approximately 40% combined with fibrin hydrogel, with approximately 40% of the cells redistributed to the lungs, whereas only cells in saline showed approximately 20% cardiac retention. The cells in saline showed a redistribution of 40% to the liver, whereas the cells in combination with the fibrin glue showed a redistribution of 20%. Cellular redistribution for the saline injections was shown in the kidneys (~9%) and spleen (~5%), whereas almost no redistribution was shown in these organs when the cells were encapsulated in the hydrogels. In our group, we showed a ureido-pyrimidinone-based hydrogel that was labeled with a radioactive tracer ([111]Indium), traceable in vivo.[133] Here, a small pilot showed the redistribution 4 h after injection in a healthy porcine heart, with 8% of the hydrogel being retained at the inject spot, whereas a high content redistributed to the lungs (29% n = 1, 9.5% n = 2) and bladder and urine (16% n = 1, 22% n = 2). When the hydrogel was modified with a recombiant collagen type-1 based material, cardiac retention was around 16% after 4 h, displaying redistribution of the hydrogel mainly to the lungs (13% n = 1, 19% n = 2), as well as the bladder and urine (10% n = 1, 13% n = 2). It should be noted that the injection in a healthy porcine heart could differ from retention in an infarction model.

These studies show possible redistribution of the injectate, and possible corresponding off-target effects. A screening of material redistribution can give a broader comprehension of the possible side-effects.

4.1. Retention and Redistribution Evaluation

As mentioned previously, only a limited amount of studies focus on visualizing the retention and redistribution of hydrogels in vivo. Several imaging methods are challenging, with fluorescence imaging having a low penetration depth, single-photon emission computed tomography (SPECT-CT) imaging often needs a tracer in combination with radiation dosage being received, and magnetic resonance imaging (MRI) being less quantifiable (Figure 5).[134] Furthermore, labeling with fluorophores or contrast agents can influence the properties of the hydrogels.[135]

Hydrogels are often labeled with fluorophores, whereafter the hydrogel content can be visualized ex vivo,[7,16,57,95,136] While this gives an indication on the injectate remnants and degradation, it is unclear how much of the total injectate volume is retained at the injection site, and how much of the injectate is redistributed to other organs.

Bakker et al. showed a pH-responsive hydrogel, being a viscous liquid at a pH of 9, facilitating injection at basic conditions, whilst gelating under physiological conditions at neutral pH.[137] A DOTA-gadolinium(III) label was added to hydrogel to allow MRI analysis of the gel, which was injected in a healthy porcine heart in vivo with a volume of 0.2 mL. The injected hydrogel was visualized ex vivo and post-injection volume analysis showed matching pre-injection volume, indicating retention of the hydrogel in vivo.

With SPECT-CT, a hyaluronic acid-based hydrogel was imaged upon addition of a contrast agent (iohexol) after being injected in an infarcted porcine model.[138] Nine injections of 0.1 mL hydrogel were performed, and directly after injection, the location was verified in vivo. The in vivo degradation rate and hydrogel amount retained at the injection site were unknown, making it challenging to link the hydrogel content in vivo to the therapeutic effect. Redistribution of an alginatetype hydrogel was examined by radio-metal indium-111 labeling, which enabled non-invasive in vivo nuclear imaging of the hydrogel.[139] An intra-myocardial injection was performed in mice and imaged over a week, with a volume of 50 μL containing 2% (w/v) alginate hydrogel, imaged over 7 days after injection. At 2 h post-injection, the majority of injected alginate was not retained in the heart and was cleared from the body. Redistribution was observed mainly in the kidney and bladder. After 7 days, a fraction of approximately 4 to 8% of the material was still observed in the heart, which clarifies the importance of biomaterial tracking in vivo.

The detection of biomaterials post-injection is feasible, but determination of the retention and redistribution of these
biomaterials is challenging, with only a handful of studies examining these biomaterial retention and remnants in vivo. These characteristics, however, are of significant importance when linking the therapeutic effect of the biomaterials to the retention post-injection.

5. Conclusion

Scientific development for cardiac therapies has shown great progress, with medicine in combination with biomaterials, as well as biomaterials alone showing therapeutic benefits. A
deeper understanding of the effectiveness of these biomaterials in the cardiac environment could be obtained by considering parameters that influence their retention, such as injection timing, cardiac contraction, and material characteristics at the target site (Figure 6).

Thus, while current injectable biomaterials are already demonstrating a significant improvement in cardiac functioning, visualization of the biomaterials in vivo illuminates the retention at the target site, from which the optimal biomaterial-dependent injection volume could be determined. Furthermore, the aspect of redistribution should be considered, which can predict possible side-effects. The drug dosage could be adapted to complement the retention of the biomaterial.

We propose a focus change to explore the direct role of the biomaterial in cardiac therapies, instead of investigating indirect parameters considering the cardiac response. Only by creating a deeper understanding of the exact dosing and functioning of the biomaterials in vivo, further innovation in biomaterial design can enhance therapeutic efficacy of the injectate in locally administered medicine after MI.

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Conflict of Interest
The authors declare no conflict of interest.

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