Acta Biomaterialia 7 (2011) 1–15

Contents lists available at ScienceDirect

Acta Biomaterialia

journal homepage: www.elsevier.com/locate/actabiomat

Review

Intra-myocardial biomaterial injection therapy in the treatment of heart failure: Materials, outcomes and challenges

Devin M. Nelson [a], Zuwei Ma [b,c], Kazuro L. Fujimoto [b,c], Ryotaro Hashizume [b,c], William R. Wagner [a,b,c,*]

[a] Department of Bioengineering, University of Pittsburgh, Pittsburgh, PA, USA
[b] McGowan Institute for Regenerative Medicine, University of Pittsburgh, Pittsburgh, PA 15219, USA
[c] Department of Surgery, University of Pittsburgh, Pittsburgh, PA, USA

ARTICLE INFO

Article history:
Received 13 May 2010
Received in revised form 25 June 2010
Accepted 29 June 2010
Available online 07 July 2010

Keywords:
Injectable biomaterial
Myocardial infarction
Cardiac tissue engineering
Hydrogels
Thermoresponsive polymer

ABSTRACT

Heart failure initiated by coronary artery disease and myocardial infarction (MI) is a widespread, debilitating condition for which there are a limited number of options to prevent disease progression. Intra-myocardial biomaterial injection following MI theoretically provides a means to reduce the stresses experienced by the infarcted ventricular wall, which may alter the pathological remodeling process in a positive manner. Furthermore, biomaterial injection provides an opportunity to concurrently introduce cellular components and depots of bioactive agents. Biologically derived, synthetic and hybrid materials have been applied, as well as materials designed expressly for this purpose, although optimal design parameters, including degradation rate and profile, injectability, elastic modulus and various possible bioactivities, largely remain to be elucidated. This review seeks to summarize the current body of growing literature where biomaterial injection, with and without concurrent pharmaceutical or cellular delivery, has been pursued to improve functional outcomes following MI. The literature to date generally demonstrates acute functional benefits associated with biomaterial injection therapy across a broad variety of animal models and material compositions. Further functional improvements have been reported when cellular or pharmaceutical agents have been incorporated into the delivery system. Despite these encouraging early results, the specific mechanisms behind the observed functional improvements remain to be fully explored and future studies employing hypothesis-driven material design and selection may increase the potential of this approach to alleviate the morbidity and mortality of heart failure.

1. Introduction

A diverse array of treatment methods and technologies has been developed in an attempt to alleviate the morbidity and mortality associated with cardiac failure [1]. With coronary artery disease contributing to two out of three cases of heart failure, interventional procedures that seek to revascularize the myocardium through coronary artery bypass grafting and coronary stent placement have become both common and highly effective following myocardial infarction (MI) [2,3]. Cardiac pacing in appropriate patients has been shown to increase the energy efficiency of the heart [4]. Pharmacological regimens are useful to improve systolic performance and decrease workload [5,6]. The gold standard for those with end-stage heart failure remains cardiac transplantation, but donor hearts far outstrip the number of people who could benefit from transplantation [7]. To address this need, ventricular assist device implantation can take over the pumping function of the ventricle by independently circulating blood in late stage heart failure patients [8,9]. Biomaterials development has played a critical role in the creation of medical devices that have advanced heart failure treatment, from membrane oxygenator microporous hollow fibers to stents and stent coatings, prosthetic heart valves, pacing leads and many other devices. An area of cardiovascular biomaterials research and development that has opened and grown over the past decade is the investigation of injectable biomaterials to treat cardiac failure [10]. This area of development has grown largely in parallel with cell injection therapy, but it has become clear that the mechanical effects that may be achieved with ventricular biomaterial injection may be beneficial independently of cellular delivery.

2. Mechanical approaches to heart disease

Myocardial infarction sets off a series of complicated processes, including cell death, scar formation and ventricular dysfunction, that alter both the cellular, structural and mechanical properties of the heart [11–13]. Not only does the heart lose systolic capacity

* Corresponding author at: McGowan Institute for Regenerative Medicine, University of Pittsburgh, Pittsburgh, PA 15219, USA. Tel.: +1 412 624 5324; fax: +1 412 624 5363.
E-mail address: wagnerwr@upmc.edu (W.R. Wagner).

1742-7061/$ - see front matter © 2010 Acta Materialia Inc. Published by Elsevier Ltd. All rights reserved.
doi:10.1016/j.actbio.2010.06.039

due to a decrease in the amount of functional myocardium after MI, simple geometric changes that take place in remodeling also play a role in heart failure progression. As pumping efficiency decreases, blood backs up in the left ventricle (LV), leading to increased intraventricular pressures contributing to LV dilation (Fig. 1). While the initial dilation following infarction is believed to be a coping mechanism by which cardiac output can be maintained through the Frank–Starling mechanism, it has been shown that over time the cardiomyocytes lose the ability to respond with increased contractility when stretched, resulting in a dilated, underperforming ventricle [14]. Ventricular dilation in terms of LV sphericity, and particularly LV volume, is strongly linked to poor outcomes following MI [15,16].

Pathological LV dilation is propagated through a positive feedback loop with LV wall stress [13,17]. This stress is the preload against which the cardiomyocytes must contract during systole. As this stress increases due to stretching from dilation the cardiomyocytes lose the capacity to shorten effectively, leading to further stretching and continued decreases in cardiac pumping efficiency, quantified as the ejection fraction (EF). The physics behind this unfortunate positive feedback system can be explained in part by the Law of Laplace, where the stress in the wall of a round chamber (T) is directly related to the pressure in the chamber (P), the radius of curvature (R) and the thickness of the wall (h), as shown in Eq. (1):

$$T = \frac{PR}{h} \tag{1}$$

During the ventricular remodeling process following an MI, pressure and radius increase and the LV free wall thins. This increases the cardiac wall stress, which ultimately leads to more dilation, thinning and stress. The heart can proceed down a pathway towards end-stage heart failure where transplantation, hospice care or ventricular assist device implantation are the only options.

Many treatments exist that use mechanical approaches to discourage cardiac dilation, restore geometry and reduce ventricular wall stress and thinning [18]. Cardiac restraint devices such as the CorCap (Acorn Cardiovascular Inc.) and HeartNet (Paracor Medical Inc.) employ Dacron and nitinol wraps, respectively, to provide physical support for the failing ventricular wall (Fig. 2) [19–22]. Experimental devices such as the Myosplint (Myocor Inc.) and CardioClasp (CardioClasp Inc.) force a dilated ventricle into two smaller lobes to reduce the intraventricular radius and thereby decrease wall stress [23,24]. Advanced surgical procedures such as endoventricular patch plasty (the Dor procedure) and partial left ventriculectomy (the Batista procedure) physically restructure a spherical, dilated ventricle into a more natural elongated shape [25,26]. While involving highly invasive procedures, these methods have demonstrated some clinical efficacy, even in chronic heart failure patients. An elastic cardiac patch based on degradable porous polyurethane was shown to halt LV dilation when sutured onto the epicardium. This material prevented further dilation and was also associated with the formation of a new smooth muscular layer in the infarction zone, possibly due to the stress shielding provided by the patch [27].

The use of biomaterials for cardiac repair has primarily focused on applications where the material is anchored to and interacts with the outer edges of the myocardium to provide support. Incorporating the material completely within the heart wall is an alternative approach, where direct contact with cardiac cells occurs as the material acts as a bulking agent for the heart wall. Generally, materials are delivered through direct epicardial injection at distinct locations in and around the infarct, leading to focal points of biomaterial presence (Fig. 3). Current methods for direct injection require sternotomy or thoractomy, although thorascopic or intravascular procedures could be feasible to decrease procedure-related morbidity. Not only may the injected material alter the mechanical environment upon injection, but appropriate biomaterials can have biological functions that encourage cardiac repair. Functions such as angiogenesis, cardiomyocyte protection and stem cell recruitment may be another primary means to improve the efficacy of material injections for treating heart disease.

In 2006 a report by Wall et al. utilized a finite element model to evaluate the theoretical effect on cardiac wall stress of injecting a non-contractile biomaterial into the LV wall [28]. The injected volume changes the LV geometry by increasing the wall thickness, thus lowering local wall stress. The simulation showed that injection of a volume of 4.5% of the total LV wall volume and with a stiffness of 20% of the natural LV tissue into the infarct border zone could decrease the wall fiber stress in the border zone by 20% compared with a control simulation in which there was no injection

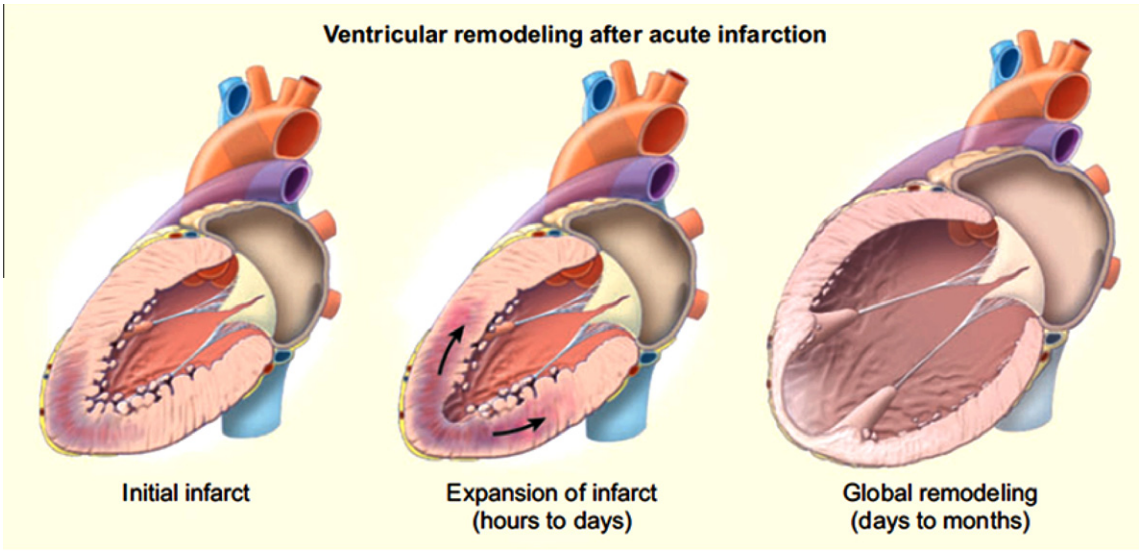

Fig. 1. Ventricular dilation associated with progressive heart failure. After the initial insult, infarct expansion and ventricular wall thinning contribute to further ventricular remodeling, ultimately causing increased intraventricular pressure and decreased cardiac output. (From Jessup and Brozena [1].).