Journal of Molecular and Cellular Cardiology xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Journal of Molecular and Cellular Cardiology

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

Review article

Modifying the mechanics of healing infarcts: Is better the enemy of good?

Samantha A. Clarke [a], William J. Richardson [a,c], Jeffrey W. Holmes [a,b,c,*]

[a] Department of Biomedical Engineering, University of Virginia, United States
[b] Department of Medicine, University of Virginia, United States
[c] Robert M. Berne Cardiovascular Research Center, University of Virginia, United States

ARTICLE INFO

Article history:
Received 16 September 2015
Received in revised form 9 November 2015
Accepted 26 November 2015
Available online xxxx

Keywords:
Biomechanics
Computational modeling
Extracellular matrix
Heart
Myocardial infarction

ABSTRACT

Myocardial infarction (MI) is a major source of morbidity and mortality worldwide, with over 7 million people suffering infarctions each year. Heart muscle damaged during MI is replaced by a collagenous scar over a period of several weeks, and the mechanical properties of that scar tissue are a key determinant of serious post-MI complications such as infarct rupture, depression of heart function, and progression to heart failure. Thus, there is increasing interest in developing therapies that modify the structure and mechanics of healing infarct scar. Yet most prior attempts at therapeutic scar modification have failed, some catastrophically. This article reviews available information about the mechanics of healing infarct scar and the functional impact of scar mechanical properties, and attempts to infer principles that can better guide future attempts to modify scar. One important conclusion is that collagen structure, mechanics, and remodeling of healing infarct scar vary so widely among experimental models that any novel therapy should be tested across a range of species, infarct locations, and reperfusion protocols. Another lesson from past work is that the biology and mechanics of healing infarcts are sufficiently complex that the effects of interventions are often counterintuitive; for example, increasing infarct stiffness has little effect on heart function, and inhibition of matrix metalloproteases (MMPs) has little effect on scar collagen content. Computational models can help explain such counterintuitive results, and are becoming an increasingly important tool for integrating known information to better identify promising therapies and design experiments to test them. Moving forward, potentially exciting new opportunities for therapeutic modification of infarct mechanics include modulating anisotropy and promoting scar compaction.

Contents

* Corresponding author at: Department of Biomedical Engineering, University of Virginia Health System, Box 800759, Charlottesville, VA 22908, United States.
E-mail address: holmes@virginia.edu (J.W. Holmes).
URL: http://bme.virginia.edu/holmes/index.html (J.W. Holmes).

http://dx.doi.org/10.1016/j.yjmcc.2015.11.028
0022-2828/

1. Introduction

The articles in this special issue attest to the wealth of knowledge now available regarding the biology of cardiac extracellular matrix synthesis, degradation, and remodeling, as well as the complex inflammatory and wound healing processes that occur in response to cardiac injury. Building on this knowledge, it may soon be possible to selectively manipulate the composition, structure, and mechanical properties of healing post-infarction scar tissue. Yet such therapies must be designed with particular care, because post-infarction scar plays the essential role of maintaining the mechanical integrity of the heart. Prior interventions that intentionally or accidentally modified scar structure frequently produced unexpected, even counterintuitive results, illustrating the difficulty of intervening in the complex, evolving network of biological, chemical, and mechanical interactions that govern scar structure. The goal of this review is to first outline what is known about the structure and mechanical properties of healing post-infarction scar; then to discuss how those properties affect likelihood of rupture, depression of pump function, and long-term remodeling leading to heart failure; and finally to formulate principles that could help guide the design of future interventions.

2. Mechanical properties of healing myocardial infarcts

Following occlusion of a coronary artery, the affected myocardium stops contracting within minutes [1] and myocytes begin to die within hours [2]. Over the next several weeks, dead myocytes are gradually removed through an inflammatory response and replaced by collagenous scar tissue generated by fibroblasts. The evolving mechanical properties of the healing infarct are an important determinant of several of the most important complications of myocardial infarction, including infarct rupture, depression of pump function of the infarcted left ventricle (LV), and LV remodeling leading to heart failure. Infarct mechanical properties appear to be determined primarily by the amount and organization of large collagen fibers; accordingly, in addition to direct mechanical testing, histologic studies of collagen structure can provide some insight into how infarct mechanical properties evolve during the natural course of healing. Available data suggest remarkable variability across animal models, complicating efforts to test interventions designed to alter infarct structure or mechanics.

2.1. Collagen content and structure in healing infarcts

Collagen content begins to rise 4–7 days after infarction and typically reaches a plateau by 3–6 weeks, depending on the animal model. Following coronary ligation, collagen area fraction (the fraction of a histologic section occupied by collagen) rises from 3% to approximately 30% in the rat [3] and 60% in the pig [4] and dog [5]. Biochemical estimates of collagen content based on hydroxyproline concentration tend to be slightly lower but show a similar disparity among animal models, ranging from 25% collagen by weight in mature rat infarcts [3,6] to 40–50% (55–70 μg hydroxyproline/mg dry weight) in dogs [7] and sheep [8]. In addition to collagen content, the degree of crosslinking of the collagen molecules can affect tissue mechanical properties. Studies of crosslinking during infarct healing suggest that crosslink density initially rises with a similar time course to collagen, but may continue to rise even after collagen content plateaus [3,9,10].

Early studies of infarct healing focused on collagen content, but the arrangement of collagen fibers within the healing infarct is also an important determinant of mechanical properties. When the heart is pressurized, the wall is under tension in the circumferential and longitudinal directions; collagen fibers in healing infarcts lie in planes parallel to the epicardium, where they resist this tension [11]. Following coronary ligation in dogs [5,12] and pigs [4], collagen fibers in the midwall are strongly aligned in the circumferential direction (Fig. 1), while at the epicardium and endocardium collagen is oriented obliquely and less strongly aligned [4,5]. By contrast, Fomovsky reported that coronary ligation in rats produces structurally and mechanically isotropic infarcts in which collagen fibers at any depth are randomly oriented in the circumferential-longitudinal plane (Fig. 1) [3].

Compared to large-animal models, the standard coronary ligation model in the rat tends to create larger infarcts that involve more of the LV, including the apex. To investigate the potential influence of infarct location on scar structure, Fomovsky and colleagues used liquid-nitrogen-cooled probes to create cryoinfarcts in different locations on the rat LV [11]. They found that infarcts in different locations experienced different patterns of stretch, which correlated with the collagen fiber structure 3 weeks later. Infarcts at the apex stretched similarly in both the circumferential and longitudinal directions during healing and formed scars with randomly oriented collagen fibers; those near the equator stretched primarily in the circumferential direction and contained circumferentially aligned collagen fibers. Therefore, differences in regional mechanics during healing may explain the different collagen fiber structures reported in different animal models, although the basis for the large reported differences in collagen content remains unclear. It is also unclear whether human infarcts show similar variation in collagen fiber structure with infarct location. Further complicating the question of the relevance of various animal models to human disease, most animal work is conducted in young animals and therefore ignores potentially important effects of aging on ECM biology [13].

2.2. Mechanical properties of healing infarcts

There are two experimental approaches for assessing the mechanical properties of healing infarcts. One option is to excise infarct tissue and perform direct *ex vivo* mechanical tests. The major advantage of this approach is the ability to directly measure applied forces and resulting stretches; the disadvantage is that excision can alter mechanics due to loss of coronary perfusion pressure and/or myocyte contracture induced by cutting injury and reduced oxygenation. The alternative is to track pressures, geometry, and deformation in the intact heart, and use formulas or computational models to estimate the forces acting on the infarct. This approach maintains perfusion and viability of surviving myocardium, and allows tracking of changes over time in individual animals. However, the estimates of *in situ* forces depend strongly on the model employed to calculate them, and cannot be experimentally verified.

2.2.1. In vivo deformation

Most early studies of infarct mechanics focused on *in vivo* deformation. Tyberg et al. sutured strain gauges to the surface of the canine LV and plotted gauge length in the fiber direction against LV pressure [14]. Prior to occlusion, these plots traced out counterclockwise loops reminiscent of pressure–volume loops, with segment length increasing during diastolic filling, decreasing during ejection, and remaining nearly constant during isovolumic contraction and relaxation. Following occlusion of the coronary artery supplying the study region, the area inside the pressure-length loops rapidly decreased – reflecting the loss of active mechanical work by the muscle fibers – and segments began to

Please cite this article as: S.A. Clarke, et al., Modifying the mechanics of healing infarcts: Is better the enemy of good?, J Mol Cell Cardiol (2015), http://dx.doi.org/10.1016/j.yjmcc.2015.11.028