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Nanoparticles administered intrapericardially enhance payload myocardial distribution and retention

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ABSTRACT

Pharmacological therapies for cardiovascular diseases are limited by short-term pharmacokinetics and extracardiac adverse effects. Improving delivery selectivity specifically to the heart, wherein therapeutic drug levels can be maintained over time, is highly desirable. Nanoparticle (NP)-based pericardial drug delivery could provide a strategy to concentrate therapeutics within a unique, cardiac-restricted compartment to allow sustained drug penetration into the myocardium. Our objective was to explore the kinetics of myocardial penetration and retention after pericardial NP drug delivery. Fluorescently-tagged poly(lactic-*co*-glycolic acid) (PLGA) NPs were loaded with BODIPY, a fluorophore, and percutaneously administered into the pericardium via subxiphoid puncture in rabbits. At distinct timepoints hearts were examined for presence of NPs and BODIPY. PLGA NPs were found non-uniformly distributed on the epicardium following pericardial administration, displaying a half-life of ~2.5 days in the heart. While NPs were mostly confined to epicardial layers, BODIPY was capable of penetrating into the myocardium, resulting in a transmural gradient. The distinct architecture and physiology of the different regions of the heart influenced BODIPY distribution, with fluorophore penetrating more readily into atria than ventricles. BODIPY proved to have a long-term presence within the heart, with a half-life of ~7 days. Our findings demonstrate the potential of utilizing the pericardial space as a sustained drug-eluting reservoir through the application of nanoparticle-based drug delivery, opening several exciting avenues for selective and prolonged cardiac therapeutics.

1. Introduction

Limited cardiac specificity of systemically-administered drugs severely dampens therapeutic efficacy and increases adverse side effects. Advances in catheter-based approaches have enabled strategies aimed at local delivery of therapeutics, including intracoronary [1,2] and intramyocardial [3] administration. Local delivery overcomes shortcomings associated with systemic delivery by amassing drugs at the site of action, leading to high local concentrations, less required dose, and reduced toxicity. Intracoronary approaches are capable of localizing therapeutics specifically within coronary artery walls, but suffer from inconsistent delivery, rapid washout, and insufficient distribution to the myocardium [4,5]. Intramyocardial delivery results in high myocardial drug deposition [6,7], but is limited by injury to the muscle and poor local retention of injectate over time [8,9].

The fluid-filled pericardial sac represents a unique compartment for local drug delivery, a reservoir that allows for transmural migration of therapeutics into the heart. Pericardial drug delivery has several advantages, chief among them being ease of access, proving a more safe, convenient, and reproducible procedure when compared to other cardiac delivery approaches [10]. Higher local drug concentrations can be obtained in the heart, owing principally to lower clearance rates [7,11]. Consequently, lower doses are required for therapeutic effect, resulting in less systemic exposure of drug, which in turn reduces off-target toxicities [12]. Pericardial delivery has been used to administer a variety of drugs for the treatment of disease, including paclitaxel for

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inhibition of vascular smooth muscle cell proliferation in restenosis [13], procainamide and digitalis for antiarrhythmic therapy [14], and insulin-like growth factor I for treatment of chronic heart failure [15].

Despite the numerous advantages afforded by pericardial drug delivery, clearance by epicardial vasculature and lymphatics presents a challenge to long-term drug retention, with small molecular weight drugs cleared faster than larger peptides and constructs [16]. Nano- and micron-scale particles, ranging in size from 10 to 1000 nm, have been used as local drug depots to enhance and maintain therapeutic levels of drug within their immediate surroundings [17–19]. Formulating drugs within biodegradable nanoparticle (NP) constructs allows for drug stabilization and solubilization, and importantly, prolonged and controllable release profiles of therapeutics over time. With these advantages in mind, nanoparticle-based drug delivery to the heart has been explored previously. Nanoconstructs have been administered intravenously to target failing [20] and ischemic [21–24] hearts, as well as locally through intramyocardial administration for the treatment of infarcts [25,26] and intracoronary delivery for the treatment of in-stent restenosis [27].

Our objective was to examine the potential of exploiting the pericardial space as a reservoir for nanoparticle-based drug delivery to the heart (Fig. 1a and b). Combining sustained release of therapeutics from NPs with low clearance from the pericardium was hypothesized to result in a prolonged, site-specific drug-eluting depot for delivery to the myocardium. Fluorescently-tagged poly(lactic-*co*-glycolic acid) (PLGA) NPs encapsulating a fluorophore, BODIPY, were administered intrapericardially to rabbits and retention and distribution in the myocardium evaluated at different timepoints. PLGA NPs had a sustained epicardial presence for prolonged times, a result of low clearance of the carrier construct from the pericardial space. While NPs did not migrate great distances past the epicardium, BODIPY was capable of permeating deep into the myocardium with pronounced accumulation in the atria and the apex. Both PLGA NPs and BODIPY displayed long-term retention in cardiac tissues, with half-lives on the order of days. Findings from this study highlight the prospect of utilizing pericardial-based delivery of nanotherapeutics for the sustained treatment of a variety of diseases.

2. Materials and methods

2.1. Chemicals and reagents

Ester-terminated (50:50, 0.26–0.54 inherent viscosity, Mn 15,000 Da) and carboxy-terminated (50:50, 0.52–0.75 inherent viscosity, Mn 17,100 Da) PLGA were obtained from Durect Corporation (Birmingham, AL). BODIPY® 630/650-X NHS Ester (BODIPY) was purchased from Life Technologies (Waltham, MA). Cyanine7 (Cy7) amino was purchased from Lumiprobe (Hallandale Beach, FL). Polyvinyl alcohol (PVA, Mw 9000–10,000, 80% hydrolyzed) was purchased from Sigma-Aldrich (St. Louis, MO). All organic solvents were purchased from Thermo Fisher Scientific (Waltham, MA).

2.2. Cy7 labeling of PLGA

Briefly, carboxy-terminated PLGA was dissolved in anhydrous dichloromethane (DCM). Pre-dried triethylamine (TEA) in a DCM

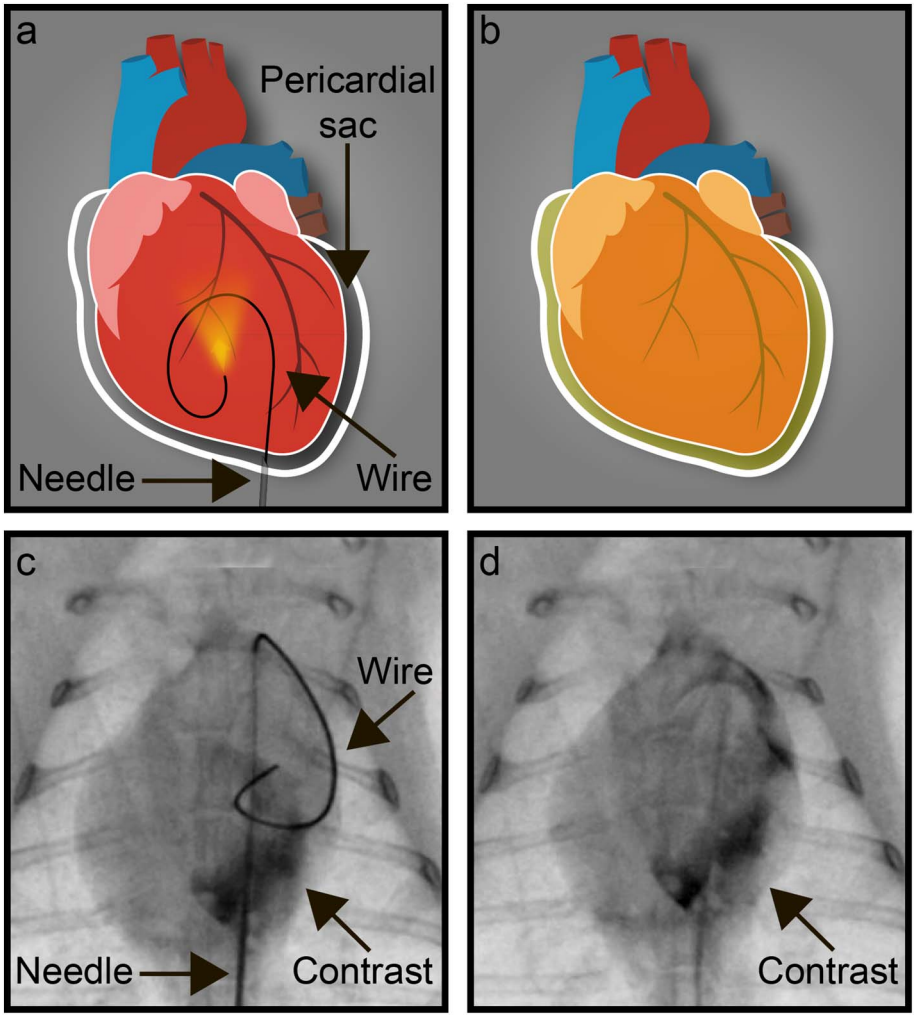

Fig. 1. Pericardial administration of NPs for local, site-specific drug delivery to the heart. a) The pericardial space can be readily accessed with a needle, after which cannulation allows for direct delivery of NPs (yellow) within the compartment. b) NPs (yellow) distribute within the pericardial sac, whose low clearance rate contributes to a sustained release drug reservoir for prolonged exposure of therapeutics to the heart. c) X-ray fluoroscopy image highlighting access of the pericardial space in a rabbit with a micropuncture needle advanced under the sternum, administration of iohexol to direct pericardial entrance, and insertion of a guide wire. d) Radiographic contrast present in the pericardial sac following the procedure. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)