Local Epicardial Inotropic Drug Delivery Allows Targeted Pharmacologic Intervention with Preservation of Myocardial Loading Conditions

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ABSTRACT: Local myocardial application of inotropes may allow the study of pharmacologically augmented central myocardial contraction in the absence of confounding peripheral vasodilating effects and alterations in heart loading conditions. Novel alginate epicardial (EC) drug releasing platforms were used to deliver dobutamine to the left ventricle of rats. Pressure–volume analyses indicated that although both local and systemic intravenous (i.v.) use of inotropic drugs increase stroke volume and contractility, systemic infusion does so through heart unloading. Conversely, EC application preserves heart load and systemic blood pressure. EC dobutamine increased indices of contractility with minimal rise in heart rate and lower reduction in systemic vascular resistance than i.v. infusion. Drug sampling showed that dobutamine concentration was 650-fold higher in the anterior wall than in the inferior wall. The plasma dobutamine concentration with local delivery was about half as much as with systemic infusion. These data suggest that inotropic EC delivery has a localized effect and augments myocardial contraction by different mechanisms than systemic infusion, with far fewer side effects. These studies demonstrate a pharmacologic paradigm that may improve heart function without interference from effects on the vasculature, alterations in heart loading, and may ultimately improve the health of heart failure patients. © 2011 Wiley-Liss, Inc. and the American Pharmacists Association J Pharm Sci 100:4993–5006, 2011

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INTRODUCTION

Classic teaching holds that local delivery avoids the dosing inefficiency of systemic delivery. Intravascular infusion attains whole-body drug exposure rapidly and is ideal for circulating or systemic diseases, but problematic when drug needs to be delivered to specific organs or tissues. In this latter case, systemic administration delivers drug everywhere, reducing the net amount of administered drug that reaches the desired target along with an associated potential for systemic side effects and toxicities. Dose reduction can eliminate the toxic effects but reduces benefit as well. Local application to a site-specific organ or target has the potential to confine drug to the target tissues, potentially reducing cost, side effect, and toxicity. The focus on the detriment of toxic dosing to undesired targets and beneficial effects of targeted administration has obscured other important issues related to local delivery. In particular, emerging data suggest that the high levels of vascularization of some organs will lead to clearance of drug from the target and therefore significant systemic drug concentrations.[1,2] The question then arises as to whether and why local delivery can demonstrate beneficial effects even at doses that lead to detectable drug in the periphery. Is it possible, for example, that there is a fundamentally different pharmacologic effect or differential pharmacokinetics for systemic infusion and local delivery?

Inotropic therapies for heart failure offer a perfect example of the complexity of local delivery. The cardiovascular system involves organs of complex structure but also a linked system where effects on one organ element elicit reflex responses throughout the

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system. Changes in myocardial function induce reflex effects on the entire vasculature, and alterations in vascular tone change the loading conditions on the heart. Thus, local cardiovascular drug delivery can affect organs at a distance through a direct contact effect as drug is rapidly transported from local site through the arterial system, and indirectly as a result of rapid reflex responses to cardiac output, tissue perfusion, and myocardial loading conditions. Moreover, the density and variety of receptors and target proteins for the same drug can vary widely. Adrenergic receptor subtype differs in the heart (β1) and blood vessels (β2) and response to the same stimuli is mediated through different pathways in the myocardium (stimulatory G proteins) and vasculature (inhibitory and stimulatory G proteins).[3–5] Systemic toxicity is indeed reduced with reduction of systemic dose but there might well be a benefit to local delivery that transcends reduction in toxicity.

We postulate therefore that the local administration of drugs that affect myocardial contraction will not only enhance the therapeutic window for these drugs but also potentially allow them to act in a more selective manner. Local delivery might not only reduce toxicity from high doses but induce physiologic responses that are distinctly different than systemic infusion. We created a model system, which divorced the central contractile effects of inotropic drug therapy from the arterial-dilating peripheral effects using a local polymeric controlled epicardial (EC) release preparation, which delivered drug to the outer surface of the heart. Biconcave calcium-cross-linked alginate disks released dobutamine to the heart surface with zero-order kinetics over a wide range of controlled rates. These alginate drug delivery devices allowed us to compare the dose response of local EC dobutamine application with that of intravenous (i.v.) infusion, in terms of indices of contractility and peripheral side effect, which were assessed using Millar left ventricular pressure–volume (PV) conductance catheters in healthy adult rats.[6,7] These experiments allowed us to study the impact of drugs on the myocardium itself, without the confounding effects of altered loading conditions.

MATERIALS AND METHODS

Fabrication and *In Vitro* Characterization of EC Inotrope Delivery Platform

A novel system for precisely controlling the rate of dobutamine release to the EC surface of the heart over a wide range of doses allowed characterization of the dose response for comparison to i.v. infusion. EC drug releasing platforms were constructed from calcium-cross-linked alginate hydrogels[8–10] and served to apply drug over the anterior surface of the rat heart. Alginate (#71238; Sigma–Aldrich, St. Louis, MO) disks were made by cross-linking 45 μL of a 2% slurry in double-distilled water (ddH_2 0) at room temperature in the upper chamber of a transwell permeable coculture support (6.5 mm, polyester, 3 μm pore size, #3472; Corning, Corning, NY). The transwell support was immersed in 1 mL of 3% $CaCl_2$ in ddH_20 for 1.5 h using a leveled 24-well culture plate (#353047, 15.75 mm; Corning). The meniscus in the original alginate slurry along the walls of the transwell support was preserved during calcium-cross-linking, so the resulting concave disk had a minimal thickness at the center of 0.6 mm and a maximal thickness along the edge of 1.4 mm. The alginate slabs were removed from the transwell support by carefully cutting away the polyester membrane. Drug added in liquid solution to the top of the concave alginate disk diffuses across and is released out through the bottom. The calcium was removed from the concave disks prior to use *in vitro* or *in vivo* by soaking in 40 mL of ddH_20 for 1.5 h.

Preliminary experiments showed that starting with 1.5% alginate yielded flimsy hydrogels that lacked mechanical integrity, whereas 2.5% and 3% alginate produced hydrogels that were too rigid to conform to the heart surface. Other preliminary experiments showed that the 6.5 mm diameter produced devices that fit the heart surface better than 12 mm diameter hydrogels. The final weight of the devices were minimized to allow it to stay on the heart while beating, yet provided a reasonable minimal thickness in the center of the concavity to provide mechanical resilience and prevent an initial burst release of drug.

The *in vitro* release of dobutamine from calcium-cross-linked concave alginate disks was characterized (Fig. 1a). The alginate disk was placed into a new transwell support, which was immersed in ddH_20 (340 μL) in the lower chamber of a 24-well culture plate. The culture plate was placed on a rocker platform (20 rpm). In separate experiments, a 5 μL volume of dobutamine (1.39, 2.08, 3.125, 4.69, 6.25, 9.38, or 12.5 mg/mL in ddH_20; Hospira, Lake Forest, IL) was placed on the upper surface of the alginate disk. Samples for drug concentration measurements (60 μL) were withdrawn at three time points. These relatively large volumes were needed to meet the sensitivity of the detection assay; however, they limited the number of samples that could be withdrawn from the small-volume lower drug-receiving chamber. In order to increase the temporal resolution of the measured drug release kinetics, parallel experiments were performed so that in one set, samples were taken at 5, 9, and 13 min and in another, samples were withdrawn at 7, 11, and 15 min. Each of these experiments was repeated for each concentration of applied dobutamine eight times.