


unwanted effects of the gene product. Our aim was to develop an extracorporeal delivery system that would deliver a vector to our target organ, the heart, with little or no systemic leakage. Recirculation of the vector would allow even distribution of the vector through the target organ.

METHODS

A low volume extracorporeal circuit was designed using commercially available components. Using an ovine pacing induced heart failure model, the animals were placed on percutaneous extracorporeal cardiac support via a 9 Fr cannula in the Left coronary artery (LCA) and a novel 9Fr cannula in the Coronary Sinus (CS). After establishing cardiac support and stabilizing the subject. The vector was introduced into the circuit and recirculated for 10 minutes. At the end of this period to prevent the vector entering the systemic circulation, the circuit was emptied into a collection bag.

RESULTS

We delivered adenovirus (3.5x10^12 vp) encoding a pseudophosphorylated mutant PLN (AdS16EPLN, n = 9) or AdLacZ (n = 6, 4.7x10^12 vp) to sheep with pacing induced HF. Despite 2 weeks further pacing, treatment with adenS16E PLN significantly improved contractile function despite ongoing pacing stress and prevented ventricular remodeling in contrast to AdLacZ animals.

<table>
<thead>
<tr>
<th>Parameter (% change vs baseline)</th>
<th>AdS16EPLN</th>
<th>AdLacZ</th>
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</thead>
<tbody>
<tr>
<td>LV End Diastolic Area</td>
<td>−14**</td>
<td>+13**</td>
</tr>
<tr>
<td>LV Ejection Fraction</td>
<td>.87+++</td>
<td>−23*</td>
</tr>
<tr>
<td>LV End Diastolic Pressure</td>
<td>−24*</td>
<td>+5</td>
</tr>
<tr>
<td>dP/dt</td>
<td>+31*</td>
<td>−5</td>
</tr>
</tbody>
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*p < 0.05, **p < 0.01, ***p < 0.001

CONCLUSIONS

Together the deployment of targeted delivery strategies and targeted molecular therapy has major potential for the treatment of heart failure. The V-Focus system is capable of delivering a vector to a target organ with little systemic leakage.

Thrombin Inhibitors and Cardiopulmonary Bypass

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INTRODUCTION

Unfractionated heparin (UFH) has almost always been the drug chosen for controlled anticoagulation in cardiac surgery (1). Coronary artery bypass grafting (CABG) was first undertaken in 1953 (2). Off-pump coronary artery bypass surgery (OPCAB) has not been established as definitively superior to CABG using cardiopulmonary bypass (CPB). Important complications with either technique include death, perioperative myocardial infarction, bleeding, stroke, defects in postoperative neurocognitive function, and renal failure and are still relatively frequent compared with other common operations (3).

There are many factors in the causation of these problems (4–6). The management of anticoagulation may affect the complex interplay between the endothelium, drugs, the coagulation cascade and the inflammatory response which characterizes all cardiac surgery (7).

LIMITATIONS OF HEPARIN AND PROTAMINE

Unfractionated heparin is an animal extract of variable composition and activity. It has been associated with platelet activation and dysfuncion and with the inflammatory response to surgery and cardiopulmonary bypass (8).

Unfractionated heparin binds to and augments antithrombin III (antithrombin) and heparin cofactor II. Antithrombin inhibits factors IIa (thrombin) and Xa (and to a lesser extent IXa, XIa, and XIIa). Heparin cofactor II also inhibits thrombin. The ratio of anti-IIa activity produced by UFH to the anti-Xa activity is 1. Unfractionated heparin is only effective against thrombin in the fluid phase. Platelet bound factor Xa is also protected from inhibition by the heparin/antithrombin complex (9). In addition, heparin is neutralized by platelet factor 4 (PF4) and high-molecular-weight multimers of van Williebrand factor released from active platelets.

Resistance to heparin may develop, typically by depletion of the antithrombin needed for its activity. Congenital antithrombin deficiency is rare. Acquired antithrombin deficiency may be associated with certain chemotherapeutic regimens, nephrotic syndrome, liver failure, pre-eclampsia, shock, disseminated intravascular coagulation and chronic or excessive...