

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 (3.5×10^{12} vp) encoding a pseudophosphorylated mutant PLN (AdS16EPLN, $n = 9$) or AdLacZ ($n = 6$, 4.7×10^{12} vp) to sheep with pacing induced HF. Despite 2 weeks further pacing, treatment with adenoS16E PLN significantly improved contractile function despite ongoing pacing stress and prevented ventricular remodeling in contrast to AdLacZ animals.

| Parameter (% change vs baseline) | AdS16EPLN | AdLacZ |
|----------------------------------|-----------|--------|
| LV End Diastolic Area | -14** | +13** |
| LV Ejection Fraction | -87*** | -23* |
| LV End Diastolic Pressure | -24* | +5 |
| dP/dt | +31* | -5 |

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

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 dysfunction 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 von Willebrand 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

heparin administration. It is usually relatively easily managed by the administration of plasma (or, if available antithrombin concentrate) (10).

Heparin releases PF4 from endothelial cells, and forms complexes with it which bind to the surface of platelets and activate them. Antibodies may form and interact with these complexes. Anaphylactic reactions to heparin are uncommon, but antibodies to the heparin/PF4 complex are seen more often, and may be prothrombotic, predict myocardial infarction (MI) during acute coronary syndromes (11–13) and be a risk factor for 30 day mortality following cardiac interventions (14,15). These antibodies lead to heparin induced thrombocytopenia (HIT) (16) with thrombosis in 1%–3% of these cases (7,17). The use of heparin is contraindicated in HIT.

Protamine is also an animal extract, and is prone to anaphylactoid and anaphylactic reactions. It has a short half-life (4.5 minutes) (18) which predisposes to un-opposed heparin effects post-operatively. It stimulates the systemic inflammatory response when complexed with heparin (19,20). These two drugs in combination probably contribute to excessive bleeding after cardiac surgery in some patients. Heparin is difficult to use for CPB without protamine.

Options for anticoagulation in cardiac surgery when heparin or protamine is contraindicated include:

- Low molecular weight heparins (LMWHs: e.g., nadroparin, enoxaparin, and dalteparin) (16,21–24);
- Danaparoid (a mixture of the heparinoids heparan, dermatan, and chondroitin sulfate) (25);
- Ancrod (a serine protease isolated from the Malayan pit viper) (26);
- Antiplatelet drugs (aspirin and dipyridomole (27–29);
- Iloprost (a stable prostacyclin analogue with a half-life of 15–30 minutes) (27); Platelet glycoprotein (GP) IIb/IIIa antagonists (e.g., tirofiban) (30–31);
- Delay of surgery (32);
- Direct thrombin inhibitors (e.g., the uivalent argatroban, efegatran and inogatran, and the bivalent hirudin and bivalirudin).

DIRECT THROMBIN INHIBITORS

The direct thrombin inhibitors bind directly and specifically to thrombin. They do not require antithrombin, platelet factor II, or any other cofactor for their effect.

Hirudin (lepirudin, Refludan[®]) is a 65 amino-acid polypeptide originally isolated from leech saliva. Its amino-terminal domain interacts with the active site of thrombin and its acidic carboxyterminal domain binds to exosite 1 of thrombin (9) forming an irreversible 1:1 complex. Recombinant hirudin lacks a sulphated tyrosine residue at position 63, and is therefore called desulfatohirudin or desirudin (Revasc[®]). Desirudin's affinity for thrombin is lower. Desirudin is eliminated by the kidney; it has a plasma half-life of about 60 minutes which is prolonged in renal insufficiency (9). Dialysis requires a polymethyl-methyl acrylate (PMMA) membrane. Desirudin is a protein and therefore potentially antigenic, but there have been no reports of antibody formation associated with its use in CPB. However there have been reports of fatal anaphylaxis following re-exposure to lepirudin. It is possible that some of these reactions are attributable to traces of yeast proteins in preparations of the drug (33). Desirudin is active against fibrin-bound as well as fluid phase thrombin. Its effect is not easily reversed, although in rats it can be neutralised by recombinant meizothrombin, a naturally occurring prothrombin conversion intermediate (34–36) and has been used in CPB (37, check).

Argatroban, an arginine derivative, acts as a competitive thrombin inhibitor at only the active (or catalytic) site of thrombin (9,38). Its half life is 45 minutes and is prolonged with hepatic dysfunction, but not renal failure. Its has been used during CPB in two patients with HIT, both of whom bled excessively and died shortly following their operations (21), two patients with chronic renal failure (39,40) and one patient with severe liver dysfunction (41).

Bivalirudin (Angiomax[®], previously known as Hirulog[®]) is a synthetic 20 amino-acid peptide in which the functional carboxy and amino terminals of hirudin have been retained. It is unlikely to be immunogenic. Bivalirudin binds bivalently with thrombin. There is no reversal agent. The Arg-Pro bond at the amino-terminal of bivalirudin is cleaved by thrombin, so the drug's antithrombotic effect wears off rapidly. It is metabolized by proteolytic cleavage and residual drug is eliminated by the kidneys (42). A 20% reduction in bivalirudin clearance occurs with moderate renal impairment and a greater reduction with severe renal failure (42). Its plasma elimination half-life is 25 minutes. It inhibits clot-bound and fluid-phase thrombin and thrombin-mediated platelet aggregation. It has a low propensity for the generation of immune or inflammatory responses (9,43). As an enzymatic reaction, the hydrolysis of bivalirudin is temperature dependent, which may influence its kinetics during hypothermic CPB.

There is considerable experience with the use of bivalirudin in acute coronary syndromes. During coronary angioplasty for unstable angina the recommended initial intravenous bolus is 1 mg/kg, followed by an infusion of 2.5 mg/kg/h.

MONITORING OF ANTICOAGULATION WITH THROMBIN INHIBITORS

The aim in anticoagulation is to ensure an adequate effect without excessive blood concentrations of drug. With most drugs the relationship between concentration and effect varies substantially, so direct information about the status of the coagulation system (i.e., the effect of the drug) is needed. Unfortunately, many of the tests used to assess coagulation are non-specific, so it is helpful also to know the drug concentration.

The PT, APPT, thrombin time, and ACT are all prolonged by direct thrombin inhibitors. The APPT has been used to monitor anticoagulation with direct thrombin inhibitors, including bivalirudin (44–46). Prolongation of the APTT correlates well with increasing plasma levels of bivalirudin in doses between 0.05 mg/kg and 0.6mg/kg (43), but less well with plasma levels of lepirudin (47). The APPT is not useful at the doses of direct thrombin inhibitor needed for cardiac surgery (48).

There is a poor correlation between the ACT and the concentration of desirudin (49), and disproportionate prolongation

occurs with concentrations $\geq 2 \mu\text{g/ml}$. This is partly attributable to hemodilution of coagulation factors and platelets and can be overcome the addition of normal plasma to the ACT samples (48). Similar comments apply to UFH on CPB (49,50).

The ecarin clotting time (ECT) is a more specific test of thrombin inhibition and has been used to monitor anticoagulation with desirudin on CPB (35) and during OPCAB (51) and bivalirudin on CPB (37,52). Ecarin is a snake venom enzyme. It converts prothrombin to meizothrombin thereby stimulating the blood to form clot. Meizothrombin is rapidly neutralized by direct thrombin inhibitors (including lepirudin and bivalirudin) (52) resulting in a dose-dependent prolongation of the time for clot to form. Although the test is specific for antithrombin agents, heparin cofactor II-mediated thrombin inhibitors are capable of prolonging the ECT (53). The ECT provides a more accurate assessment of bivalirudin-mediated anticoagulation than the ACT up to blood concentrations of about $12 \mu\text{g/ml}$, but the place of this test is probably not yet fully established (21). The thromboelastograph has been used to monitor desirudin on CPB (54).

There is a dose-proportional relationship between blood concentration of bivalirudin and the ACT (55,56). The threshold for prevention of ischemic events in percutaneous coronary intervention (PCI) seems to be a blood concentration of $6.5 \mu\text{g/ml}$ (56). A bolus of 0.75 mg/kg followed by an infusion of 1.75 mg/kg/h usually results in a plasma concentration of $7\text{--}10 \mu\text{g/ml}$ and an ACT between 300 and 350 seconds. An ACT in this range has been reported as appropriate for OPCAB (57).

Experience with bivalirudin on CPB is still limited and the relationship between dose, effect, other influences on the coagulation system and the ACT in this setting is not entirely clear. It is essential to avoid stasis in the blood in the bypass circuit. Bivalirudin (with its shorter half life) is probably easier to manage during CPB than lepirudin.

COULD DIRECT THROMBIN INHIBITORS INFLUENCE GRAFT PATENCY?

In the first few months after surgery, flow through conduits is influenced by technical and surgical considerations, the caliber of the native artery, and neointimal hyperplasia and thrombus formation. Drugs may influence graft patency and perioperative myocardial infarction via the last two factors.

Advantages have been shown for direct thrombin inhibitors over heparin (typically without protamine reversal) in patients with acute coronary syndromes or undergoing PCI (44,58–60). These include a lower risk of the combined outcome, death or myocardial infarction (primarily due to an effect on myocardial infarction). The benefit is not seen with the univalent agents. Major bleeding is typically reduced with bivalirudin, but not with desirudin. In HERO-2 (4), there was an increase in moderate bleeding with bivalirudin. A key point about these studies in acute coronary syndromes is that the heparin was not reversed. Also the levels of anticoagulation were lower than those needed for CPB.

DIRECT THROMBIN INHIBITORS IN OFF-PUMP CORONARY ARTERY SURGERY

The degree of anticoagulation typically used in OPCAB surgery is less than with CPB, and postoperative bleeding is less often a problem (61,62). Because OPCAB surgery may produce a postoperative procoagulant state, heparin is sometimes only partially reversed after these operations (57,58,63,64).

In the first randomized comparison of an alternative to heparin in cardiac surgery it was confirmed that anticoagulation for OPCAB with bivalirudin could be provided without a clinically important increase in perioperative blood loss in comparison to heparin with protamine reversal (1). There was also a significant advantage for bivalirudin in the secondary outcome variable of graft flow at 3 months.

The findings of the OPCAB study should not be extrapolated to the management of patients undergoing CPB. However experience is increasing in the use of bivalirudin in cardiac surgery, both on pump and off (37,65,66).

The following studies are currently in progress: two studies comparing bivalirudin to heparin with protamine reversal in patients undergoing OPCAB (“EVOLUTION-off”); and CABG surgery on CPB (“EVOLUTION-on”); two studies of bivalirudin in patients with HIT and HITT undergoing OPCAB (CHOOSE-off) and CABG surgery on CPB (“CHOOSE-on”).

CONCLUSION

Experience with bivalirudin in the management of CPB is increasing and it is clear that it is possible to use the drug in patients who have a contraindication to heparin or protamine. Bivalirudin may provide an advantage over heparin with protamine reversal in respect to flow through grafted arteries. It is disappointing that no studies are currently underway in which this important outcome is the primary endpoint.

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Urban Myths and the ACT: What is Not True and What Really Matters When it Comes to Monitoring Anticoagulation

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INTRODUCTION

The activated clotting time (ACT) was developed in 1966 by Hattersley (1). However, it was Bull et al. that first suggested that Hattersley's test should be applied to coagulation monitoring of the systemically heparinized CPB patient (2). In their cornerstone manuscript it was noted that visible clot formation rarely occurred below ACT times of 300 seconds. Consequently, a safety margin was added to this minimum time and the recommendation was made that regular monitoring and maintenance of ACT values of >480 seconds was appropriate for CPB. This recommendation quickly became the gold standard. Since that time nearly a dozen automated machines and tests have been developed to provide ACT results and ACT monitoring has become standard of care for the CPB patient. Despite the widespread acceptance of the ACT test, there is no shortage of references which mischaracterize the ACT test thereby promulgating a degree of misinformation which permeates our profession. Therefore, the purpose of this presentation is to dispel some of the most common myths associated with ACT test results. Original data from our laboratory will be used to compliment an extensive literature review on this topic.

MYTH: AN ACT IS AN ACT IS AN ACT . . .

All too commonly the results of ACT tests have been generically referred to in scientific literature and conversation as if there were no more difference between the results of different ACT tests than there is between the flow rates of different roller pumps. In an effort to provide evidence of the similarity or disparity between results of different ACT tests we initiated a project to identify the comparability and reproducibility of all the major ACT tests available in the USA (3,4).