3. Grocott HP, Newman MF, El-Moalem H, Bainbridge D, Butler A, Laskowitz DT. Apolipoprotein E genotype differentially influences the proinflammatory and anti-inflammatory response to cardiopulmonary bypass. J Thorac Cardiovasc Surg. 2001;122:622–3.
4. Welsby IJ, Podgoreanu MV, Phillips-Bute B, et al. Genetic factors contribute to bleeding after cardiac surgery. J Thromb Haemost. 2005;3:1206–12.
5. Grocott HP, White WD, Morris RW, et al. Genetic polymorphisms and the risk of stroke after cardiac surgery. Stroke. 2005;36:1854–8.
6. Tardiff BE, Newman MF, Saunders AM, et al. Preliminary report of a genetic basis for cognitive decline after cardiac operations. Ann Thorac Surg. 1997;64:715–20.
7. Lasocki S, Iglarz M, Seince PF, et al. Involvement of renin-angiotensin system in pressure-flow relationship: role of angiotensin-converting enzyme gene polymorphism. Anesthesiology. 2002;96:271–5.
8. Booth JV, Spahn DR, McRae RL, et al. Esmolol improves left ventricular function via enhanced beta-adrenergic receptor signaling in a canine model of coronary revascularization. Anesthesiology. 2002;97:162–9.
9. Gaudino M, Andreotti F, Zamparelli R, et al. The -174G/C interleukin-6 polymorphism influences postoperative interleukin-6 levels and postoperative atrial fibrillation. Is atrial fibrillation an inflammatory complication? Circulation. 2003;108(Suppl 1):II195–9.
10. Tomasdottir H, Hjartarson H, Ricksten A, Wasslavik C, Bengtsson A, Ricksten SE. Tumor necrosis factor gene polymorphism is associated with enhanced systemic inflammatory response and increased cardiopulmonary morbidity after cardiac surgery. Anesth Analg. 2003;97:944–9.
11. Schroeder S, Borger N, Wrigge H, et al. A tumor necrosis factor gene polymorphism influences the inflammatory response after cardiac operation. Ann Thorac Surg. 2003;75:534–7.
12. Saunders A, Strittmatter W, Schmechel D, et al. Association of apolipoprotein E allele epsilon 4 with late-onset familial and sporadic Alzheimer's disease. Neurology. 1993;43:1467–72.
13. Coria F, Rubio I, Nunez E, et al. Apoplipoprotein E variants in ischemic stroke. Stroke. 1995;26:2375.
14. Alberts M, Graffagnino C, McClenny C, et al. ApoE genotype and survival from intracerebral haemorrhage (letter). Lancet. 1995;346:575.
15. Mayeux R, Ottman R, Maestre G, et al. Synergistic effects of traumatic head injury and apolipoprotein-ε4 in patients with Alzheimer's disease. Neurology. 1995;45:555–6.
16. Ti LK, Mathew JP, Mackensen GB, et al. Effect of apolipoprotein E genotype on cerebral autoregulation during cardiopulmonary bypass. Stroke. 2001;32:1514–9.
17. MacKensen GB, Swaminathan M, Ti LK, et al. Preliminary report on the interaction of apolipoprotein E polymorphism with aortic atherosclerosis and acute nephropathy after CABG. Ann Thorac Surg. 2004;78:520–6.
18. Bar-Yosef, S., M. Anders, G.B. Mackensen, L.K. Ti, J.P. Mathew, B. Phillips-Bute, et al. Aortic atheroma burden and cognitive dysfunction after coronary artery bypass graft surgery. Ann Thorac Surg 2004;78:1556-62; discussion 1562–3.
19. Grunenfelder J, Umbehr M, Plass A, et al. Genetic polymorphisms of apolipoprotein E4 and tumor necrosis factor beta as predisposing factors for increased inflammatory cytokines after cardiopulmonary bypass. J Thorac Cardiovasc Surg. 2004;128:92–7.
20. Steed L, Kong R, Stygall J, et al. The role of apolipoprotein E in cognitive decline after cardiac operation. Ann Thorac Surg. 2001;71:823–6.
21. Gaynor JW, Gerdes M, Zackai EH, et al. Apolipoprotein E genotype and neurodevelopmental sequelae of infant cardiac surgery. J Thorac Cardiovasc Surg. 2003;126:1736–45.
22. Gaudino M, Di Castelnuovo A, Zamparelli R, et al. Genetic control of postoperative systemic inflammatory reaction and pulmonary and renal complications after coronary artery surgery. J Thorac Cardiovasc Surg. 2003;126:1107–12.
23. Bijlsma FJ, Bruggink AH, Hartman M, et al. No association between IL-10 promoter gene polymorphism and heart failure or rejection following cardiac transplantation. Tissue Antigens. 2001;57:151–3.
24. Densem CG, Hutchinson IV, Yonan N, Brooks NH. Influence of tumor necrosis factor-alpha gene-308 polymorphism on the development of coronary vasculopathy after cardiac transplantation. J Heart Lung Transplant. 2001;20:1265–73.
25. Densem CG, Hutchinson IV, Yonan N, Brooks NH. Tumour necrosis factor alpha gene polymorphism: a predisposing factor to non-ischaemic myocardial dysfunction? Heart. 2002;87:153–5.
26. Morgun A, Shulzhenko N, Rampim GF, et al. Interleukin-2 gene polymorphism is associated with renal but not cardiac transplant outcome. Transplant Proc. 2003;35:1344–5.
27. Bedi M, Postava LA, Murali S, et al. Effect of the TNF-alpha-promoter polymorphism on cardiac allograft rejection. J Heart Lung Transplant. 2004;23:696–700.
28. Stafford-Smith M, Podgoreanu M, Swaminathan M, et al. Association of genetic polymorphisms with risk of renal injury after coronary bypass graft surgery. Am J Kidney Dis. 2005;45:519–30.
29. Donahue BS. The response to activated protein C after cardiopulmonary bypass: impact of factor V leiden. Anesth Analg. 2004;99:1598–603.
30. Faraday N, Martinez EA, Scharpf RB, et al. Platelet gene polymorphisms and cardiac risk assessment in vascular surgical patients. Anesthesiology. 2004;101:1291–7.
31. Mathew JP, Grocott HP, Podgoreanu MV, White WD, Newman MF. Inflammatory and prothrombotic genetic polymorphisms are associated with cognitive decline after CABG surgery. Anesthesiology. 2004;101:A274.
32. Podgoreanu MV, Schwinn DA. Genomics and the circulation. Br J Anaesth. 2004;93:140–8.

Development of a Novel Perfusion Technique to Allow Targeted Delivery of Gene Therapy–The V-Focus System

Arthur C. Preovolos, BAppSci; Mark T. Mennen, BSc; Adam Bilney, B.E(Hons); J. Mariani, MD; David M Kaye, MD; John M. Power, PhD
Baker Heart Research Institute, Melbourne, Australia

BACKGROUND

Current techniques for delivery of gene therapy, deliver the vector to the target organ and also to the systemic circulation. Targeted gene therapy aims at delivering the vector to specific and restricted cell populations, thus sparing all other cells of the

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 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

Professor Alan Merry, FANZCA
Auckland City Hospital, Auckland, New Zealand

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 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