Published in final edited form as:

Atherosclerosis. 2011 February ; 214(2): 259–260. doi:10.1016/j.atherosclerosis.2010.11.016.

“Topical” HDL for vein grafts: A new solution to an old problem?

Reto Asmis, PhD

Departments of Clinical Laboratory Sciences and Biochemistry, University of Texas Health Science Center at San Antonio, Texas, USA

Coronary artery bypass graft (CABG) surgery is one of the most common operations performed in the world, accounting for more cardiovascular medical expenditures than any other single medical procedure¹. However, the lifespan of surgically implanted vein grafts, the most common of which is the saphenous vein graft, significantly limits the effectiveness of CABG. In the early days of CABG, graft failures rates reached 50%; over the past decades, technical advances and new drug therapies have contributed to significantly improved outcomes². Nevertheless, vein graft failure after CABG surgery remains a major clinical problem. Angiographic studies reported that 16% to 31% of saphenous vein grafts failed within one year. Late vein graft patency rates reached 70% to 80% at 5 years post-surgery, but dropped to 40 to 60% after 10 years^{3–7}.

The three major causes of vein graft failure are acute thrombosis during the early postoperative period, intimal hyperplasia during the subacute phase, and atherosclerosis, which is responsible for most vein graft stenosis incidents and vessel occlusions after one year or more post-surgery. Within 10 years, approximately half of all vein grafts showed either severe atherosclerosis or were completely occluded^{3, 8, 9}. Vein graft failure is associated with worse clinical outcomes after CABG surgery, is a major cause of recurrent angina^{10, 11}, and appears to be associated with both increased mortality and an increased risk for non-fatal myocardial infarctions and repeat revascularization¹². The urgency for new technical and therapeutic approaches is therefore as great as ever in order to increase the lifespan of vein grafts and improve the long-term outcomes in patients undergoing CABG surgery.

In this issue of *Atherosclerosis*, Feng et al¹³ show that human HDL applied topically to the adventitial side of vein grafts in apoE^{−/−} mice reduced graft atherosclerosis and improved blood flow through the grafted vessel. The protective effects reported for the topical application of HDL on endothelial regeneration, neointima formation and blood flow are striking and comparable to the benefits the authors observed in the same study in response to systemic HDL elevations achieved by adenoviral overexpression. Enhanced endothelial regeneration in response to topical HDL was in part due to reduced endothelial cell death after grafting. However, both the proliferation of graft-derived endothelial cells as well the incorporation of host-derived endothelial cells appear to have contributed to the accelerated regeneration of the endothelial layer. Topical HDL also reduced leukocyte adhesion to the vein grafts and decreased leukocyte content in the graft intima. It remains unclear, however, whether these anti-inflammatory effects were the result of altered gene expression induced directly by HDL or simply the consequence of the accelerated regeneration of the protective endothelial layer.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

By using a Tie2-LacZ apoE-null mouse as the graft recipient, the authors were able to provide convincing evidence that host-derived cells are incorporated into the newly formed endothelial layer and contributed to endothelial regeneration. In the absence of multiple corroborative approaches, however, the evidence that topical HDL actually increased the incorporation of host-derived cells is not conclusive as gene silencing of the transgene may have contributed to an underestimation of host-derived cells in BSA-treated vein grafts. The difficulties and potential pitfalls involved in tracing the fate of endothelial progenitor cells was recently highlighted in a landmark paper by Hagensen et al.¹⁴ Nevertheless, the authors provide intriguing data suggesting that HDL improves the functions of both early EPC and endothelial colony forming cells (ECFC), which show many of the characteristics of true endothelial progenitors¹⁵. HDL effects on ECFC were SR-B1-dependent, supporting the concept that endothelial progenitor cells activated by topical HDL contributed significantly to the vascular repair process. The experiments reported by Feng et al. provide no definite answers to which extent in this model these endothelial progenitors originated from the host or the donor vessel, and whether they directly contributed to the regeneration of new endothelium or only indirectly supported the healing process via paracrine effects. Yet these elegant studies point to a new and promising therapeutic application for HDL and contribute to a growing list of recent studies demonstrating that the anti-atherogenic properties of HDL clearly extend far beyond reverse cholesterol transport and inflammation control.

References

1. Eagle KA, Guyton RA, Davidoff R, Edwards FH, Ewy GA, Gardner TJ, Hart JC, Herrmann HC, Hillis LD, Hutter AM Jr, Lytle BW, Marlow RA, Nugent WC, Orszulak TA. ACC/AHA 2004 guideline update for coronary artery bypass graft surgery: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1999 Guidelines for Coronary Artery Bypass Graft Surgery). *Circulation* 2004;110(14):e340–e437. [PubMed: 15466654]
2. Parang P, Arora R. Coronary vein graft disease: pathogenesis and prevention. *Can J Cardiol* 2009;25(2):e57–e62. [PubMed: 19214303]
3. Lytle BW, Loop FD, Cosgrove DM, Ratliff NB, Easley K, Taylor PC. Long-term (5 to 12 years) serial studies of internal mammary artery and saphenous vein coronary bypass grafts. *J Thorac Cardiovasc Surg* 1985;89(2):248–58. [PubMed: 2857209]
4. Bourassa MG, Fisher LD, Campeau L, Gillespie MJ, McConney M, Lesperance J. Long-term fate of bypass grafts: the Coronary Artery Surgery Study (CASS) and Montreal Heart Institute experiences. *Circulation* 1985;72(6 Pt 2):V71–V78. [PubMed: 3905060]
5. Murphy ML, Hultgren HN, Detre K, Thomsen J, Takaro T. Treatment of chronic stable angina. A preliminary report of survival data of the randomized Veterans Administration cooperative study. *N Engl J Med* 1977;297(12):621–7. [PubMed: 331107]
6. Goldman S, Copeland J, Moritz T, Henderson W, Zadina K, Ovitt T, Doherty J, Read R, Chesler E, Sako Y. Saphenous vein graft patency 1 year after coronary artery bypass surgery and effects of antiplatelet therapy. Results of a Veterans Administration Cooperative Study. *Circulation* 1989;80(5):1190–7. [PubMed: 2680158]
7. Kuntz RE, Piana R, Schnitt SJ, Johnson RG, Safian RD, Baim DS. Early ostial vein graft stenosis: management by atherectomy. *Cathet Cardiovasc Diagn* 1991;24(1):41–4. [PubMed: 1913791]
8. Bourassa MG, Enjalbert M, Campeau L, Lesperance J. Progression of atherosclerosis in coronary arteries and bypass grafts: ten years later. *Am J Cardiol* 1984;53(12):102C–7C.
9. FitzGibbon GM, Leach AJ, Kafka HP, Keon WJ. Coronary bypass graft fate: long-term angiographic study. *J Am Coll Cardiol* 1991;17(5):1075–80. [PubMed: 2007706]
10. Campeau L, Lesperance J, Hermann J, Corbara F, Grondin CM, Bourassa MG. Loss of the improvement of angina between 1 and 7 years after aortocoronary bypass surgery: correlations with changes in vein grafts and in coronary arteries. *Circulation* 1979;60(2 Pt 2):1–5. [PubMed: 312705]

11. Cameron A, Kemp HG Jr, Shimomura S, Santilli E, Green GE, Hutchinson JE III, Mekhjian HA. Aortocoronary bypass surgery: a 7-year follow-up. *Circulation* 1979;60(2 Pt 2):9–13. [PubMed: 312713]
12. Halabi AR, Alexander JH, Shaw LK, Lorenz TJ, Liao L, Kong DF, Milano CA, Harrington RA, Smith PK. Relation of early saphenous vein graft failure to outcomes following coronary artery bypass surgery. *Am J Cardiol* 2005;96(9):1254–9. [PubMed: 16253593]
13. Feng Y, Gordts SC, Chen F, Hu Y, Van Craeyveld E, Jacobs F, Carlier V, Feng Y, Zhang Z, Xu Q, Ni Y, De Geest B. Topical HDL administration reduces vein graft atherosclerosis in apoE deficient mice. *Atherosclerosis*. 2010
14. Hagensen MK, Shim J, Thim T, Falk E, Bentzon JF. Circulating endothelial progenitor cells do not contribute to plaque endothelium in murine atherosclerosis. *Circulation* 2010;121(7):898–905. [PubMed: 20142446]
15. Ingram DA, Mead LE, Tanaka H, Meade V, Fenoglio A, Mortell K, Pollok K, Ferkowicz MJ, Gilley D, Yoder MC. Identification of a novel hierarchy of endothelial progenitor cells using human peripheral and umbilical cord blood. *Blood* 2004;104(9):2752–60. [PubMed: 15226175]