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GLUCOSE MANAGEMENT, HEART FAILURE AND TRANSPLANTATION

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Introduction

Glucose control before, during, and after orthotropic heart transplantation presents unique challenges. The presence of advanced heart failure contradicts the use of oral metformin and thiozolidinediones (TZDs). The benefit of insulin has been questioned, and recent investigations question the degree of glycemic control in the ICU.[1] Scant published data report on the efficacy of oral hypoglycemics on graft function and survival. The purpose of this summary is to present our approach to patients either listed for or undergoing heart transplantation at The Methodist Hospital.

Heart Failure and Insulin Resistance

Heart failure produces and exacerbates whole-body insulin resistance.[2,3] The relationship between diabetes and heart failure has been recognized/[5] and the link to insulin resistance might be fundamental to this relationship.[6] Even in the absence of diabetes, heart failure prevalence is increased with insulin resistance.7-g The presence of insulin resistance and diabetes portends poor outcomes for patients with advanced heart failure.10

Whole-body insulin resistance refers to impaired insulin action on several organs. The liver, adipose, and skeletal muscle compromise the classic triad.[11] The heart is also affected. Myocardial insulin resistance alters cardiac metabolism and function.12 In the instance of a patient progressing from advanced heart failure to heart transplantation, the pathophysiology is altered. Whole-body resistance persists, **but** the newly implanted heart retains insulin sensitivity.

Very little has been written to support therapeutic strategies for post-transplant diabetes in general and for heart transplant diabetes in particular. In 2003, international guidelines on new-onset diabetes after transplantation were published;[13] however, diabetes after heart transplantation was not reported in depth. Guidelines are considered in a review published in 2005.[14] With this background, we have developed strategies that address the needs of the patient at each step. The remainder of this article will highlight these strategies.

The Patient With Advanced Heart Failure (Pre-Transp lant)

There may be an association between glycemic control during hospitalization and/or death in patients with heart failure.g This and the finding that heart failure produces whole- body insulin resistance form the basis for our current treatment goals and recommendations.

The traditional oral agents that reduce insulin resistance are contraindicated in NYHA III and IV heart failure. TZDs exacerbate volume status, and metformin can perpetuate lactic acidosis. Insulin secretagogues (sulfonylurea agents) have limited value in the face of prolonged insulin resistance and beta cell failure.

Insulin has been the mainstay for glycemic control. As heart failure and insulin resistance progress, high insulin doses often become necessary, e.g., greater than 2.0 units/kg/day. This holds true even with the newer insulin analogs. To cloud the picture, there is epidemiologic evidence that insulin-treated diabetes is associated with increased mortality in patients with advanced heart failure.15

Mimicking or enhancing glucagon-like peptide-1 (GLP-1) action has emerged as a promising new therapeutic strategy. GLP-1 improves glucose control, reduces insulin resistance, and promotes myocardial uptake of glucose.[16, 17] In animal studies it has been shown to improve mechanical efficiency.

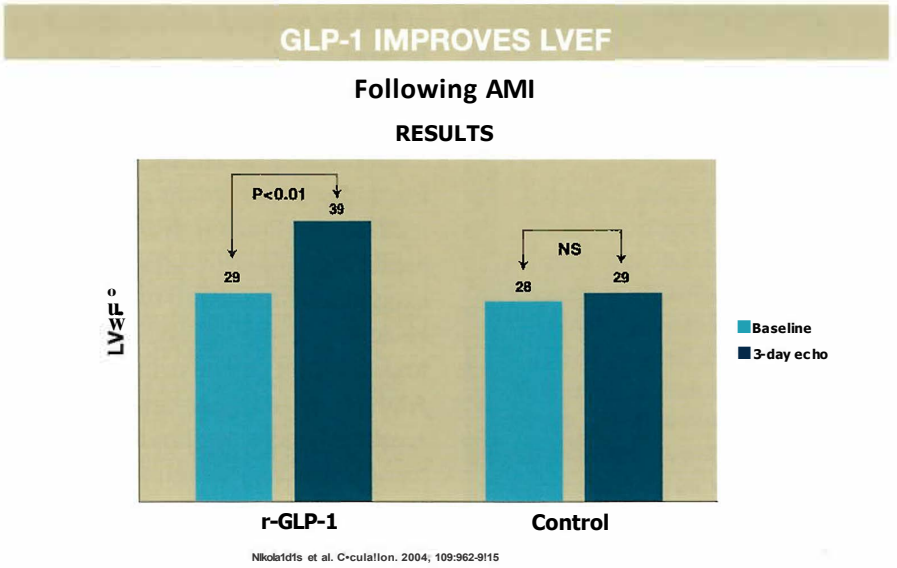

Figure 1. Glucagon-like peptide-1 (GLP-1) infusion has been found to improve left ventricular ejection fraction (LVEF) and functional status in patients with chronic heart failure.

GLP-1 infusion has been found to improve LVEF and functional status in patients with CHF (Figure 1).[18] Finally, and not without notice, exenatide, an injectable GLP-1 mimetic, promotes weight loss in nearly 50% of patients.

We have incorporated exenatide and sitagliptin, an oral inhibitor of GLP-1 breakdown, into treatment of these patients. A typical patient might be treated with exenetide injections or sitagliptin plus short-acting oral secretogogues (repaglinide or nateglinide). If uncontrolled, then insulin is used with injectable pramlintide, an amylin analogue.

Inpatient Perioperative Management

Hyperglycemia is linked to poor wound healing and increased infection rates in post-operative patients.[19] Glucose control with continuous insulin infusion (CII) in cardiovascular surgery patients is associated with shorter ICU stays and reduced mortality. Our team supports the use of CII during the immediate post-operative hours.

Transition from CII to subcutaneous insulin, however, can be difficult and frustrating. The resulting glucose variability increases the frequency of glucose measurements, err restarts, and hypoglycemic episodes. We have studied and reported on a strategy to smooth this transition. In an !RB-approved study, our group at The Methodist Hospital showed that the subcutaneous injection of insulin glargine captured the err if started early during the Cll infusion. This strategy reduced the glucose fluctuations and stop-restart cycling of err without increasing hypoglycemic events (Figure 2). It also reduced the average glucose concentration in the initial 24 hours following transfer from the ICU.

The benefits of CII are limited. Hypoglycemia is associated with poorer outcomes including increased mortality rates.[1] This risk accounts for the high frequency of finger sticks and laboratory glucose measurements. Continuous glucose monitoring systems (CGMS) provide a potential solution: Like oximetry, CGMS produce continuous real-time data. The technology includes a subcutaneous sensor and a beeper-sized recorder. A preliminary study using CGMS and completed in Japan showed excellent correlation with finger-stick testing.[20] They reported 99.8% of the paired measurements in zone A on the Clarke error grid. Our group conducted a similar study in the CVICU, with the findings presented in abstract (Figure 3) and the full report submitted to *Critical Care.*

Several modifying factors and comorbidities complicate glucose control in the heart transplant recipient. High-dose steroids that are tapered over two to three weeks lead the list. We have developed steroid coverage strategies to minimize

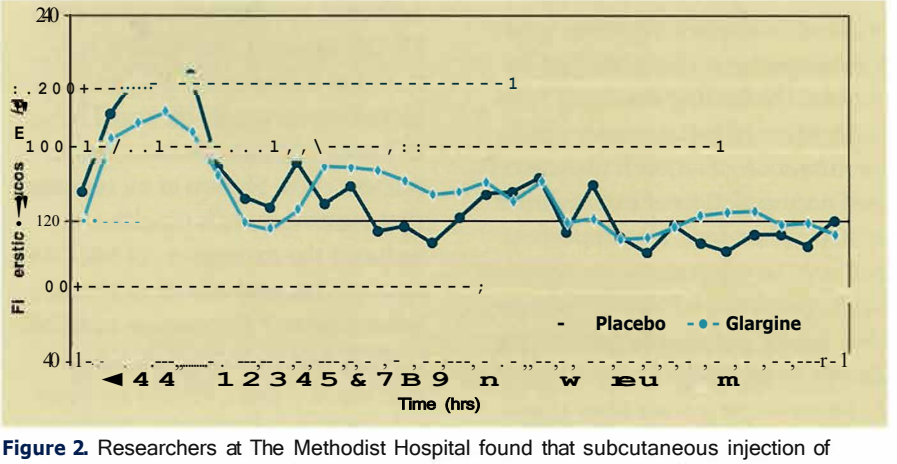

Figure 2. Researchers at The Methodist Hospital found that subcutaneous injection of insulin glargine reduced the glucose fluctuations and stop-restart cycling of CII without increasing hypoglycemic events.

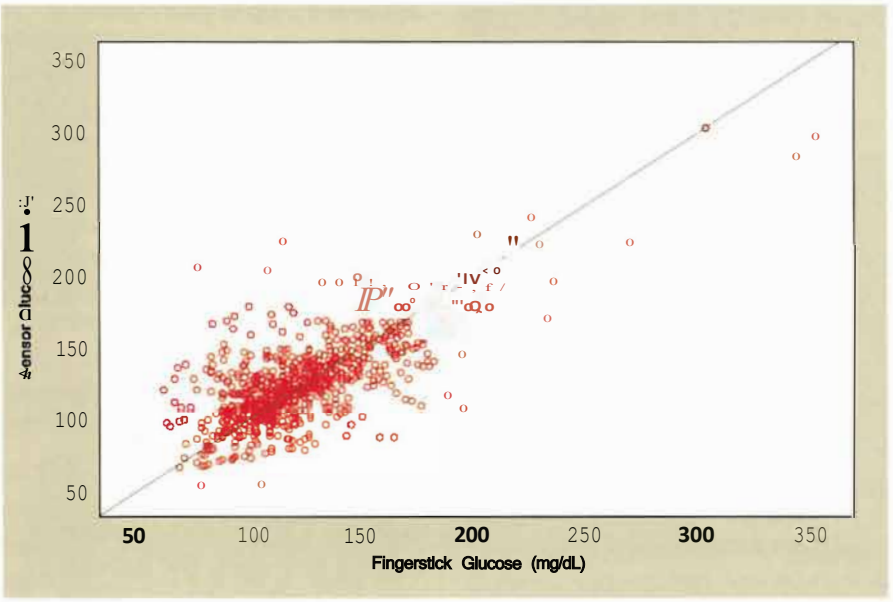

Figure 3. Continuous glucose monitoring systems use a subcutaneous glucose-sensing device and a beeper-sized recorder to record blood sugar levels throughout the day, producing continuous real-time data that correlates with finger-stick testing.

the hyperglycemic effect of these potent glucocorticoids. Independent of the patient's basal and meal-time insulin needs, the steroid coverage can be independently tapered and stopped.

The First Year {Post-Transplant)

Despite advances in immunosuppressive agents, acute and chronic rejection remain the major causes of graft failure after cardiac transplantation. Graft rejection involves immune responses and inflammation. In chronic rejection, graft vasculopathy is characterized by intimal thickening resulting from infiltration of inflammatory cells, proliferation of smooth muscle cells, and accumulation of extracellular matrix. Therefore, it is important not only to suppress acute rejection with conventional immunosuppressive agents but also to prevent the development of graft vasculopathy to improve prognosis after transplantation. In 2006, Kosuge, et al. reported that pioglitazone, a PPARy agonist, played an important role in suppressing graft vasculopathy and rejection after cardiac transplantation.21

Inflammation is characterized by the expression of adhesion molecules and infiltration by inflammatory cells such as macrophages and T cells. PPARy agonists play important roles in regulating inflammation. It has been reported that PPARy agonists suppress expression of vascular cell adhesion molecule-1 and intercellular adhesion molecule-1 by activated human endothelial cells. PPARy agonists also inhibit synthesis of inflammatory cytokines, including IFN-y, IL-1, and TNF-a, in human peripheral blood mononuclear cells. Shiomi et al. reported that treatment with pioglitazone reduced the expression of MCP-1 in an experimental model of chronic heart failure.22 Expression of PPARy mRNA occurs in human peripheral blood T cells. PPARy agonists inhibit IL-2 secretion by T cells and decrease cell proliferation. Several studies have shown the effects of PPARy agonists on neointimal hyperplasia after vascular injury; however, the role of PPARy agonists in allograft rejection is not known.[21]

Our treatment strategies for this post-transplant group include pioglitazone and incretin-based therapies (e.g., sitagliptin, exenatide). Metformin use is limited because of the progressive nephrotoxic effect of calcineurin inhibitors. Alpha-glucosidase inhibitors (e.g., acarbose) and metiglinides (e.g., repaglinide and netaglinide) also have a role. A typical patient here would be taking a combination of oral medications, some with basal or mixed insulin. Each stage, from advanced heart failure to long-term post-transplant care, requires target therapy based on pathophysiologic principles.

References

1. NICE-SUGAR Study investigators, Finfer S, Chittock DR, Su SY, Blair D, Foster D, Dhingra V, Bellomo R, Cook D, Dodek P, Henderson WR, Hebert PC, Heritier S, Heyland DK, McArthur C, McDonald E, Mitchell I, Myburgh JA, Norton R, Potter J, Robinson BG, Ronco JJ. Intensive versus conventional glucose control in critically ill patients. N Engl J Med. 2009 Mar 26;360(13):1283-97.
2. Nikolaidis LA, Sturzu A, Stolarski C, Elahi D, Shen YT, Shannon RP. The development of myocardial insulin resistance in conscious dogs with advanced dilated cardiomyopathy. Cardiovasc Res. 2004 Feb 1; 61(2):297-306.
3. Al-Zadjali MA, Godfrey V, Khan F, Choy A, Doney AS, Wong AK, Petrie JR, Struthers AD, Lang CC. Insulin resistance is highly prevalent and is associated with reduced exercise tolerance in nondiabetic patients with heart failure. J Am Coll Cardiol. 2009 Mar 3;53(9): 747-53.

4. Kannel WB, Hjortland M, Castelli WP. Role of diabetes in congestive heart failure: the Framingham study. Am J Cardiol. 1974 Jul;34(1):29-34.
5. Amato L, Paolisso G, Cacciatore F, Ferrara N, Ferrara P, Canonico S, Varricchio M, Rengo F. Congestive heart failure predicts the development of non-insulin-dependent diabetes mellitus in the elderly. The Osservatorio Geriatrico Regione Campania Group. Diabetes Metab. 1997 Jun;23(3):213-8.
6. Witteles RM, Tang WH, Jamali AH, Chu JW, Reaven GM, Fowler MB. Insulin resistance in idiopathic dilated cardiomyopathy: a possible etiologic link. J Am Coll Cardiol. 2004 Jul 7;44(1):78-81.
7. Ingelsson E, Arnlov J, Lind L, Sundstrom J. Metabolic syndrome and risk for heart failure in middle-aged men. Heart. 2006 Oct;92(10):1409-13.
8. Ingelsson E, Sundstrom J, Arnlov J, Zethelius B, Lind L. Insulin resistance and risk of congestive heart failure. JAMA. 2005 Jul 20; 294(3):334-41.
9. Iribarren C, Karter AJ, Go AS, Ferrara A, Liu JY, Sidney S, Selby JV. Glycemic control and heart failure among adult patients with diabetes. Circulation 2001 Jun 5;103(22): 2668-73.
10. From AM, Leibson CL, Bursi F, Redfield MM, Weston SA, Jacobsen SJ, Rodeheffer RJ, Roger VL. Diabetes in heart failure: prevalence and impact on outcome in the population. Am J Med. 2006 Jul;ll9(7):591-9.
11. Reaven GM. Banting lecture 1988. Role of insulin resistance in human disease. Diabetes. 1988. Dec;37(12):1595-607. Review
12. Ashrafian H, Frenneaux MP, Opie LH. Metabolic mechanisms in heart failure. Circulation. 2007 Jul 24;116(4):434-48.
13. Davidson J, Wilkinson A, Dantal J, Dotta F, Haller H, Hernandez D, Kasiske BL, Kiberd B, Krentz A, Legendre C, Marchetti P, Markell M, van der Woude FJ, Wheeler DC; International Expert Panel. New-onset diabetes after transplantation: 2003 International consensus guidelines. Proceedings of an international expert panel meeting. Barcelona, Spain, 19 February 2003. Transplantation. 2003 May 27;75 (10 Suppl):SS3-24.
14. Wilkinson A, Davidson J, Dotta F, Home PD, Keown P, Kiberd B, Jardine A, Levitt N, Marchetti P, Markell M, Naicker S, O'Connell P, Schnitzler M, Stancil E, Torregosa JY, Uchida K, Valantine H, Villamil F, Vincenti F, Wissing M. Guidelines for the treatment and management of new-onset diabetes after transplantation. Clin Transplant. 2005 Jun;19(3):291-8. Review.
15. Smooke S, Horwich TB, Fonarow GC. Insulin-treated diabetes is assodated with a marked increase in mortality in patients with advanced heart failure. Am Heart J. 2005 Jan;149(1):168-74.
16. Thrainsdottir I, Malmberg K, Olsson A, Gutniak M, Ryden L. Initial experience with GLP-1 treatment on metabolic control and myocardial function in patients with type 2 diabetes mellitus and heart failure. Diab Vase Dis Res. 2004 May;l(l): 40-3.
17. Sokos GG, Nikolaidis LA, Mankad S, Elahi D, Shannon RP. Glucagon-like peptide-1 infusion improves left ventricular ejection fraction and functional status in patients with chronic heart failure. J Card Fail. 2006 Dec;12(9):694-9.
18. Essop MF, Opie LH. Metabolic therapy for heart failure. Eur Heart J. 2004 Oct;25(20):1765-8.
19. van den Berghe G, Wouters P, Weekers F, Verwaest C, Bruyninckx F, Schetz M, Vlasselaers D, Ferdinande P, Lauwers P, Bouillon R. Intensive insulin therapy in the critically ill patients. N Engl J Med. 2001 Nov 8;345(19):1359-67.
20. Yamashita K, Okabayashi T, Yokoyama T, Yatabe T, Maeda H, Manabe M, Hanazaki K. Accuracy and reliability of continuous blood glucose monitor in post-surgical patients. Acta Anaesthesiol Scand. 2009 Jan;53(1):66-71.
21. Kosuge H, Haraguchi G, Koga N, Maejima Y, Suzuki J, Isobe M. Pioglitazone prevents acute and chronic cardiac allograft rejection. Circulation. 2006 Jun 6;113(22):2613-22.
22. Shiomi T, Tsutsui H, Hayashidani S, Suematsu N, Ikeuchi M, Wen J, Ishibashi M, Kubota T, Egashira K, Takeshita A. Pioglitazone, a peroxisome proliferator-activated receptor-gamma agonist, attenuates left ventricular remodeling and failure after experimental myocardial infarction. Circulation 2002 Dec 10;106(24):3126-32.