

Heinrich Taegtmeyer,¹ Christophe Beauloye,² Romain Harmancey,³ and Louis Hue⁴



COMMENT ON NOLAN ET AL.



Insulin Resistance as a Physiological Defense Against Metabolic Stress: Implications for the Management of Subsets of Type 2 Diabetes. *Diabetes* 2015;64:673–686

Diabetes 2015;64:e37 | DOI: 10.2337/db15-0655

We read with much interest the article by Nolan et al. (1) on insulin resistance (IR) as a defense against metabolic stress. This is the third in a cluster of reviews beginning with the hypothesis that IR protects the heart from fuel overload in dysregulated metabolic states (2) and coincides with a review by Connor et al. (3). In our article (2), we stressed the deleterious effects of dysregulated glucose and fat metabolism on the function of the heart and proposed physiologic and biochemical mechanisms by which IR protects the heart from fuel overload. Nolan et al. (1) focused on insulin-induced metabolic stress and expanded on the view that overriding IR with intensive insulin treatment could be harmful (4). Lastly, Connor et al. (3) stressed that many of the adaptations occurring in metabolic diseases characterized by nutritional excess can be viewed as protective in nature rather than pathogenic per se. The observations that excessive insulin signaling exacerbates systolic dysfunction when the heart is subjected to pressure overload (5) and the demonstration that IR improves metabolic and contractile efficiency in the inotropically challenged heart (6) complement each other. Lowering blood glucose levels at all costs may be harmful. We have proposed that in the management of diabetes of patients with heart failure the target should be the source rather than the destination of excess fuel (7). The three reviews and other published work (8) argue in support of the concept that IR is a physiological defense

mechanism against metabolic stress. One can only hope that the concept will gain further traction.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

References

1. Nolan CJ, Ruderman NB, Kahn SE, Pedersen O, Prentki M. Insulin resistance as a physiological defense against metabolic stress: implications for the management of subsets of type 2 diabetes. *Diabetes* 2015;64:673–686
2. Taegtmeyer H, Beauloye C, Harmancey R, Hue L. Insulin resistance protects the heart from fuel overload in dysregulated metabolic states. *Am J Physiol Heart Circ Physiol* 2013;305:H1693–H1697
3. Connor T, Martin SD, Howlett KF, McGee SL. Metabolic remodelling in obesity and type 2 diabetes: pathological or protective mechanisms in response to nutrient excess? *Clin Exp Pharmacol Physiol* 2015;42:109–115
4. Nolan CJ, Ruderman NB, Prentki M. Intensive insulin for type 2 diabetes: the risk of causing harm. *Lancet Diabetes Endocrinol* 2013;1:9–10
5. Shimizu I, Minamino T, Toko H, et al. Excessive cardiac insulin signaling exacerbates systolic dysfunction induced by pressure overload in rodents. *J Clin Invest* 2010;120:1506–1514
6. Harmancey R, Lam TN, Lubrano GM, Guthrie PH, Vela D, Taegtmeyer H. Insulin resistance improves metabolic and contractile efficiency in stressed rat heart. *FASEB J* 2012;26:3118–3126
7. Khalaf KI, Taegtmeyer H. After avandia: the use of antidiabetic drugs in patients with heart failure. *Tex Heart Inst J* 2012;39:174–178
8. Agius L. High-carbohydrate diets induce hepatic insulin resistance to protect the liver from substrate overload. *Biochem Pharmacol* 2013;85:306–312

¹Division of Cardiovascular Medicine, Department of Internal Medicine, The University of Texas Medical School at Houston, Houston, TX

²Pôle de Recherche Cardiovasculaire, Institut de Recherche Expérimentale et Clinique, Université catholique de Louvain, Brussels, Belgium

³Department of Physiology and Biophysics, The University of Mississippi Medical Center, Jackson, MS

⁴Protein Phosphorylation Unit, de Duve Institute, Université catholique de Louvain, Brussels, Belgium

Corresponding author: Heinrich Taegtmeyer, heinrich.taegtmeyer@uth.tmc.edu.

© 2015 by the American Diabetes Association. Readers may use this article as long as the work is properly cited, the use is educational and not for profit, and the work is not altered.