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Insulin Resistance: Marker or Mediator?

Guha Ashrith, MD, Mohammed F. Algahim, BS, and Heinrich Taegtmeyer, MD, DPhil
University of Texas School of Medicine at Houston, Department of Medicine

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To the Editor

We read with interest, the excellent review by Aneja et al. on diabetic cardiomyopathy.¹ The authors have stressed the central role of hyperglycemia in the pathogenesis of diabetic cardiomyopathy, but they have almost forgotten the association of hyperinsulinemia or insulin resistance and cardiomyopathy. Though it is still not clear whether insulin resistance is the cause or effect of heart failure, it is for certain associated with heart failure.² From cohort and observational studies we know that: a) Insulin resistance is associated with an increase in left ventricular mass. This relation is stronger in women and may be related to obesity.³ b) Insulin resistance is associated with an increased risk of heart failure in elderly men, and this increased risk was seen even in non-diabetic elderly men.⁴ Though the study by Ingelsson et al suggests that insulin resistance may pre-date cardiomyopathy, causative relationship and evidence for biological basis is still lacking. c) Chronic systolic heart failure is associated with insulin resistance and it is independent of the cause of cardiomyopathy.⁵ Despite all epidemiological studies on the association of insulin resistance and heart failure, there is no evidence that insulin resistance alone actually *causes* heart failure.

Animal models with hyperinsulinemia without hyperglycemia have demonstrated increased left ventricular mass and diastolic dysfunction. However they did not demonstrate any systolic dysfunction in the absence of hyperglycemia.⁶ Hypertrophy is thought to be mediated via the Akt-1/mTOR pathways. Apart from insulin and glucose, sympathetic stimulation also seems to play a role.

These studies indicate that insulin resistance by itself does not cause a cardiomyopathy, but is definitely associated with it. We consider insulin resistance an early adaptive myocardial response. As systolic dysfunction sets in, insulin resistance may become more of an effect of worsening dysfunction rather than a contributing factor. In other words insulin resistance is a marker rather than a mediator of contractile dysfunction.

Address correspondence and request for reprints to: Heinrich Taegtmeyer, MD, DPhil, Professor of Medicine, University of Texas Houston Medical School, Department of Medicine/Cardiology, 6431 Fannin, MSB 1.246, Houston, TX 77030, Tel: (713) 500-6569, Fax: (713) 500-0637, E-mail: Heinrich.Taegtmeyer@uth.tmc.edu.

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