Obesity and Insulin Resistance: “Window” for Myocardial Dysfunction

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Obesity is a global epidemic[1], whose prevalence increases progressively. The cardiovascular and metabolic implications of obesity are multiple (especially diabetes mellitus and insulin resistance) and can occur even in early stages of the disease. Thus, the study published by Dr. Ana Paula Lima-Leopoldo et al[2] evaluated the effects of obesity on myocardial performance, specifically investigating the change in concentration of extracellular calcium, the effect of post-rest potential and beta-adrenergic stimulation with isoproterenol, using isolated papillary muscle preparation of Wistar rats subjected to hypercaloric diet (Ob) for 15 weeks or standard diet (C).

Interestingly, Ob animals, despite *not* having final body weight gain, had increased body fat (96.1%) and increased insulin resistance after oral glucose overload compared to control rats. Yet, although the performance of isolated papillary muscle was similar between groups at baseline, there was functional impairment of the papillary muscle of Ob rats when exposed to progressively higher concentrations of extracellular calcium (2.5 to 8 mM) and after the effect of post-rest potential, especially shown by the lower response of peak developed tension (DT) and the lower maximum speed of the variation of decrease in developed tension (-dT/dt) compared to C. In addition, beta-adrenergic stimulation with isoproterenol decreased the maximum speed of positive variation in developed tension (+dT / dt) in Ob versus C animals.

Although other studies have observed functional changes in cardiomyocytes of obese rats, even at baseline[3,4], the authors of this study conclude that obesity may promote regulatory Ca^{+2} channels dysfunction, more specifically related to the Na^{+}/Ca^{+2} exchanger, L-type channels from the sarcolemma, sarcoplasmic reticulum (SR) and changes in myofilaments sensitivity to Ca^{+2}, functionally assessed by rising concentration of extracellular Ca^{+2} and evaluating post-rest potential of the papillary muscles in isolated preparation. Moreover, decreased -dT/dt found with high concentrations of cytosolic Ca^{+2} has led the authors to speculate that activation of SERCA2 via Ca^{+2}-calmodulin kinase could be depressed in obese rats, thereby reducing the uptake of calcium by the SR of cardiomyocytes, resulting in a decrease in stocks of Ca^{+2} and lower release of Ca^{+2} by ryanodine receptors. However, the expression and activity of these proteins have not been studied in this investigation, as well as the influx/efflux, concentration and intracellular compartmentalization of calcium. Yet, the authors conclude that the reduction of -dT/dt in obese rats after stimulation with isoproterenol may be due to decreased phosphorylation of phospholamban via Ca^{+2}- calmodulin kinase.

A recent publication by Howarth et al[5] coincidentally demonstrated that the time to maximal diabetic Zucker rat cardiomyocyte contraction and relaxation was longer (about 30%) compared to cardiomyocytes of control rats. Although the amplitude of Ca^{+2} flow was normal, the time for Ca^{+2} influx was increased in cardiomyocytes of Zucker rats. This was explained by the decrease in eletric current density through L-type channels, which was attributed to the change in expression of genes that synthesize the myosin heavy chain, L-type Ca^{+2} channels and intracelular Ca^{+2} transport regulation proteins. In addition to treatment and prevention of diabetes, obesity and insulin resistance, the investigation of new molecular mechanisms that may explain the pathophysiological changes of early myocardial and cardiomyocytes dysfunction, will certainly corroborate the early diagnosis, as well as unveiling potential targets for treatment of heart failure related to obesity even in subclinical settings.

“Editorial under the responsibility of Cardiosource – Portuguese version. http://cientifico.cardiol.br/cardiosource2/default.asp”

Keywords

Obesity; diabetes mellitus / metabolism; myocardium/ physiopathology; insulin resistance; rats, zucker.

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Manuscript received July 08, 2011, revised manuscript received July 13, 2011, accepted July 13, 2011.

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