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What can adiponectin say about left ventricular function?

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Adiponectin is an adipocyte-derived cytokine that is abundantly present in human plasma.¹² Adiponectin levels are highest in lean subjects, but levels decline as body mass increases. Work in experimental models has shown that adiponectin mediates beneficial actions in cardiovascular and metabolic-associated diseases. For example, in mouse models, adiponectin modulates hypertrophic signals in the heart and exhibits direct anti-hypertrophic properties; in addition to improving vascular function and pathological remodelling.³⁴ Despite the agreement and consistency of experimental studies on adiponectin, a number of clinical findings have questioned the utility of this adipokine as a biomarker for human diseases. On one hand, depressed adiponectin levels have been associated with greater cardiovascular risk and inflammation since hypoadiponectinaemia occurs in coronary artery disease, hypertension and insulin resistance.^{5–8} On the other hand, high adiponectin levels are present in chronic inflammatory and autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus, type 1 diabetes and inflammatory bowel disease independently of adiposity.⁹ In addition, chronic systolic heart failure is associated with elevated adiponectin levels.^{10–13} Now, Unno and colleagues report that adiponectin levels are elevated in non-obstructive hypertrophic cardiomyopathy (HCM) with diastolic dysfunction (*see page 357*).¹⁴

Hypertrophic cardiomyopathy (HCM), a genetic disease of the cardiac sarcomeres, is caused by mutations in one of the many genes that encode components of the contractile apparatus of the heart. HCM has an autosomal dominant pattern of inheritance and is characterised by left ventricular hypertrophy (LVH), with variable clinical, morphological and haemodynamic phenotypes. In this study by Unno *et al*, the patients with HCM had no left ventricular (LV) outflow tract obstruction, which probably explains the paucity of cardiac symptoms such as dyspnoea and angina (New York heart Association functional class I/II or mild chest pain). However, the left ventricle is often not compliant in HCM resulting in diminished diastolic function. Thus, the significance of diastolic dysfunction is unclear in this minimally symptomatic patient population studied by Unno *et al*. This subject is of concern because *diastolic heart failure* is a clinical syndrome of pulmonary congestion in the presence of preserved LV ejection fraction; whereas *diastolic dysfunction* denotes an abnormality of mechanical properties that exist during LV relaxation and filling.¹⁵¹⁶ If diastolic dysfunction were considered a 'preclinical' diagnosis to the development of symptoms in HCM or diastolic heart failure then its early recognition, by biomarker analysis, would represent a means of identifying patient populations at high risk of developing congestive heart failure.¹⁷ However, Unno *et al* did not conduct a longitudinal study, and this hypothesis remains to be tested.

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In the study by Unno *et al*, the relationship between HCM and diastolic dysfunction as determined by LV pressure half-time ($T_{1/2}$) and adiponectin level appears to be at odds with a prior cross-sectional analysis of non-hypertensive and hypertensive patients demonstrating that low adiponectin levels were associated with LVH progression and diastolic dysfunction.¹⁸ Taken together, these findings suggest that elevated adiponectin may not necessarily be associated with LVH and/or diastolic dysfunction but with non-obstructive HCM. Thus, hyperadiponectinaemia may identify patients with stable HCM and evidence of impaired LV relaxation. However, because LV pressure half time ($T_{1/2}$) is not a definitive measure of impaired diastolic function, additional measures of diastolic dysfunction such as measures of mitral Doppler, tissue Doppler and determinants of E/e' by echocardiography would strengthen the case for diastolic dysfunction in the patient population studied by Unno *et al*.

It should be noted that adiponectin levels are increased in other diseases. For example, hyperadiponectinaemia occurs in renal failure and is associated with increased mortality.¹⁹²⁰ The increase is thought to be due to impaired kidney clearance since renal transplantation lowers adiponectin levels. With regard to heart failure,^{11–13} the reason for the rise in adiponectin levels is not known but a number of hypotheses are possible. First, it is conceivable that the upregulation of adiponectin levels may be a compensatory response to the stress of heart failure, similar to the mechanism described for B-type natriuretic peptide (BNP) secretion.²¹ The molecular mechanisms underlying such a process are unknown; however, BNP levels correlate with adiponectin levels in human heart failure,¹⁰²¹ and it has been reported that BNP directly stimulates human adipocytes to release adiponectin via a cGMP-dependent pathway.²²

Another possible explanation for the rise in adiponectin levels in cardiac disease is the development of 'adiponectin resistance'. Adiponectin resistance has been described by a small number of studies examining human tissue²³²⁴ and animal models,²⁵ but again the mechanistic details have not been defined. Increased adiponectin levels may reflect dysfunction at the level of adiponectin receptors with a resulting increase in adiponectin secretion as a compensatory response as may occur in systolic heart failure.^{11–13} In the study by Unno *et al* non-obstructive HCM with increased $T_{1/2}$ was associated with a decrease in the expression of AdipoR1, a putative adiponectin receptor. Thus the elevated adiponectin levels might be a reflection of a compensatory response to decreased adiponectin signalling in target tissues.

Unno *et al* correlated adiponectin levels with haemodynamic and physiological measures of HCM. However, it remains unclear if adiponectin serves as a useful marker in HCM for identifying patients at risk of developing heart failure symptoms or angina. The study of Unno *et al* should stimulate further activity in this area. Because this study does not inform us about the relationship between LV dysfunction and adiponectin, future investigations should examine whether adiponectin levels correlate with classic measures of diastolic function such as rate and extent of LV filling, E and A waves on Doppler echocardiography, passive elastic stiffness properties as well as the rate of isovolumic relaxation. Furthermore, it would be important to consider if adiponectin levels may serve as a marker to identify patients at risk for developing heart failure with preserved LV ejection fraction.

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