Cardiovascular journals

Obesity is associated with left ventricular dysfunction

Mark Kearney, Cardiologist, King's College Hospital, London

This article by Wong et al is important as it explores the mechanistic relationship between obesity and left ventricular (LV) dysfunction. Previously it has been shown in the Framingham population that obesity is a predictor of the subsequent development of heart failure. Severe obesity has long been recognised to be linked with a form of cardiomyopathy caused by chronic volume overload. However, potential mechanisms underlying the link between obesity and myocardial dysfunction are unclear, particularly in obese patients with only minor functional impairment. In fact, some groups have suggested that changes in cardiac function seen in obesity may simply be caused by associated comorbidities, such as hypertension, diabetes and coronary artery disease.

Using state-of-the-art echocardiographic techniques, Wong et al studied 142 healthy patients with a mean age of 44 years across a wide range of body mass divided into four groups: body mass index (BMI) <24.9, 25–29.9, 30–34.9, and >35.0 kg/m^2. The results of this study showed that severely obese subjects and, in some cases, subjects with lesser degrees of obesity have:

- LV diastolic dysfunction (BMI remaining a predictor of this after correction for blood pressure, insulin and LV mass index)
- Increased LV tissue density, which is thought to reflect the presence of myocardial fibrosis, a feature of many different cardiomyopathies.

The authors went on to speculate on potential mechanisms; they correlated plasma insulin levels with measurements of systolic and diastolic dysfunction and found a weak but positive relationship with some of these measurements. However, the authors did not explore potential relationships between cardiac function and leptin or other cytokines, which would have enhanced the paper further. Nevertheless, this article is an important addition to our understanding of obesity-related cardiovascular disease, demonstrating subtle but important abnormalities of cardiac function in obese people.

This study should discourage clinicians from blaming breathlessness in obese patients on their body mass; we should always consider and look for cardiac as well as vascular dysfunction in our obese patients.

STROKE

J-shaped link for fasting plasma glucose and stroke

Readability	✓✓✓✓
Applicability to practice	✓✓✓✓
WOW! factor	✓✓

1 The aim of the study was to examine the associations between categories of fasting plasma glucose levels and the risk of incident ischaemic stroke.

2 Patients with documented coronary heart disease (n=13 999) were followed up; 1037 cases of ischaemic cerebrovascular disease were identified, of which 576 cases were verified as having ischaemic stroke or transient ischaemic attacks.

3 Increasing fasting glucose level categories were positively associated with increasing age, male gender, body mass index, hypertension, total cholesterol and triglycerides, and were inversely associated with high-density lipoprotein cholesterol and percent high-density lipoprotein of total cholesterol.

4 The association between fasting plasma glucose and incident ischaemic cerebrovascular events in patients with pre-existing atherothrombotic disease was found to be J-shaped. Rates increase for fasting plasma glucose levels >5mmol/l and also for those with low fasting glucose levels.

5 These findings may carry important implications for prevention strategies.

Tanne D, Koren-Morag N, Goldbourt U (2004) Fasting plasma glucose and risk of incident ischemic stroke or transient ischemic attacks. Stroke **35**: 2351–55

CIRCULATION

Obesity is a risk factor for LV dysfunction

Readability	✓✓✓✓
Applicability to practice	✓✓✓✓
WOW! factor	✓✓✓✓

1 This article sought to define the preclinical effects of obesity on the cardiovascular system, independent of other factors, by examining left ventricular (LV) performance using sensitive new echocardiographic techniques including tissue Doppler imaging, myocardial strain imaging and integrated backscatter in 109 healthy subjects with excess body weight and in 33 healthy control patients (body mass index [BMI] <25 kg/m^2).

2 The authors also sought the associations of these changes with insulin levels, duration of obesity and exercise capacity.

3 LV wall thickness, diameters, volumes and LV mass indexed to height increased with increasing BMI. Severely obese patients (BMI >35 kg/m^2) had reduced LV systolic and diastolic function and increased myocardial reflectivity compared with controls, with the LV ejection fraction remaining normal.

4 Similar but lesser degrees of reduced LV function and increased reflectivity were observed in overweight (BMI 25–29.9 kg/m^2) and mildly obese (BMI 30–35 kg/m^2) groups.

5 Although tissue Doppler measures were not associated with duration of obesity, they did correlate with fasting insulin levels and reduced exercise capacity.

6 Obesity is an independent risk factor for subclinical LV dysfunction, even after adjusting for age, mean arterial pressure, LV mass index and insulin.

Wong CY, O'Moore-Sullivan T, Leano R, Byrne N, Beller E, Marwick TH (2004) Alterations of left ventricular myocardial characteristics associated with obesity. Circulation **110**: 3081–87

EUROPEAN HEART JOURNAL

Most patients with CAD have abnormal glucose regulation

Readability	✓✓✓✓
Applicability to practice	✓✓✓✓✓
WOW! factor	✓✓

1 The Euro Heart Survey on diabetes and the heart studied the prevalence of abnormal glucose regulation in adults with coronary artery disease (CAD).

2 The survey engaged 110 centres in 25 countries and recruited 4961 patients referred to a cardiologist as a result of CAD; 2107 were acute hospital admissions and 2854 were elective consults.

3 Patient data were collected by means of a web-based case record form. An oral glucose tolerance test (OGTT) was used for the characterisation of glucose metabolism.

4 In total, 31% of patients had diabetes. An OGTT was performed on the 1920 patients without known diabetes, of whom 923 had acute and 997 had a stable manifestation of CAD, respectively. In patients with acute CAD, 36 % had impaired glucose regulation and 22 % newly detected diabetes. In the stable group, these proportions were 37 % and 14 %.

5 The main finding of this study is that most patients with CAD have abnormal glucose metabolism. This strongly underlines the importance of including diagnostic testing of glucose abnormalities when investigating patients with CAD.

6 An OGTT easily discloses the glucometabolic state and should be a routine procedure; about two-thirds of patients with abnormalities would have been missed using fasting plasma glucose only.

7 In patients with impaired glucose tolerance it is possible to prevent or retard the onset of diabetes; for those with diabetes, a meticulous control of hyperglycaemia can retard atherothrombotic vascular disease and improve survival.

Bartnik M, Rydén L, Ferrari R et al (2004) The prevalence of abnormal glucose regulation in patients with coronary artery disease across Europe. European Heart Journal **25**: 1880–90

AMERICAN HEART JOURNAL

Polymorphism of G894T linked with markers of CHD

Readability	✓✓✓✓
Applicability to practice	✓
WOW! factor	✓

1 The authors studied the effect of the point mutation of guanine to thymine at nucleotide position 894 (G894T) of the endothelial nitric oxide synthase (eNOS) gene on oxidative stress and inflammatory markers.

2 DNA analysis of 270 men (18–87 years old) and 325 women (18–89 years old) who were free of cardiovascular disease showed that 10.6 % were Asp-homozygotes (Asp/Asp), 40 % heterozygotes (Asp/Glu) and 49.4 % Glu-homozygotes (Glu/Glu). Compared with the Asp/Glu and Glu/Glu groups, those in the Asp/Asp group had higher levels of fibrinogen, white blood cells and oxidised low-density lipoprotein cholesterol, after adjustment for several potential confounders.

3 An insignificant association was found between homocysteine, C-reactive protein and the distribution of G894T polymorphism. No association between the distribution of the polymorphism and hypertension status of the participants was observed.

4 This work revealed an association between polymorphism G894T of the eNOS gene and the inflammation and oxidation markers related to coronary heart disease (CHD).

Chrysohoou C, Panagiotakos DB, Pitsavos C et al (2004) Evidence for association between endothelial nitric oxide synthase gene polymorphism (G894T) and inflammatory markers: the ATTICA study. American Heart Journal **148**: 733–38

STROKE

An increased BMI in mid-life increases risk for later stroke

Readability	✓✓✓
Applicability to practice	✓✓✓
WOW! factor	✓✓✓

1 Data on the association between obesity and stroke are limited. This study examined the possible association between mid-life body mass index (BMI) and risk of stroke in the prospective Multifactor Primary Prevention Study in Sweden.

2 Data were derived from 7402 apparently healthy men aged 47–55 years at baseline who were followed up over 28 years. Incidence of fatal and non-fatal stroke was recorded in a stroke registry.

3 A total of 873 first strokes were recorded, including 495 ischaemic, 144 haemorrhagic and 234 unspecified strokes.

4 Compared with men with low normal weight (BMI 20.0–22.49 kg/m^2), men with BMI >30.0 kg/m^2 had a multiple adjusted hazard ratio of 1.93 (95 % confidence interval (CI) 1.44–2.58) for total stroke, 1.78 (95% CI 1.22–2.60) for ischaemic stroke and 3.91 (95 % CI 2.10–7.27) for unspecified stroke. There was no significant association between BMI and haemorrhagic stroke.

5 Adjustment for potential mediators, such as hypertension, diabetes and serum cholesterol levels, attenuated but did not eliminate the risk.

6 The result supports the role of mid-life BMI as a risk factor for stroke later in life and suggests a differentiated effect on stroke subtypes. The risk was partly independent of established risk factors, which underlines the importance of reducing obesity for stroke prevention.

Jood K, Jern C, Wilhelmsen L, Rosengren A (2004) Body mass index in mid-life is associated with a first stroke in men: a prospective population study over 28 years. Stroke **35**: 2764–69

'Data on the association between obesity and stroke are limited. This study examined the possible association between mid-life body mass index (BMI) and risk of stroke...'

'The result supports the role of mid-life BMI as a risk factor for stroke later in life and suggests a differentiated effect on stroke subtypes.'

'Weight loss in obese insulin-resistant, but not in insulin-sensitive, people reduces the risk of coronary heart disease. To what extent changes in gene expression are related to atherosclerosis and cardiovascular function is unknown.'

'Induction of PPAR-α and PPAR-γ in adipose tissue, heart and aortic arch is a key mechanism for reducing atherosclerosis and improving cardiovascular function resulting from weight loss.'

CIRCULATION

Induction of PPAR-α and PPAR-γ reduces atherosclerosis

Readability	✓✓✓
Applicability to practice	✓✓
WOW! factor	✓✓✓✓

1 Weight loss in obese insulin-resistant, but not in insulin-sensitive, people reduces the risk of coronary heart disease. To what extent changes in gene expression are related to atherosclerosis and cardiovascular function is unknown.

2 The authors studied the effect of diet restriction-induced weight loss on gene expression in adipose tissue, the heart and the aortic arch and on atherosclerosis and cardiovascular function in mice with combined leptin and low-density lipoprotein (LDL)-receptor deficiency.

3 Compared with lean mice, the expression of peroxisome proliferator-activated receptors (PPAR)-α and PPAR-γ were downregulated in obese double-knockout mice. Diet restriction caused a 45 % weight loss, an upregulation of PPAR-α and PPAR-γ, and a change in the expression of genes regulating glucose transport and insulin sensitivity, lipid metabolism, oxidative stress and inflammation, most of which are under the transcriptional control of these PPARs.

4 Induction of PPAR-α and PPAR-γ in adipose tissue, heart and aortic arch is a key mechanism for reducing atherosclerosis and improving cardiovascular function resulting from weight loss. Improved lipid metabolism and insulin signalling is associated with decreased tissue deposition of oxidised LDL that increases cardiovascular risk in people with the metabolic syndrome.

Verreth W, De Keyzer D, Pelat M et al (2004) Weight loss-associated induction of peroxisome proliferator-activated receptor-α and peroxisome proliferator-activated receptor-γ correlate with reduced atherosclerosis and improved cardiovascular function in obese insulin-resistant mice. Circulation **110**: 3259–69

CIRCULATION

Resistin promotes smooth muscle cell proliferation

Readability	✓✓✓
Applicability to practice	✓
WOW! factor	✓✓✓✓

1 Resistin, a novel adipokine, is elevated in patients with type 2 diabetes and may play a role in the vascular complications of this disorder. This study assessed whether resistin could induce smooth muscle cell (SMC) proliferation and examined the possible molecular pathways involved in this action.

2 Human aortic SMCs (HASMCs) were stimulated with increasing concentrations of resistin for 48 hours. Cell proliferation was induced by resistin in a dose-dependent manner as assessed by direct cell counting.

3 To gain more insight into the mechanism of action of resistin, the extracellular signal-regulated kinase (ERK) and/or phosphatidylinositol 3-kinase (PI3K) signalling pathways were investigated. Transient phosphorylation of the p42/44 mitogen-activated protein kinase (ERK 1/2) occurred after addition of resistin to HASMCs. U0126, a specific inhibitor of ERK phosphorylation, significantly inhibited ERK 1/2 phosphorylation and reduced resistin-simulated proliferation of HASMCs. LY294002, a specific PI3K inhibitor, also significantly inhibited HASMC proliferation after resistin stimulation.

4 Results demostrate that resistin exerts direct effects on SMC proliferation; moreover, in HASMCs, resistin causes activation of both the ERK 1/2 and PI3K signalling pathways.

5 These data support the hypothesis that the resistin molecule can play a role in the development of the atherosclerotic process, accounting in part for the increased incidence of restenosis in patients with diabetes.

Calabro P, Samudio I, Willerson JT, Yeh ETH (2004) Resistin promotes smooth muscle proliferation through activation of extracellular signal-regulated kinase 1/2 and phosphatidylinositol 3-kinase pathways. Circulation **110**: 3335–40

AMERICAN HEART JOURNAL

Diabetes increases risk for HF in patients with ALVD

Readability	✓✓✓
Applicability to practice	✓✓✓
WOW! factor	✓✓

1 Whether diabetes is a risk factor for the progression from asymptomatic left ventricular systolic dysfunction (LVD) to symptomatic heart failure (HF) in patients with left ventricular dysfunction of an ischaemic cause is not known.

2 The authors performed a retrospective analysis of 2821 patients with asymptomatic LVD from the Studies of Left Ventricular Dysfunction Prevention Trial.

3 There was a statistically significant interaction between the cause of LVD and diabetes on the risk of development of HF symptoms. Patients with ischaemic cardiomyopathy and diabetes had an increased risk of progression to symptomatic HF, hospitalisation for HF and death or the development of symptoms, compared with patients with ischaemic cardiomyopathy without diabetes.

4 However, diabetes was not associated with an increased risk of reaching these end points in patients with non-ischaemic cardiomyopathy.

5 Diabetes is a risk factor for the progression from asymptomatic LVD to symptomatic HF, but this risk appears to be confined to those patients with ischaemic cardiomyopathy.

Das SR, Drazner MH, Yancy CW et al (2004) Effects of diabetes mellitus and ischaemic heart disease on the progression from asymptomatic left ventricular dysfunction to symptomatic heart failure. American Heart Journal **148**: 883–88