Heart Metab. (2013) 61:15–19

Imaging metabolism and perfusion in patients with diabetes and heart failure

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Abstract

Recent advances in imaging technologies have made it possible to quantify myocardial substrate handling and perfusion in humans. This review examines results obtained in patients with type 2 diabetes and/or heart failure. To establish how this knowledge can be profitable for patient management, we summarize a series of targeted intervention studies addressing the causal relationship between cardiac metabolism and cardiac function or perfusion. ■ Heart Metab; 2013;61:15–19

Keywords: Cardiac fat; intervention; fatty acid oxidation; magnetic resonance spectroscopy; myocardial insulin resistance; positron emission tomography.

Introduction

Fatty acids (FAs) are the main fuel of the heart. After a meal, hyperinsulinemia stimulates myocardial glucose utilization and suppresses the use of endogenous FAs, while chylomicron-bound FAs become available through gut absorption. A metabolic shift in favor of glucose consumption also occurs when the oxygen supply does not meet the demands of the heart. Glucose is a more efficient and oxygen-sparing energy source than FAs. Most FAs entering the myocardium are oxidized, but a significant 15% (fasting state) to 33% (hyperinsulinemia) of them are channeled into triglycerides, representing a local depot of mobile energy [1]. Heart metabolism responds to the cardiac workload, and is finely tuned to the surrounding hormonal and substrate milieu, and to the delivery of oxygen through myocardial perfusion.

Recent advances in imaging technologies have made it possible to quantify myocardial substrate handling and perfusion in humans (*Figure 1*).

Myocardial metabolism and perfusion in type 2 diabetes and heart failure

Uncomplicated type 2 diabetes mellitus (T2DM), cardiovascular disease, heart failure and their combination are characterized by myocardial insulin resistance [2–4], which is related to a lower ejection fraction [2] and worse prognosis after revascularization [5]. Myocardial FA uptake and oxidation are high in patients with T2DM [3], and can be either elevated or reduced in individuals with heart failure [6–8]. Imaging of the absorption and distribution of a labeled FA meal has revealed that the myocardial uptake of dietary (chylomicron-derived) FA was also greater in patients with impaired glucose tolerance compared to controls [9]. It was correlated with myocardial oxidative metabolism and lower systolic and diastolic function. The content of triglycerides is increased in the hearts of individuals with diabetes, compared to those without diabetes, irrespective of body mass index, and in patients with ischemic, but not with other kinds of cardiomyopathy [10, 11].

Abbreviations

FA: fatty acid; **GLUT-4:** glucose transporter 4; **LVEF:** left ventricular ejection fraction; **T2DM:** type 2 diabetes mellitus

Myocardial glucose and FA metabolism are reciprocally regulated, and both are highly dependent on the circulating levels of FAs.

In the healthy heart, perfusion responds to the energy and oxygen requirements of the organ. Both T2DM and heart failure, even in the absence of significant macrovascular disease, are frequently characterized by an impaired coronary flow reserve, which is a negative prognostic indicator [12, 13]. Within the myocardium, segments with a lower perfusion reserve show greater glucose uptake in individuals with T2DM and heart disease [4], which may reduce the consumption of oxygen in the poorly perfused myocardium.

In synthesis, the metabolic features observed in the myocardium of patients with T2DM or heart disease represent the expected, physiological response to variations in the lipolytic FA load and coronary vasodilator capacity, both of which are commonly abnormal in these patients. To profit from these observations and apply them to patient management, fundamental questions need to be answered:

1. Do these physiological adaptations contribute to cardiac disease?
2. Is it safe to intervene against these adaptive responses?
3. If so, which one(s) should be counteracted to improve cardiac health?

Cause–effect relationships between cardiac metabolism and function

The manipulation of substrate delivery to the heart or the direct modulation of myocardial metabolism (*Figure 2*) may indicate therapeutic strategies to improve cardiac function and/or perfusion.

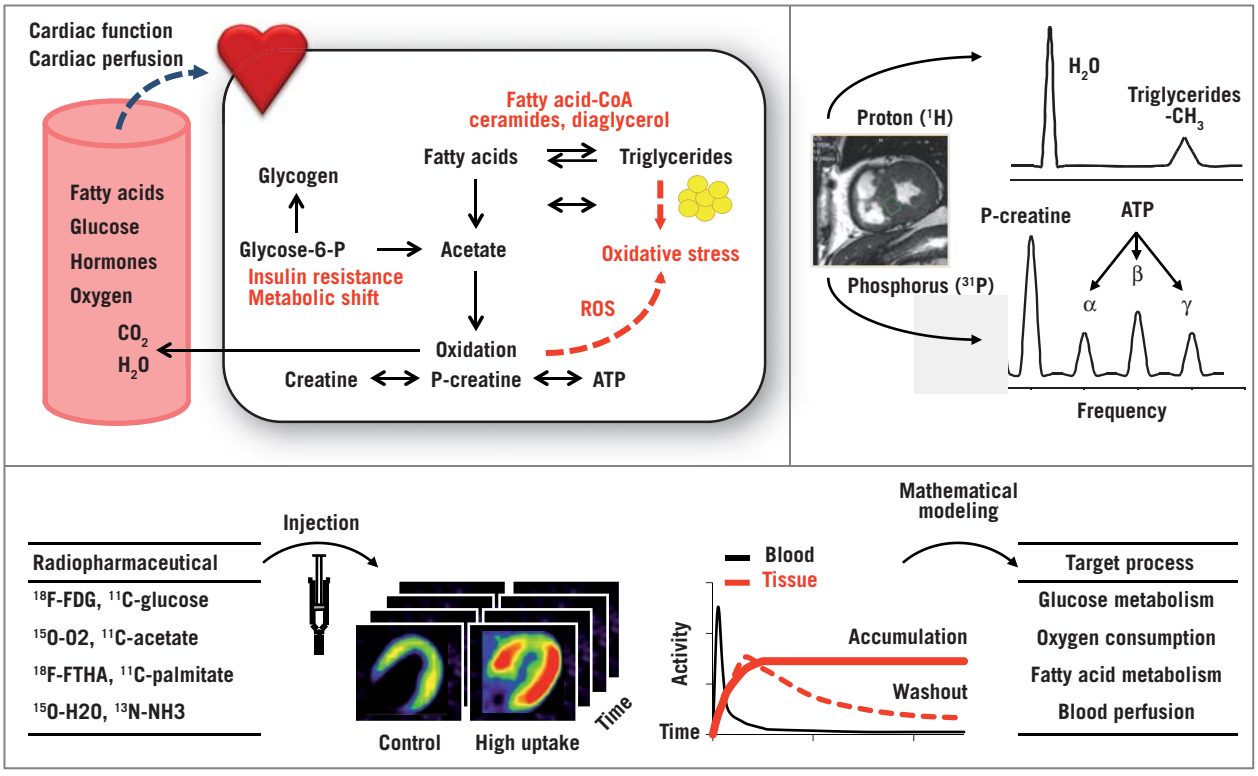

Fig. 1 *Positron emission tomography (bottom panel) allows the kinetics of labeled molecules in the heart to be followed over time. Depending on the radiopharmaceutical used, metabolic rates or perfusion can be computed. Magnetic resonance proton spectroscopy (top right panel) enables molecules to be distinguished based on chemical shift properties and has been validated to quantify the pools of triglycerides and high-energy phosphate compounds in the heart. The top left panel shows the processes of interest, including: myocardial insulin resistance, which may indicate an inability of the heart to shift from FAs to glucose use under the appropriate conditions, including ischemia; FA oxidation, which is paralleled by the formation of ROS, leading to oxidative damage and to the inefficient formation of high-energy phosphate compounds; and triglyceride storage, which may protect the heart by buffering the FA in excess, but is also a substrate of peroxidation. The saturation of this depot may promote the formation of toxic lipid intermediates. Fatty acid CoA, fatty acid co-enzyme A; ROS, reactive oxygen species*

Improving myocardial insulin resistance

Glitazones enhance myocardial insulin sensitivity in patients with T2DM with and without ischemic heart disease or diastolic dysfunction, in parallel with the decline in circulating FA levels [14, 15]. Fasting myocardial FA metabolism, cardiac lipids and myocardial perfusion were unaffected. Those studies included subjects with normal systolic left ventricular function and diastolic dysfunction [15], which makes it difficult to establish the relationship between myocardial insulin sensitivity and clinically significant cardiac dysfunction. They suggest that myocardial insulin resistance can be partly reversed by reducing the FA supply to the heart, and that the improvement in diastolic function is not a direct outcome of the change in myocardial glucose uptake.

Suppressing fasting myocardial FA uptake

The acute administration of the antilipolytic agent acipimox in healthy controls and patients with heart failure resulted in a massive suppression of myocardial FA uptake [16]. Myocardial perfusion was unaffected. The metabolic change was associated with a reduction in cardiac work in patients and controls, and a reduction in oxygen consumption in healthy controls. Therefore, the efficiency of forward work declined in

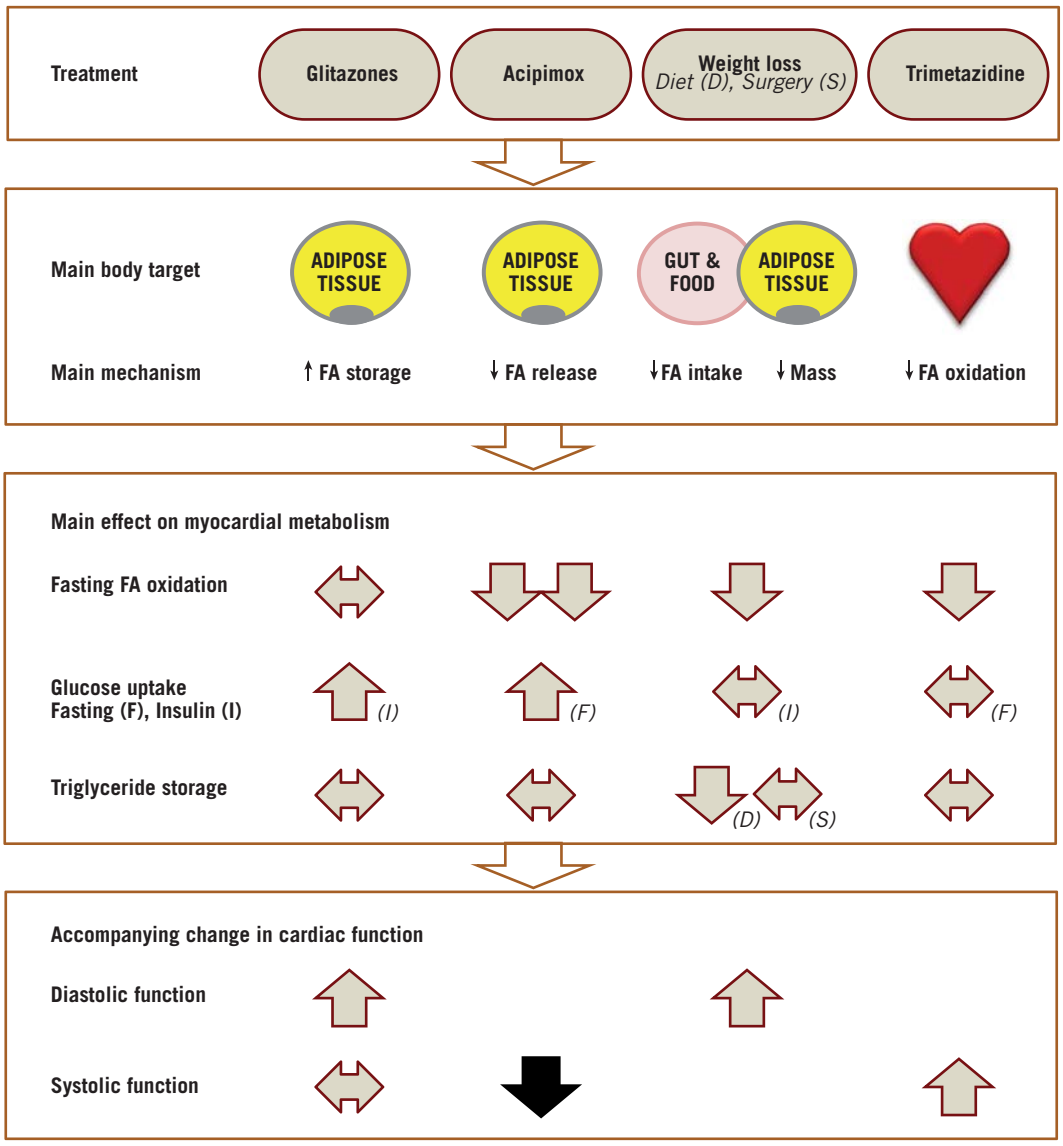

Fig. 2 *The figure exemplifies the main outcomes of intervention studies evaluating the relationship between myocardial metabolic modulation and cardiac function. In a majority of cases, peripheral tissues are the primary targets of treatment, consistent with the adaptive nature of cardiac metabolism in response to the systemic supply of substrates. Indirect and/or direct mechanisms may link cardiac metabolism and function, because their changes are not always statistically correlated, as described in the text. The black arrow indicates an unequivocally negative outcome. (D), effect of low-calorie diet; FA, fatty acid; (F), fasting; (I), insulin; (S), effect of bariatric surgery*

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patients with heart failure, especially in those with insulin resistance, who may have been less responsive to FA suppression. A subsequent study attempted to target myocardial triglycerides [17]. We postulated that a sustained 1-week suppression of FA by acipimox would reduce cardiac fat, allowing its effects on cardiac function to be examined, but no change in cardiac fat was observed. The intervention resulted in a significant impairment in left ventricular work and function, and in left ventricular ejection fraction (LVEF). Under conditions of very low FA levels, all body tissues become glucose avid and insulin levels tend to decline, which may limit any compensatory rise in myocardial glucose uptake. We therefore concluded that the depletion of FA beyond a certain threshold cannot be compensated by glucose in the heart. Consistently, we interpreted the lack in myocardial triglyceride changes to indicate that, once the heart senses conditions of fuel depletion it prioritizes the replenishment of lipid stores by using dietary lipids at meal times. A reduction in FA intake may thus be required to abate the triglyceride stores of the heart as illustrated in the next section.

Reducing post-prandial myocardial FA uptake

Low or very low-calorie diets reduce cardiac triglycerides [18–20] in obese individuals with and without T2DM, independent of dietary composition [19], but bariatric surgery does not [21]. Changes in lipid-lowering or insulin treatments may have impacted triglyceride hydrolysis in opposite ways. The important observation was that both dietary and surgically induced weight losses led to a similar decrease in left ventricular mass, heart rate and cardiac output, and a similar improvement in diastolic function, independent of whether cardiac triglycerides were reduced or unchanged. Instead, the reduction in fasting myocardial oxidative metabolism was directly correlated with the improvement in diastolic function after weight loss [21]. These findings suggest that a selective and moderate suppression of myocardial FA oxidation can improve cardiac function in obese and T2DM individuals.

Direct inhibition of myocardial FA oxidation

A partial inhibition of β-oxidation can be achieved by using the metabolic modulator trimetazidine [22]. Placebo controlled studies conducted in patients with heart failure have documented that this drug improves cardiac function, with no change in myocardial perfusion [23, 24]. In addition, the drug alleviated systemic insulin resistance and increased the phosphocreatine to ATP ratio, as an index of preservation of myocardial high-energy phosphates in these patients [24]. The drug showed a significant, but limited effect on the fractional oxidation of plasma-derived FAs [23]. In a subsequent study addressing the mechanism of action of trimetazidine in slightly overweight individuals with normal cardiac function, we observed a marked reduction in the oxidation of intramyocardial rather than plasma-derived FAs [25]. This change was accompanied by a significant increase in LVEF and stroke volume, in the absence of changes in cardiac fat and fasting myocardial glucose uptake or circulating FA levels. These studies in humans lend support to the concept that in conditions of FA overload and in heart failure, a selective and modest reduction in oxidative metabolism results in an improvement in cardiac function.

Effects of metabolic modulation on myocardial perfusion

Acutely, insulin increases myocardial blood flow and this response does not seem to be compromised in T2DM and/or heart disease [4]. Chronic insulin therapy did not change perfusion in individuals with T2DM and left ventricular dysfunction, but the achievement of a better glucose control was a significant predictor of positive changes in hyperemic myocardial perfusion and coronary flow reserve [26]. Pooled data from glyburide alone or in combination with metformin showed a stimulatory effect in relation to the degree of systemic glucose lowering [27].

Conclusions

Myocardial insulin resistance is a consequence of FA overload and is at least partly reversible. It parallels the decline in LVEF and may contribute to cardiac dysfunction in cardiovascular patients. FA oxidation correlates positively with the cardiac workload, and negatively with the efficiency of work and with post-prandial systolic and diastolic function. A moderate reduction in FA oxidation is beneficial, but interventions aimed at reducing FA oxidation need to guarantee an adequate energy supply to the heart, and may require caution in patients in whom FA oxidation is already depressed. Cardiac triglycerides correlate, but do not change consensually with diastolic dysfunction. They are resistant to a reduction, and may exert a protective role in situations of FA overload

or extreme depletion. The coronary vasodilator response is a negative prognostic marker and responds to hypoglycemic agents. Consistent with the adaptive nature of cardiac metabolism, imaging studies addressing its relationship with adipose tissue dysregulation in patients with heart disease would focus attention on primary rather than secondary causes of cardiac dysfunction. ■

REFERENCES

1. Coggan AR, Kisrieva-Ware Z, Dence CS, Eisenbeis P, Gropler RJ, Herrero P (2009) Measurement of myocardial fatty acid esterification using [1-11C]palmitate and PET: comparison with direct measurements of myocardial triglyceride synthesis. J Nucl Cardiol 16:562–570
2. Iozzo P, Chareonthaitawee P, Dutka D, Betteridge DJ, Ferrannini E, Camici PG (2002) Independent association of type 2 diabetes and coronary artery disease with myocardial insulin resistance. Diabetes 51:3020–3024
3. Rijzewijk LJ, van der Meer RW, Lamb HJ, de Jong HW, Lubberink M, Romijn JA et al (2009) Altered myocardial substrate metabolism and decreased diastolic function in nonischemic human diabetic cardiomyopathy: studies with cardiac positron emission tomography and magnetic resonance imaging. J Am Coll Cardiol 54:1524–1532
4. Masi S, Lautamäki R, Guiducci L, Di Cecco P, Porciello C, Pardini S et al (2012) Similar patterns of myocardial metabolism and perfusion in patients with type 2 diabetes and heart disease of ischaemic and non-ischaemic origin. Diabetologia 55:2494–2500
5. Fath-Ordoubadi F, Pagano D, Marinho NV, Keogh BE, Bonser RS, Camici PG (1998) Coronary revascularization in the treatment of moderate and severe postischemic left ventricular dysfunction. Am J Cardiol 82:26–31
6. Tuunanen H, Engblom E, Naum A, Scheinin M, Någren K, Airaksinen J et al (2006) Decreased myocardial free fatty acid uptake in patients with idiopathic dilated cardiomyopathy: evidence of relationship with insulin resistance and left ventricular dysfunction. J Card Fail 12:644–652
7. Davila-Roman VG, Vedala G, Herrero P, de las Fuentes L, Rogers JG, Kelly DP, Gropler RJ (2002) Altered myocardial fatty acid and glucose metabolism in idiopathic dilated cardiomyopathy. J Am Coll Cardiol 40:271–277
8. Taylor M, Wallhaus TR, Degrado TR, Russell DC, Stanko P, Nickles RJ, Stone CK (2001) An evaluation of myocardial fatty acid and glucose uptake using PET with [18F]fluoro-6-thia-heptadecanoic acid and [18F]FDG in patients with congestive heart failure. J Nucl Med 42:55–62
9. Labbé SM, Grenier-Larouche T, Noll C, Phoenix S, Guérin B, Turcotte EE, Carpentier AC (2012) Increased myocardial uptake of dietary fatty acids linked to cardiac dysfunction in glucose-intolerant humans. Diabetes 61:2701–2710.
10. Iozzo P, Lautamaki R, Borra R, Lehto HR, Bucci M, Viljanen A et al (2009) Contribution of glucose tolerance and gender to cardiac adiposity. J Clin Endocrinol Metab 94:4472–4482
11. Nakae I, Mitsunami K, Yoshino T, Omura T, Tsutamoto T, Matsumoto T et al (2010) Clinical features of myocardial triglyceride in different types of cardiomyopathy assessed by proton magnetic resonance spectroscopy: comparison with myocardial creatine. J Card Fail 16:812–822
12. Murthy VL, Naya M, Foster CR, Gaber M, Hainer J, Klein J et al (2012) Association between coronary vascular dysfunction and cardiac mortality in patients with and without diabetes mellitus. Circulation 126:1858–1868
13. Neglia D, Michelassi C, Trivieri MG, Sambuceti G, Giorgetti A, Pratali L et al (2002) Prognostic role of myocardial blood flow impairment in idiopathic left ventricular dysfunction. Circulation 105:186–193
14. Lautamäki R, Airaksinen KE, Seppänen M, Toikka J, Luotolahti M, Ball E et al (2005) Rosiglitazone improves myocardial glucose uptake in patients with type 2 diabetes and coronary artery disease: a 16-week randomized, double-blind, placebo-controlled study. Diabetes 54:2787–2794
15. van der Meer RW, Rijzewijk LJ, de Jong HW, Lamb HJ, Lubberink M, Romijn JA et al (2009) Pioglitazone improves cardiac function and alters myocardial substrate metabolism without affecting cardiac triglyceride accumulation and high-energy phosphate metabolism in patients with well-controlled type 2 diabetes mellitus. Circulation 119:2069–2077
16. Tuunanen H, Engblom E, Naum A, Någren K, Hesse B, Airaksinen KE et al (2006) Free fatty acid depletion acutely decreases cardiac work and efficiency in cardiomyopathic heart failure. Circulation 114:2130–2137
17. Lehto HR, Pärkkä J, Borra R, Tuunanen H, Lepomaki V, Parkkola R et al (2012) Effects of acute and one-week fatty acid lowering on cardiac function and insulin sensitivity in relation with myocardial and muscle fat and adiponectin levels. J Clin Endocrinol Metab 97:3277–3284
18. Utz W, Engeli S, Haufe S, Kast P, Böhnke J, Haas V et al (2012) Moderate dietary weight loss reduces myocardial steatosis in obese and overweight women. Int J Cardiol Apr 9 [Epub ahead of print]
19. Hammer S, Snel M, Lamb HJ, Jazet IM, van der Meer RW, Pijl H et al (2008) Prolonged caloric restriction in obese patients with type 2 diabetes mellitus decreases myocardial triglyceride content and improves myocardial function. J Am Coll Cardiol 52:1006–1012
20. Viljanen AP, Karmi A, Borra R, Pärkkä JP, Lepomäki V, Parkkola R et al (2009) Effect of caloric restriction on myocardial fatty acid uptake, left ventricular mass, and cardiac work in obese adults. Am J Cardiol 103:1721–1726
21. Gaborit B, Jacquier A, Kober F, Abdesselam I, Cuisset T, Boullu-Ciocca S et al (2012) Effects of bariatric surgery on cardiac ectopic fat: lesser decrease in epicardial fat compared to visceral fat loss and no change in myocardial triglyceride content. J Am Coll Cardiol 60:1381–1389
22. Kantor PF, Lucien A, Kozak R, Lopaschuk GD (2000) The antianginal drug trimetazidine shifts cardiac energy metabolism from fatty acid oxidation to glucose oxidation by inhibiting mitochondrial long-chain 3-ketoacyl coenzyme A thiolase. Circ Res 86:580–588
23. Tuunanen H, Engblom E, Naum A, Någren K, Scheinin M, Hesse B et al (2008) Trimetazidine, a metabolic modulator, has cardiac and extracardiac benefits in idiopathic dilated cardiomyopathy. Circulation 118:1250–1258
24. Fragasso G, Perseghin G, De Cobelli F, Esposito A, Palloshi A, Lattuada G et al (2006) Effects of metabolic modulation by trimetazidine on left ventricular function and phosphocreatine:/adenosine triphosphate ratio in patients with heart failure. Eur Heart J 27:942–948
25. Bucci M, Borra R, Någren K, Pärkkä JP, Del Ry S, Maggio R et al (2012) Trimetazidine reduces endogenous free fatty acid oxidation and improves myocardial efficiency in obese humans. Cardiovasc Ther 30:333–341
26. Masi S, Iozzo P, Simi C, Frassi F, Emdin M, Pisani P et al (2008) Effects of insulin treatment on myocardial function, perfusion and glucose metabolism in patients with primary left ventricular dysfunction and type 2 diabetes: a pilot study. Diabetologia 51(Suppl. 1):S396
27. Schindler TH, Facta AD, Prior JO, Cadenas J, Hsueh WA, Quinones MJ, Schelbert HR (2007) Improvement in coronary vascular dysfunction produced with euglycaemic control in patients with type 2 diabetes. Heart 93:345–349