Size of myocardial infarction induced by ischaemia/reperfusion is unaltered in rats with metabolic syndrome

Troels THIM, Jacob F. BENTZON, Steen B. KRISTIANSEN, Ulf SIMONSEN, Heidi L. ANDERSEN, Karsten WASSERMANN and Erling FALK
Department of Cardiology and Institute of Clinical Medicine, Aarhus University Hospital (Skejby), Aarhus, Denmark

ABSTRACT

Obesity is associated with metabolic syndrome and increased incidence of and mortality from myocardial infarction. The aim of the present study was to develop an animal model with metabolic syndrome and examine how that influences size of myocardial infarcts induced by occlusion and reperfusion of the left anterior descending coronary artery. Sprague–Dawley rats (n = 105) were fed either LF (low-fat) or MHF (moderately high-fat) diets for 13 weeks before coronary occlusion for 45 min, followed by reperfusion for 60 min. Compared with LF-fed and lean MHF-fed rats, obese MHF-fed rats developed metabolic disturbances similar to those seen in the metabolic syndrome, including being overweight by 24% (compared with lean MHF-fed rats), having 74% more visceral fat (compared with LF-fed rats), 15% higher blood pressure (compared with LF-fed rats), 116% higher plasma insulin (compared with lean MHF-fed rats), 10% higher fasting plasma glucose (compared with LF-fed rats), 35% higher non-fasting plasma glucose (compared with lean MHF-fed rats), 36% higher plasma leptin (compared with lean MHF-fed rats) and a tendency to lower plasma adiponectin and higher plasma non-esterified fatty acids. Infarct size was similar in the three groups of rats (36 ± 14, 42 ± 18 and 41 ± 14 % in obese MHF-fed, lean MHF-fed and LF-fed rats respectively). In conclusion, rats fed a MHF diet developed metabolic syndrome, but this did not influence myocardial infarct size.

INTRODUCTION

T2DM (Type II diabetes mellitus) is the most common form of diabetes [1]. It has a strong polygenic background on which environmental factors act and to a large extent determine the clinical presentation [2–4]. Overt T2DM is usually preceded by and/or associated with the MS (metabolic syndrome), which usually develops because of an excess intake of calories and a sedentary lifestyle, and is characterized by visceral obesity, insulin resistance, hyperinsulinaemia, hypertension, atherogenic dyslipidaemia [high triacylglycerols (triglycerides), low HDL (high-density lipoprotein) and an increase in small-dense LDL (low-density lipoprotein)] and a prothrombotic state [1–6].

The risk of MI (myocardial infarction) increases not only in T2DM, but also in MS without T2DM [1,2,6]. Furthermore, the acute case fatality rate, long-term mortality and incidence of heart failure after infarction are increased markedly in T2DM [1,7,8]. An increased susceptibility of the myocardium to ischaemia in the diabetic and dysmetabolic state, leading to increased infarct size [8], has been suggested to play a role for the poor prognosis of MI in T2DM.

Key words: diabetes mellitus, diet, ischaemia/reperfusion injury, metabolic syndrome, myocardial infarction, obesity.

Abbreviations: AAR, area at risk; BP, blood pressure; HDL, high-density lipoprotein; LAD, left anterior descending artery; LF, low-fat; LV, left ventricle; MHF, moderately high-fat; MI, myocardial infarction; MS, metabolic syndrome; NEFA, non-esterified fatty acids; PPAR-α, peroxisome-proliferator-activated receptor-α; T2DM, Type II diabetes mellitus.

Correspondence: Dr Troels Thim (email troels.thim@ki.au.dk).
Infarct size is an important determinant of mortality and heart failure after MI [9,10], but conflicting clinical results have been reported regarding the influence of T2DM on the development of MI in patients assumed to have acute coronary occlusion [8]. In animal models, myocardial necrosis after ischaemia/reperfusion injury was smaller in the obese Zucker diabetic fatty rat [11,12] and the lean Goto–Kakizaki rat [12], whereas, in the db/db mouse, infarct size was larger [13].

In the present study, we hypothesized that MS would be associated with larger infarction. The hypothesis was addressed in a recently developed human-like animal model of MS, the fat-fed obese Sprague–Dawley rat. When fed a LF (low-fat) diet, all Sprague–Dawley rats remain lean; however, as in humans, approximately half of the males develop diet-induced obesity when fed a MHF (moderately high-fat) diet (obesity-prone), whereas the other half will remain lean (obesity-resistant) and gain no more weight than LF-fed rats [14–17]. In this model, diet-induced obesity shares characteristic features with the human MS and T2DM, including polygenic inheritance, insulin and leptin resistance, visceral obesity and hypertension [14–19]. Thus, in this rat model of diet-induced obesity, the effect of a human-like MS on the development of MI after temporary coronary occlusion (ischaemia/reperfusion injury) was studied.

METHODS

All experiments conducted on animals in this study were performed with approval from the Danish Institutional Animal Care and Use Committee.

Rats and diets

Male Sprague–Dawley rats (n = 105) were obtained from Charles River Laboratories. The rats were individually caged and were provided throughout the study with diets and water ad libitum.

At 9 weeks of age, corresponding to a mean body weight of 324 ± 16 g, rats were randomized into two diet groups: one group (n = 75) was fed a MHF diet with 31.8 kcal % fat (D12266B; Research Diets) and the other group (n = 30) was fed a LF diet with 10.6 kcal % fat (D12489B; Research Diets) for a period of 13 weeks. At baseline, a 5-h fasting blood sample was obtained from the retro-orbital venous plexus in all rats and conscious tail-cuff systolic BP (blood pressure) was determined in a subgroup, as described previously [20].

Body weight and food intake were determined weekly throughout the study. After 13 weeks, a 5-h fasting blood sample and the final body weight were obtained and, in a subgroup of rats, BP and a non-fasting blood sample were also obtained.

To secure accurate sampling of obesity-prone and obesity-resistant rats for the subsequent ischaemia/reperfusion study, only MHF-fed rats with a final body weight in the upper third were considered obesity-prone (obese MHF-fed; n = 24), whereas those belonging to the lower third were considered obesity-resistant (lean MHF-fed; n = 24). Among the LF-fed rats, 24 were selected randomly and the remainder were killed.

Myocardial ischaemia/reperfusion

Rats were anaesthetized by an intraperitoneal injection of ketamine (100 mg/kg of body weight) and midazolam (3 mg/kg of body weight). Supplements were given throughout the experiment.

Anaesthetized rats were placed on a heating pad (CMA Microdialysis) controlled by a thermostat, and temperature was monitored by a rectal probe. Rats were placed on a ventilator (Hewlett Packard), by means of a tracheotomy, set for 75 strokes/min of 8 ml of room air. The efficacy of the ventilation was controlled by monitoring of the peripheral oxygen saturation (Ohmeda). A fluid-filled catheter was placed in the aorta via the right carotid artery for continuous monitoring of mean aortic pressure (Siemens), and subcutaneous needles were placed for continuous monitoring of ECG lead II (Hewlett Packard).

After midline thoracotomy, 45 min of regional myocardial ischaemia was induced by occluding the LAD (left anterior descending artery) with a snare. Subsequently, 60 min of reperfusion was established by releasing the snare.

To delineate the ischaemic myocardium, i.e. the AAR (area at risk) of necrosis, the LAD was re-occluded after reperfusion and 1 ml of a 10 % (v/v) Evan’s Blue solution (ICN Biomedicals) was injected into the inferior cava to stain the non-ischaemic myocardium blue. At 1 min after injection of Evan’s Blue, rats were killed under deep anaesthesia by intravenous injection of 3 ml of 10 % (v/v) KCl.

Infarct size

The arrested heart was excised and cross-sectioned into approx. 3-mm thick slices. To delineate the necrotic myocardium within the AAR, slices were immersed in a 2 % (v/v) buffered triphenyltetrazolium chloride (ICN Biomedicals) at 37 °C for 10 min and subsequently immersed in buffered formaldehyde to enhance any colour differences. Each myocardial slice was weighed and photographed (Olympus), and the total left ventricular area, the AAR and the necrotic area were measured by planimetry (analySIS; Soft Imaging System). Based on these weight and area measurements, the weights of the LV (left ventricle), AAR and myocardial necrosis were calculated. Infarct size was expressed as the percentage of necrosis within the AAR. Rats with an AAR of the LV < 20 % were excluded. To obtain a measure of visceral obesity, epididymal fat pads were weighed in a subgroup of rats.
Myocardial infarction in rats with metabolic syndrome

Plasma analysis
EDTA plasma was used for all measurements. The sample was spiked with NaF [final concentration, 0.5% (w/v)] for determination of NEFA (non-esterified fatty acids). Triacylglycerols, cholesterol, HDL-cholesterol and NEFA were all measured using standard enzyme assay kits on a fully automated analyzer (Hitachi 912; Boehringer Mannheim). Leptin, insulin and adiponectin levels were determined by immunologically based assay kits (ELISA or RIA; Linco Research Immunoassay).

Statistical analysis
Group comparisons were performed by Student's t test (Stata). As two comparisons (obese compared with lean MHF-fed rats, and obese MHF-fed compared with LF-fed rats) were performed, a Bonferroni correction was used. Thus a P value < 0.025 was considered statistically significant. For calculation of 97.5% CIs (confidence intervals), a Student's t test was used.

RESULTS
Of the 72 rats selected for myocardial ischaemia/reperfusion, two were excluded before the procedure: one LF-fed rat due to failure to thrive, and one obese MHF-fed rat due to a tumour. During the procedure, eight rats died from refractory ventricular fibrillation: three LF-fed, three lean MHF-fed and two obese MHF-fed rats. After the procedure, one lean and one obese MHF-fed rat were excluded due to an AAR < 20%. Thus 20 hearts remained in each group.

Diets, body weight and BP
At baseline, mean body weight was similar in the three groups. After 1 week, obese MHF-fed rats weighed significantly more than lean MHF-fed and LF-fed rats. These differences in body weight persisted throughout the rest of the study (Figure 1). Thus the obese MHF-fed rats were significantly overweight (24 and 17% increase in body weight compared with lean MHF-fed and LF-fed rats respectively) after 13 weeks when MI (ischaemia/reperfusion) was induced. At that time, the weight of the epididymal fat pad was also significantly higher in obese MHF-fed rats (43 and 74% increase compared with lean MHF-fed and LF-fed rats respectively; Table 1).

The feed intake was significantly higher in obese MHF-fed rats compared with both lean MHF-fed and LF-fed rats (Table 1). Furthermore, feed efficiency, defined as the observed total weight gain divided by total energy intake, was significantly higher in obese MHF-fed rats compared with both lean MHF-fed and LF-fed rats (Table 1).

Baseline BP was similar in the three groups. After 13 weeks, BP was significantly higher in obese MHF-fed rats compared with both lean MHF-fed and LF-fed rats (Table 1). Furthermore, feed efficiency, defined as the observed total weight gain divided by total energy intake, was significantly higher in obese MHF-fed rats compared with both lean MHF-fed and LF-fed rats (Table 1).

Plasma values
At baseline, the mean values of all the measured parameters were similar in the three groups. The final values, taken 13 weeks later, are shown in Table 1. The obese MHF-fed rats developed higher fasting plasma levels of insulin (116 and 27% increase compared with lean MHF-fed and LF-fed rats respectively) and glucose (5 and 10% increase compared with lean MHF-fed and LF-fed rats). Furthermore, the obese MHF-fed rats developed higher fasting plasma levels of leptin (36 and 26% increase compared with lean MHF-fed and LF-fed rats respectively) and tended to have lower fasting plasma adiponectin (8 and 18% decrease compared with
Table 1  Effect of the LF and MHF diets on body weight, epididymal fat, conscious systolic BP, fasting and non-fasting plasma values, and feed intake and feed efficiency

Values are means \( \pm \) S.D.  \( ^{*} \)Significant difference compared with the lean MHF-fed group.  \( ^{\ddagger} \)Significant difference compared with the LF-fed group.  \( ^{\sharp} \)Feed efficiency is calculated as total weight gain (in g) divided by total diet intake (in MJ).  \( |L|F\)-fed, \( n = 8; \) lean MHF-fed, \( n = 8; \) and obese MHF-fed, \( n = 7 \).  \( |L|F\)-fed, \( n = 9; \) lean MHF-fed, \( n = 2; \) obese MHF-fed, \( n = 7 \).  \( \|L|F\)-fed, \( n = 9; \) lean MHF-fed, \( n = 2; \) obese MHF-fed, \( n = 7 \).

<table>
<thead>
<tr>
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<th>Obese MHF-fed</th>
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<tr>
<td>n</td>
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<td>24</td>
<td>23</td>
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<tr>
<td>Body weight (g)</td>
<td>620 ± 44</td>
<td>586 ± 30</td>
<td>728 ± 34*†</td>
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<tr>
<td>Diet intake (MJ)</td>
<td>35.3 ± 3.2</td>
<td>35.3 ± 2.7</td>
<td>42.4 ± 2.4*†</td>
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<tr>
<td>Feed efficiency(^{\sharp} )</td>
<td>7.5 ± 1.4</td>
<td>6.7 ± 0.9</td>
<td>8.7 ± 1.0*†</td>
</tr>
<tr>
<td>Epididymal fat (g)(^{%} )</td>
<td>10.5 ± 3.7</td>
<td>12.8 ± 2.9</td>
<td>18.3 ± 3.5*†</td>
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<tr>
<td>BP (mmHg)∥</td>
<td>123 ± 6</td>
<td>134 ± 16</td>
<td>141 ± 7†</td>
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<tr>
<td>Fasting</td>
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<tr>
<td>Glucose (mmol/l)</td>
<td>8.0 ± 0.7</td>
<td>8.5 ± 0.7</td>
<td>8.9 ± 1.0†</td>
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<tr>
<td>Insulin (pmol/l)</td>
<td>407 ± 220</td>
<td>240 ± 101</td>
<td>510 ± 245*</td>
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<tr>
<td>Triacylglycerols (mmol/l)</td>
<td>2.35 ± 0.69</td>
<td>1.29 ± 0.50</td>
<td>1.60 ± 0.42†</td>
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<td>Cholesterol (mmol/l)</td>
<td>2.75 ± 0.58</td>
<td>2.37 ± 0.45</td>
<td>2.87 ± 0.47*</td>
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<td>HDL-cholesterol (mmol/l)</td>
<td>1.81 ± 0.43</td>
<td>1.87 ± 0.35</td>
<td>2.16 ± 0.40*†</td>
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<tr>
<td>Leptin (ng/ml)¶</td>
<td>18.5 ± 3.6</td>
<td>17.2 ± 1.7</td>
<td>23.4 ± 2.2*</td>
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<tr>
<td>Adiponectin ((\mu)g/ml)¶</td>
<td>8.5 ± 1.4</td>
<td>7.6 ± 1.5</td>
<td>7.0 ± 1.2</td>
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<tr>
<td>Non-fasting(^{%} )</td>
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<tr>
<td>Glucose (mmol/l)</td>
<td>10.9 ± 3.7</td>
<td>9.7 ± 2.0</td>
<td>13.1 ± 2.3*</td>
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<tr>
<td>NEFA ((\mu)mol/l)</td>
<td>139 ± 52</td>
<td>154 ± 20</td>
<td>194 ± 83</td>
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leash. MHF-fed and LF-fed respectively); however, the statistical power of the test was low, due to the limited number of observations (Table 1). Also, in the non-fasting state, obese MHF-fed rats had higher plasma levels of glucose (35 and 21% increase compared with lean MHF-fed and LF-fed rats respectively) and tended to have higher plasma NEFA (26 and 40% increase compared with MHF-fed and LF-fed rats respectively). With the exception of the triacylglycerol and HDL-cholesterol values, all of these changes were in a direction similar to that seen with MS in humans.

**Perioperative monitoring**

Peripheral oxygen saturation was stable (95–100%) in all three groups. Rectal temperature was within the range of 36.8–38.0°C and was similar in the three groups. Mean aortic BP, heart rate and thus rate pressure product were also similar in the three groups. Following LAD occlusion, a consistent fall in mean aortic BP and, consequently, the rate pressure product was observed (Figure 2).

**LV, AAR and infarct size**

Although the obese MHF-fed rats had heavier LVs compared with lean MHF-fed rats, they had a lower LV/body weight ratio (Table 2). AAR was similar in all three groups, ranging from 22 to 62% of the LV by weight. Infarct size was also similar, ranging from 9 to 69% of the AAR, but tended to be lower in obese MHF-fed rats compared with lean MHF-fed and LF-fed rats (87 and 89% respectively; Table 2).

**DISCUSSION**

By feeding a MHF diet to rats, we succeeded in producing visceral obesity and metabolic disturbances similar to those seen in MS in humans. However, in contrast with

![Figure 2](https://example.com/figure2.png)

**Figure 2**  Development in rate pressure product during ischaemia (0–45 min) and reperfusion (45–105 min) in rats on LF and MHF diets

Rate pressure product is calculated as the product of mean aortic BP (in mmHg) and heart rate (in beats/min).

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Effect of the LF and MHF diets on the LV, AAR and infarct size

Values are means ± S.D. *Significant difference compared with lean MHF-fed group. †Significant difference compared with LF-fed group.

<table>
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<tr>
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<th>Lean MHF-fed</th>
<th>Obese MHF-fed</th>
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<tbody>
<tr>
<td>n</td>
<td>20</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>LV (mg)</td>
<td>863 ± 114</td>
<td>831 ± 102</td>
<td>935 ± 95*</td>
</tr>
<tr>
<td>LV/body weight ratio (mg/g)</td>
<td>1.40 ± 0.15</td>
<td>1.41 ± 0.15</td>
<td>1.28 ± 0.10†</td>
</tr>
<tr>
<td>AAR (%)</td>
<td>43 ± 9</td>
<td>41 ± 12</td>
<td>42 ± 8</td>
</tr>
<tr>
<td>Infarct size (%)</td>
<td>41 ± 14</td>
<td>42 ± 18</td>
<td>36 ± 14</td>
</tr>
</tbody>
</table>

our expectations, the presence of MS had no influence on myocardial infarct size after 45 min of coronary occlusion, followed by 60 min of reperfusion. Thus MS does not seem to increase the susceptibility of the myocardium to ischaemia/reperfusion injury. Although counterintuitive at first glance, this result obtained in rats may in fact explain many observations obtained in patients with MI.

Metabolic state

The MHF diet used in the present study contained 31.8 kcal % of fat, which is similar to the fat content of a standard Western diet, and it contained no excess amounts of any compound, including cholesterol.

Significant differences in body weight between the obese MHF-fed, lean MHF-fed and LF-fed rats developed within the first week and persisted throughout the study. Increased intake and feed efficiency, a measure of metabolic utilization of dietary calories in weight gain, explained these differences.

The overweight nature of the obese MHF-fed rats reflected an increase in visceral obesity and was associated with higher plasma insulin and glucose levels. Elevated plasma insulin is regarded as a surrogate measure of insulin resistance, and has been shown to predict the development of T2DM independent of the presence of insulin resistance [21]. Thus these obese MHF-fed rats were most probably insulin resistant.

The leptin and adiponectin data reveal an interesting trend across the three groups; leptin increased with increasing body weight, and adiponectin decreased with increasing visceral obesity. These trends resemble those reported for humans with obesity, insulin resistance and T2DM [22,23].

The finding of increased systolic BP in the obese MHF-fed rats in the present study also mimics a classical feature of MS [1].

The lipid profile in obese MHF-fed rats differed somewhat from that seen in human MS [1]. In humans, CETP (cholesteryl ester transfer protein) is regarded as a key player in the development of dyslipidaemia associated with insulin resistance [24]. This protein is not expressed in rats [25], which may explain the differences in the plasma lipid profile; in particular, the high HDL-cholesterol levels that are typically seen in rodents. However, this does not explain the surprisingly higher triacylglycerol levels observed in LF-fed rats.

Different definitions of MS exist [26]. A general perception of the concept is that the term MS refers to a cluster of characteristic cardiovascular risk factors, and the underlying pathophysiology is thought to be related to insulin resistance [27]. In the present study, the obese MHF-fed rats developed obesity with increased visceral fat as well as elevated BP and plasma glucose, which constitute three MS-related features. However, although this animal model is regarded as a relevant model of human MS [14–19], the plasma lipid profile differed from that typically seen in humans, which might not be trivial for the development of myocardial ischaemia/reperfusion injury.

There were significant differences between the obese and lean MHF-fed groups, with no significant differences between the obese MHF-fed and LF-fed group with regards to insulin, triacylglycerols, cholesterol, leptin, glucose (non-fasting) and LV weight. The LF-fed group represents the genetically broad spectrum of both obesity-prone and obesity-resistant rats, which may explain why some of the parameters in this group are intermediate to those of the obese and lean MHF-fed groups. Differences between the LF-fed and lean MHF-fed groups have not been evident in all studies of the model [19], suggesting that a long exposure time to the diet may be required, as used in the present study and in the study characterizing this diet model [14] or restricted feeding [17].

Myocardial metabolism and infarct size

The healthy heart relies predominantly on oxidation of fatty acids for energy production. In insulin resistance, the heart increases its reliance on fatty acids for energy production [28]. This change is due to up-regulation of enzymes involved in fatty acid oxidation and down-regulation of glycolytic enzymes, which is promoted by stimulation of PPAR-α (peroxisome-proliferator-activated receptor-α) by fatty acids [29]. The importance of glycolysis increases during ischaemia, and increased oxidation of glucose relative to fatty acids during reperfusion is associated with improved cardiac function [30,31].

To the best of our knowledge, clinical evidence for an association between diabetes and increased infarct size has never been provided, although this has been sought [8]. An increased infarct size may seem logical due to the decreased ability to produce energy anaerobically through glycolysis during ischaemia. However, in the present study, this was not the case, as the infarct size tended to be smaller, rather than larger, in the obese
MHF-fed rats. Smaller infarction has, in fact, also been demonstrated recently in two other rat models of T2DM, the obese Zucker diabetic fatty rat and the lean Goto–Kakizaki rat [12]. The perioperative temperature, aortic pressure, heart rate and oxygen saturation were similar in the three groups of rats in the present study and can thus be disregarded as explanations for the failure of MS to increase infarct size in the MHF-fed rats. Interestingly, stimulation of PPAR-α, which might be increased with insulin resistance, has been shown previously to decrease infarct size in the experimental setting [32].

If the increased mortality during MI in T2DM is not caused by larger infarction, it could be caused by an increased vulnerability to ischaemia-induced ventricular fibrillation in the dysmetabolic state, possibly related to elevated plasma NEFA [33]. The latter is also supported by epidemiological studies showing an increased incidence of sudden death in diabetic compared with non-diabetic patients [34]. This is in contrast with non-sudden cardiac death which is similar in the two groups of patients [34], and this is also supported by the present findings in an experimental animal model for MS.

Study limitations
Although the changes in myocardial metabolism associated with insulin resistance, in both rats and humans, are towards a greater reliance on fatty acid oxidation for energy production, it is uncertain whether the plasma lipid profile in MS has adverse effects on the myocardium that cannot be evaluated in this model [35]. The plasma lipid profile did differ somewhat from that seen with the human MS, due to the innate differences in lipid metabolism between humans and rodents [25].

It could be speculated that the infarct size in the obese rats would have been larger if the dysmetabolic state had persisted longer. This is, however, unlikely, because the infarct size tended to be smaller, rather than larger, in the obese rats.

Conclusion
In the present study, a high-fat diet resulted in the animals being overweight and increased visceral obesity, higher BP and higher plasma levels of insulin, glucose and leptin, as well as a tendency to lower plasma adiponectin, indicating the presence of MS. However, in this rat model, diet-induced obesity and the associated MS had no effect on infarct size after temporary coronary occlusion.

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