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Treatment with low-dose resveratrol reverses cardiac impairment in obese prone but not in obese resistant rats☆

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Abstract

We hypothesized that a low-dose resveratrol will reverse cardiovascular abnormalities in rats fed a high-fat (HF) diet. Obese prone (OP) and obese resistant (OR) rats were fed an HF diet for 17 weeks; Sprague–Dawley rats fed laboratory chow served as control animals. During the last 5 weeks of study, treatment group received resveratrol daily by oral gavage at a dosage of 2.5 mg/kg body weight. Assessments included echocardiography, blood pressure, adiposity, glycemia, insulinemia, lipidemia, and inflammatory and oxidative stress markers. Body weight and adiposity were significantly higher in OP rats when compared to OR rats. Echocardiographic measurements showed prolonged isovolumic relaxation time in HF-fed OP and OR rats. Treatment with resveratrol significantly improved diastolic function in OP but not in OR rats without affecting adiposity. OP and OR rats had increased blood pressure which remained unchanged with treatment. OP rats had elevated fasting serum glucose and insulin, whereas OR rats had increased serum glucose and normal insulin concentrations. Resveratrol treatment significantly reduced serum glucose while increasing serum insulin in both OP and OR rats. Inflammatory and oxidative stress markers, serum triglycerides and low-density lipoprotein were higher in OP rats, which were significantly reduced with treatment. In conclusion, HF induced cardiac dysfunction in both OP and OR rats. Treatment reversed abnormalities in diastolic heart function associated with HF feeding in OP rats, but not in OR rats. The beneficial effects of resveratrol may be mediated through regression of hyperglycemia, oxidative stress and inflammation.

Keywords: Resveratrol; Diet-induced obesity; Cardiac function; Obese resistant; Obese prone; High-fat diet

1. Introduction

Obesity has reached the status of a global epidemic, with as many as 1.5 billion adults considered overweight and around 500 million obese [1]. Lifestyle in combination with genetic predisposition is the major cause of obesity [2]. Obesity leads to several comorbidities including hypertension, type 2 diabetes, congestive heart disease, stroke, respiratory disorders and even some types of cancers [3]. In fact, heart failure is one of the major causes of death in obese individuals [4]. Obesity induces diastolic heart failure [5], with many cellular and molecular changes triggering the onset of this pathology. Lipotoxicity [6], adipose tissue dysfunction [7] and increased release of adipokines such as interleukin 6 (IL-6) and tumor necrosis factor-α (TNF-α) are factors that favor the development of cardiovascular diseases [8]. Hypertension and elevated adrenergic stimulation also contribute to the development of obesity-induced cardiac dysfunction [9,10].

Conventional treatments for obesity have mainly targeted weight loss through controlled diet, physical exercise, pharmacotherapy and bariatric surgery. Moderate weight loss could be beneficial as a treatment, whereas rapid and extensive weight loss has been reported to be harmful [11]. In addition, drugs used in promoting weight loss and regressing cardiac abnormalities are often associated with dire outcomes [12], thus limiting treatment options for obesity and associated cardiac complications. Therefore, it is critical to explore newer therapies to prevent the development of heart failure associated with obesity. One such avenue may be the use of foods or food-derived compounds which have authenticated medical benefits and fewer complications [13,14].

Resveratrol, a polyphenol and stilbene derivative found predominantly in grapes and berries, has been widely explored for its beneficial use against a variety of ailments including cardiovascular disease [15]. Earlier studies from our laboratory have reported that resveratrol prevents as well as reverses abnormalities in cardiac

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structure and function in different models of hypertension in rats [16–18]. There is very little information on the effects of resveratrol in preventing the development of cardiovascular complications in animal models of obesity. Treatment with resveratrol was shown to reduce blood pressure in a genetic model of obesity, obese Zucker rats [19], and in a diet-induced model of obesity, high-fat (HF)-fed rats [20]. However, if resveratrol is to be used in any clinical intervention against cardiovascular diseases associated with obesity, it is important to know whether resveratrol is capable of reversing the cardiovascular complications.

In this study, we have used the model of diet-induced obesity (DIO) which was developed from outbred Sprague–Dawley (SD) rats. When fed a high-energy diet, some of these rats gained more weight, while the others did not. The rats which gained more weight were then selectively bred to maintain pure genetic lines and were termed obese prone (OP), while the other rats (which did not gain weight) were bred as obese resistant (OR) [21]. Hormonal irregularity [22,23], increased fasting triglycerides (TG), reduced fatty acid oxidation [24] and defective leptin signaling were identified as some of the factors that determine the difference in weight gain pattern among these animals. The OP rats present with increased fat pad weight, hypertension [25], increased inflammation and oxidative stress [26], impaired glucose homeostasis [21], defective renal and intestinal functions [26,27], lower antioxidant status, defective sympathetic activity and impairment in hormones that control appetite at the neuronal levels in brain [28–30].

In this study, we fed OP and OR rats with an HF diet and then treated them with resveratrol to explore its potential in the treatment of cardiac dysfunction developed as a consequence of obesity.

2. Materials and methods

The experimental protocols used in this project were approved by the University of Manitoba Animal Care Committee and are in agreement with the Canadian Council on Animal Care and Use of Experimental Animals [31].

2.1. Model of high-fat feeding

Five-week-old selectively bred male OP and OR rats purchased from Charles River, St Constant, Quebec, Canada, were used in this study; a set of normal male SD rats obtained from Central Animal Care Services at the University of Manitoba, Manitoba, Canada, served as controls. Animals were acclimatized in a temperature- and humidity-controlled room with a 12-h dark and 12-h light period cycle for 1 week prior to the start of the HF diet. OP and OR rats were fed an HF diet (energy from fat 55%, carbohydrate 30% and protein 15%), and control SD rats were fed standard diet (Prolab RMH 3000; 14% energy from fat) for a period of 17 weeks. All rats received tap water *ad libitum*. Body weight was determined weekly.

2.2. Resveratrol treatment

OP, OR and SD rats were randomly assigned to either resveratrol-treated or control groups. The number of rats in each group was as follows: OP untreated, $n=10$; OP treated, $n=10$; OR untreated, $n=11$; OR treated, $n=11$; SD untreated, $n=8$ and SD treated, $n=8$. Trans-resveratrol (>99% pure; Sigma-Aldrich Ltd, Ontario, Canada) dissolved in 50% ethanol (vehicle) was administered daily by oral gavage (1 ml/rat) at a dosage of 2.5 mg/kg body weight (an effective concentration based on our previous studies [17,18]) at the same time of the day starting at week 13 on diet. Control groups received 1 ml of 50% ethanol daily by oral gavage for the same period of time. The study was terminated after 17 weeks on HF diet.

2.3. Blood pressure measurements

Blood pressure measurement was carried out on all groups of animals at 12 and 17 weeks, as described previously [32]. A CODA multichannel, computerized, noninvasive blood pressure system (Kent Scientific, Torrington, CT, USA) with a tail-cuff sphygmomanometer was used to measure systolic and diastolic blood pressure of conscious rats.

2.4. Echocardiography

Cardiac structure and function were measured in all groups of animals using echocardiography at 6, 12 and 17 weeks; transthoracic two-dimensionally (2D) guided M-mode and pulse-wave Doppler measurements were performed using a Sonos 5500 ultrasound system (Agilent Technologies, Andover, MA, USA) equipped with a 12-MHz (s12) transducer as previously described [33]. 2D M-mode measurements included percentage of left ventricular fractional shortening, left ventricular ejection fraction (EF), cardiac output (CO), left ventricular mass, heart rate, interventricular septal wall thickness at diastole (IVSd) and systole, left ventricular posterior wall thickness at diastole (LVPWd) and systole, and left ventricular internal dimensions at diastole (LVIDd) and systole. Doppler measurements included isovolumetric relaxation time (IVRt). All echocardiography measurements were carried out on anesthetized animals.

2.5. Tissue collection

At the end of the study (17 weeks), all rats were fasted overnight and euthanized by CO_2 asphyxiation. The heart tissues were removed, weighed, flash frozen in liquid nitrogen and stored at −80°C for further analyses. Blood samples were collected with and without heparin and centrifuged at 2500 rpm for 20 min to obtain plasma and serum which were stored at −80°C for further analyses. Body weight and fat pad mass (epididymal, perirenal and mesenteric) were recorded for assessing adiposity.

2.6. Biochemical assessments

Lipid peroxidation levels in blood plasma were estimated as the amount of malondialdehyde using the Oxiselect TBARS Assay Kit (Cell Biolabs, San Diego, CA, USA). Inflammatory markers TNF-α and IL-6 were measured using appropriate kits (Thermo Scientific, ON, Canada). Assay kits were used for TG, high-density lipoprotein (HDL), low-density lipoprotein (LDL), glucose (Genzyme Diagnostics P.E.I. Inc., Charlottetown, PE, Canada) and insulin (Alpco Diagnostics, Salem, NH, USA) measurements. All assays were performed according to the manufacturer instructions.

2.7. Statistical analysis

All statistical analyses were performed using SAS statistical package (version 9.1; SAS Institute Inc., Cary, NC, USA). One-way repeated-measures analysis of variance (ANOVA) was used to analyze weekly body weight. For all other parameters, two-way ANOVA was used to assess significant main effects of model (genotype+diet; SD, OR, OP), treatment (±resveratrol) and their interactions. Significance was defined as $P<.05$ for main effects and $P<.1$ for interactions. Data were assessed for normality using the Shapiro–Wilk's test and homogeneity of variance by Levene's test. Log transformation was used when necessary to normalize data sets. All values are expressed as mean±S.E. For post hoc testing, significance ($P<.05$) among means was determined by Duncan's multiple range test.

3. Results

3.1. General characteristics of the animal model

OR rats had significantly lower body weights throughout the study when compared to OP rats. SD rats had body weights similar to HF-fed OP rats. At the end of the study, SD and OP rats had a 3.7-fold increase in their body weight, while OR rats had a 2.8-fold increase. Resveratrol treatment had no effect on the body weight in any of the models (Fig. 1A). Parallel to higher body weight, OP rats had significantly greater adiposity based on total visceral fat to body weight ratio. However, SD and OR rats had similar total visceral fat to body weight ratio. Treatment with resveratrol did not have any effect on the total visceral fat in any of the rats (Fig. 1B). Heart to body weight ratio was significantly lower in OP rats when compared to SD control rats; resveratrol treatment had no effect on this parameter (Fig. 2). Throughout the course of the study, mortality was limited to OR rats (14%).

3.2. Blood pressure

Twelve weeks of HF feeding induced a significant increase in blood pressure in OP and OR rats when compared to the corresponding SD control rats (Fig. 3). There was no further increase in blood pressure at the 17-week time point. Resveratrol treatment did not lower blood pressure in any of the groups.

3.4. Cardiac function and structure

IVRt, the diastolic function parameter, was significantly increased in OP and OR groups fed HF for 12 weeks when compared to age-

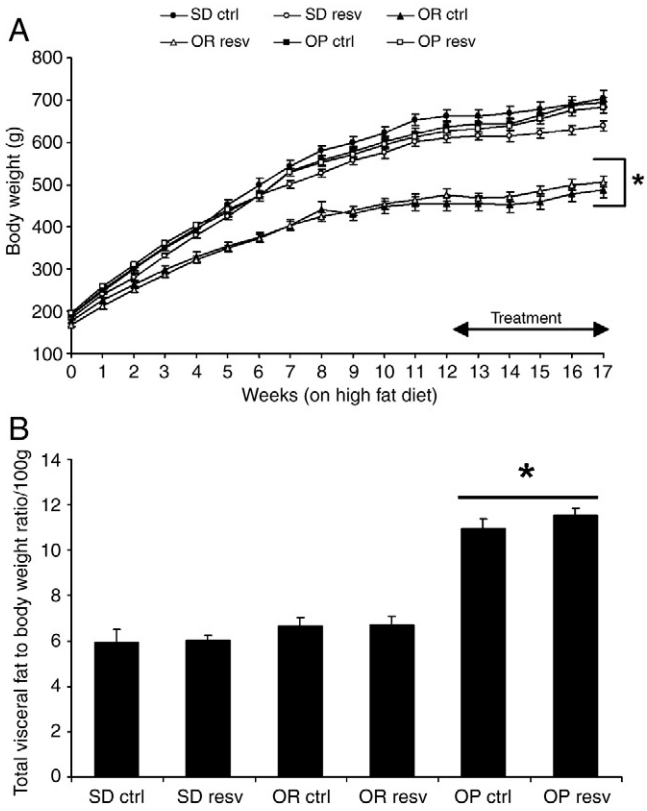

Fig. 1. Weekly body weight and total visceral fat weight to body weight ratio of SD, OR and OP rats. (A) Weekly body weight; (B) total visceral fat (visceral fat equals sum of epididymal, perirenal and mesenteric fat pads). Data are means±S.E., n=6–10. Significant main effect of model. *P<.05 vs. other two models at all time points. Ctrl, control; resv, resveratrol treated.

matched SD rats fed with normal chow; treatment with resveratrol significantly reduced prolonged IVRt in OP rats at 17 weeks. However, resveratrol treatment failed to reduce prolonged IVRt in OR rats (Fig. 4A). HF diet did not affect CO at 6, 12 and 17 weeks in OP rats. However, CO was significantly lower in OR rats at all time points when compared to corresponding SD control rats. Resveratrol treatment did not have any effect on CO of SD, OR and OP rats (Fig. 4B). EF was significantly higher in OR and OP rats at weeks 6 and 17. Resveratrol treatment had no effect on this parameter (Fig. 4C). Heart rate analysis showed a significant increase in OP rats at 6, 12 and 17 weeks, while, in OR rats, the increase was evident at

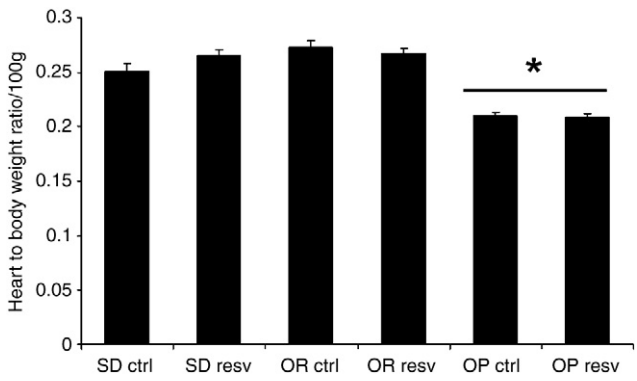

Fig. 2. Heart weight to body weight ratio of SD, OR and OP rats. Data are means±S.E., n=6–10. Significant main effect of model. *P<.05 vs. other two models.

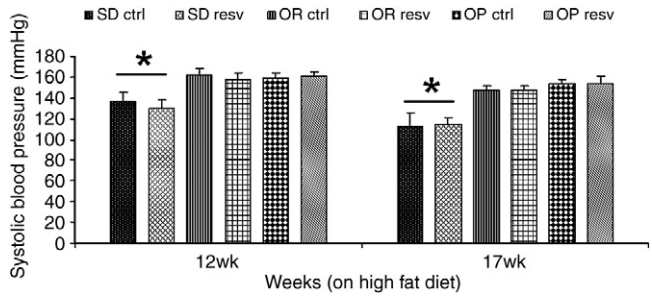

Fig. 3. Systolic blood pressure of SD, OR and OP rats. Data are means±S.E., n=6–9. Significant main effect of model. *P<.05 vs. other two models.

12 and 17 weeks. However, resveratrol treatment did not significantly reduce the heart rate at any time point in OP and OR rats (Supplementary figure 1).

Throughout the study, there was no observed change in IVSd (Fig. 5A). At 6, 12 and 17 weeks, OR and OP rats had significantly lower LVIDd and LVPWd when compared to corresponding SD control rats. At all time points, resveratrol treatment did not have any specific effect on these cardiac structure parameters of SD, OP and OR rats (Fig. 5A, B and C). The vehicle administered between weeks 13 and 17 had no effect on cardiac function or structure parameters. Supplementary figure 2 is a representative echocardiographic image from each group.

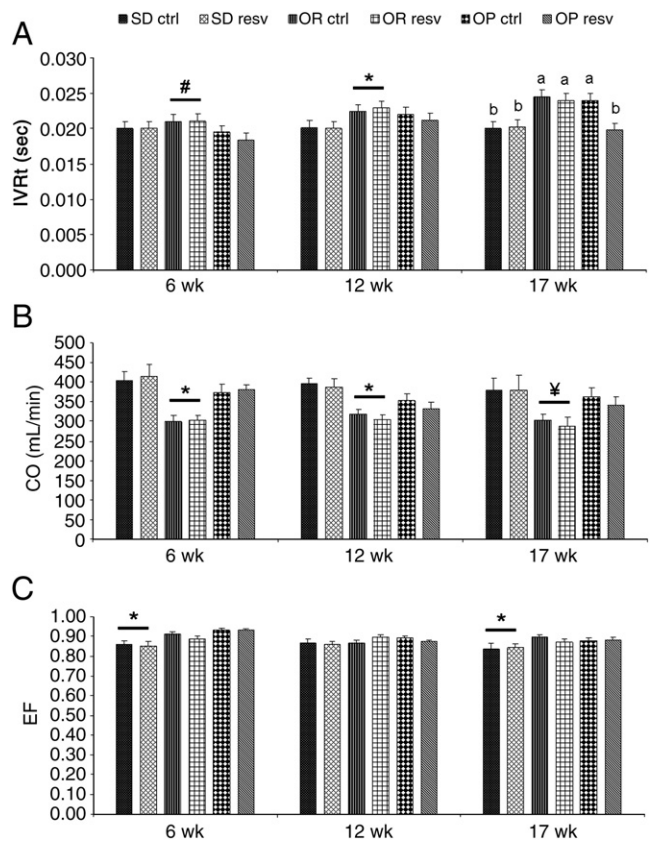

Fig. 4. Echocardiographic data showing cardiac function measurements of SD, OR and OP rats. (A) Isovolumic relaxation time (IVRt); (B) cardiac output (CO); (C) ejection fraction (EF). Data are means±S.E., n=6–10. Significant main effects of model for IVRt (6, 12 weeks), CO (6, 12, 17 weeks) and EF (6, 17 weeks) and significant model×treatment interaction for IVRt (17 weeks). *P<.05 vs. other two models; #P<.05 vs. OP; ¥P<.05 vs. SD. Means with different letters are significantly different (P<.05) from each other.

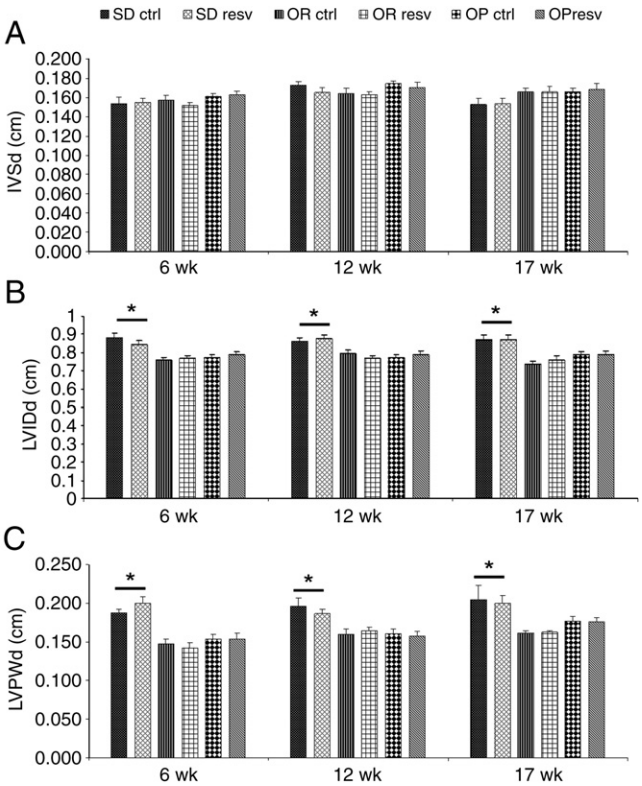

Fig. 5. Echocardiographic data showing cardiac structure measurements of SD, OR and OP rats. (A) Interventricular septal wall thickness at diastole (IVSd), (B) left ventricular internal dimension at diastole (LVIDd) and (C) left ventricular posterior wall thickness at diastole (LVPWd). Data are means±S.E., n=6–10. Significant main effects of model for LVIDd (6, 12, 17 weeks) and LVPWd (6, 12, 17 weeks). *P<.05 vs. other two models. Data for LVPWd (6 weeks) were log transformed for statistical analysis, but untransformed data are presented.

3.5. Oxidative stress and inflammatory markers

The HF diet induced a significant increase in plasma thiobarbituric acid reactive substances (TBARS) levels in 17 week OP rats when compared to their age-matched SD control rats; resveratrol treatment reduced elevated TBARS levels in OP rats to control levels. Plasma TBARS levels of OR rats were unchanged after 17 weeks on HF diet when compared to SD control rats (Fig. 6A). There was a sixfold and threefold increase in the serum TNF-α levels of OR and OP rats, respectively, when compared to SD control rats. Resveratrol treatment normalized the serum TNF-α in both OP and OR rats (Fig. 6B). Serum IL-6 levels were increased fourfold in OP rats when compared to SD control rats and were normalized upon resveratrol treatment. OR rats had a twofold increase in serum IL-6 levels when compared to SD controls; resveratrol treatment did not affect IL-6 levels (Fig. 6C).

3.6. Triglyceride, glucose and insulin

There was a threefold increase in fasting serum TG levels in OP rats when compared to their corresponding SD controls. Five weeks of resveratrol treatment significantly lowered TG levels in OP rats. However, OR rats had TG levels similar to those of SD controls (Fig. 7A). Fasting serum glucose measurement showed a 1.9- and 2.4-fold increase in OR and OP groups, respectively, when compared to SD controls. Resveratrol treatment significantly reduced elevated glucose levels in both OP and OR rats (Fig. 7B). Fasting serum insulin levels in OR rats were similar to SD control rats, while OP rats had a 2.4 times increase. However, resveratrol treatment significantly increased insulin levels in both OR and OP rats (Fig. 7C).

3.7. LDL and HDL measurements

Levels of LDL were elevated in HF-fed OP rats when compared with SD control rats, whereas LDL levels remained unchanged in OR rats. Resveratrol treatment significantly lowered LDL levels in HF-fed OP rats (Fig. 8A). HDL was elevated in OP rats when compared to SD controls. However, treatment did not have any added effect on this increase. HF feeding had no effect on HDL levels in OR rats (Fig. 8B). The LDL to HDL ratio was unchanged in all groups (Fig. 8C).

4. Discussion

Hypertension has been reported to result in diastolic heart dysfunction [34], and we have recently shown that treatment with resveratrol was effective in arresting as well as regressing this abnormality in different animal models of hypertension [16–18]. Basic and clinical studies have also reported that obesity induces abnormalities in diastolic heart function; we therefore investigated the efficacy of resveratrol in this pathology. This is a unique study reporting cardiac dysfunction in OR rats fed an HF diet. Also, we report for the first time that the treatment with resveratrol can reverse

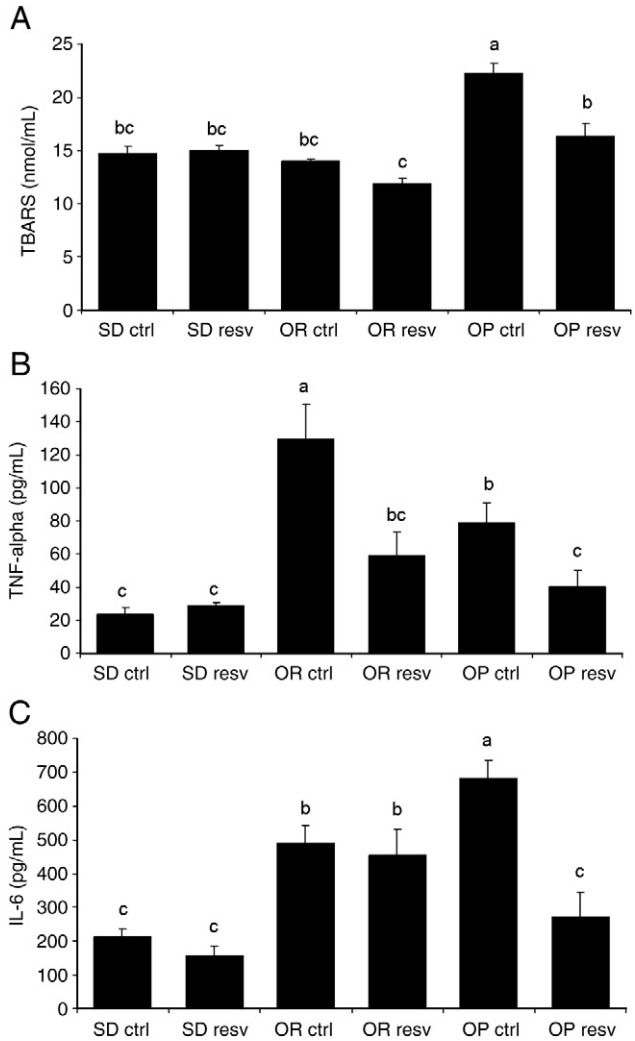

Fig. 6. Oxidative stress and inflammatory markers of SD, OR and OP rats at week 17. (A) Plasma TBARS, (B) serum TNF-α and (C) serum IL-6. Data are means±S.E., n=5–10. Significant model×treatment interaction (P<.1) for TBARS, TNF-α and IL-6. Means with different letters are significantly different (P<.05) from each other.

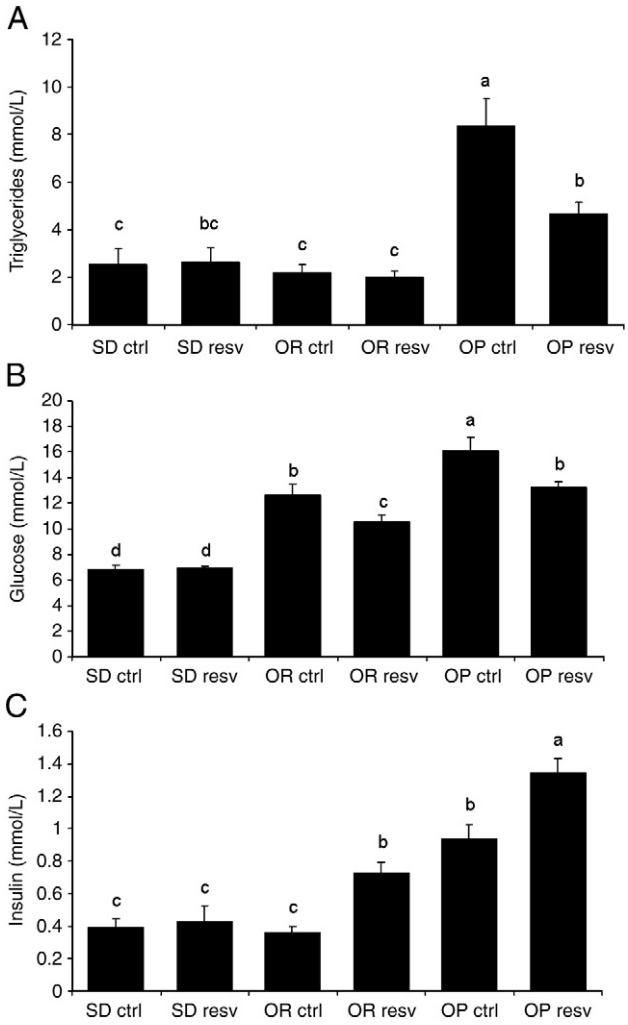

Fig. 7. Fasting serum TG, glucose and insulin concentrations of SD, OR and OP rats at week 17. (A) TG, (B) glucose and (C) insulin. Data are means±S.E., n=6–10. Significant model×treatment interaction (P<.1) for TG, glucose and insulin. Means with different letters are significantly different (P<.05) from each other. Data for TG and glucose were log transformed for statistical analysis, but untransformed data are presented.

diastolic heart dysfunction associated with obesity in OP rats. It is also important to highlight that the concentration of resveratrol used in this study (2.5 mg/kg/day in rat, which is approximately a human equivalent dose of 28 mg in a 70-kg person) is not at pharmacological levels (with hundreds of milligrams or grams) and more likely achievable through dietary means.

Lifestyles associated with increased intake of energy dense foods are widely considered to be responsible for the increasing prevalence of obesity among the global population [2]. However, it is also known that there exists a lean version of the human population that is resistant to DIO but is reported to be at increased risk of cardiovascular diseases [35]. We studied the effects of HF diet on these two populations by employing the animal models of OP and the lean counterpart, OR. SD rats fed with laboratory chow represent the low-fat diet population, and hence, it is the appropriate control for the present study.

The current study demonstrates that 17 weeks of HF feeding induces abnormality in diastolic but not in systolic heart function, with no diet-induced changes in cardiac structure of OP and OR rats; treatment with resveratrol reversed the functional impairment in OP but not OR rats. Other changes in the echocardiographic parameters as represented by lower CO, LVIDd and LVPWd values in OR rats cannot be considered as a pathological response as these changes could be attributed to the smaller size of these strains. The increase in IVRt in OP and OR rats was present at 12 weeks, and this alteration could be attributed to the HF feeding alone. Improvement in diastolic function is generally associated with limiting collagen deposition, and resveratrol has been reported to reduce it in the myocardium [36]. However, this may or may not be the case in the current study as diastolic function was not improved in HF-fed OR rats. The HF diet induced an increase in heart rate in OP and OR rats, but it was not significantly lowered with resveratrol treatment. However, the treatment did show a trend towards reducing heart rate to levels in SD rats.

The OP rats gained more weight than OR rats. Surprisingly, control SD rats also showed an increase in body weight similar to OP rats. The role of adipose tissue in etiology of obesity and its pathophysiologic changes is well recognized. Gene expression profiling of adipose tissues in OP and OR rats revealed a down-regulation in fatty acid oxidation genes in OP rats, while the OR rats were more resistant to these changes, suggesting a better utilization of lipids in OR animals [37]. Due to this characteristic difference of the strain, visceral fat deposits of OP rats were significantly higher than the OR and SD rats. Accordingly, increase in adiposity in OP rats fed an HF diet contributes to the higher body weight, while in SD rats, it could be from higher

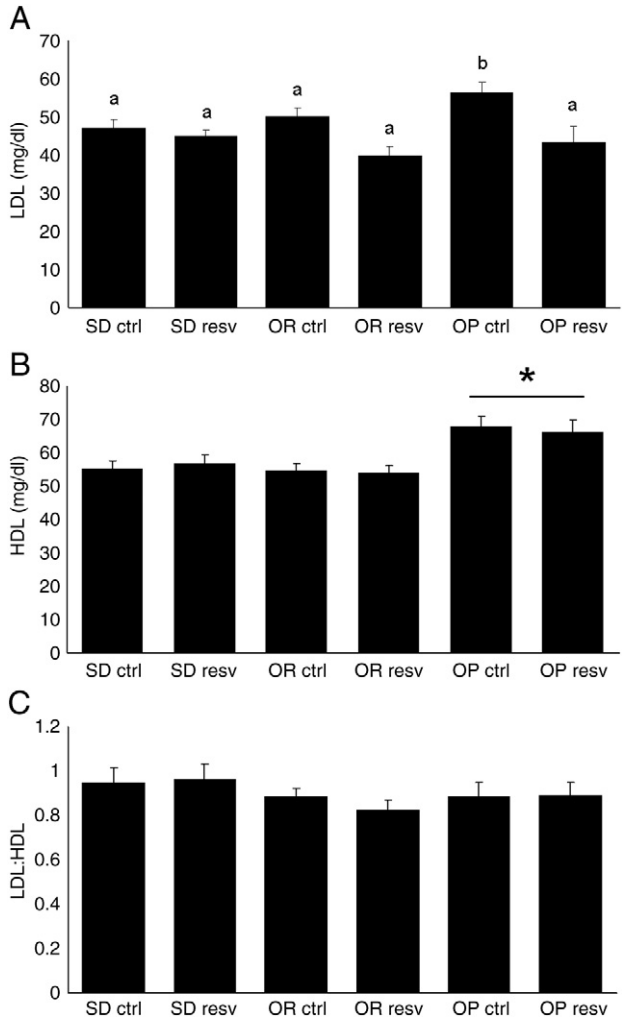

Fig. 8. LDL and HDL measurements of SD, OR and OP rats at week 17. (A) LDL, (B) HDL, (C) LDL:HDL. Data are means±S.E., n=5–10. Significant model×treatment interaction for LDL and significant main effects of model for HDL. Means with different letters are significantly different (P<.05) from each other.

lean body mass. It has been established that increased adiposity is the trigger for metabolic and cardiovascular dysfunctions [38] and could therefore be a cause for abnormal diastolic heart function observed in OP rats in our study. However, cardiac complications in OR rats have an unknown cause. Treatment with resveratrol did not reduce visceral fat deposits in OP rats, suggesting that the reversal of diastolic functional defects in OP rats by resveratrol was not mediated by limiting adiposity.

Abnormal glucose handling and hypertension collectively or independently contribute to the development of cardiac dysfunction [39]. In this study, HF-fed OP rats presented with glucose and insulin imbalance as characterized by increased levels of fasting serum glucose and insulin, whereas HF-fed OR rats had higher glucose but normal insulin levels. Reduction in glucose levels was associated with parallel increase in insulin with resveratrol treatment in both OP and OR rats. However, resveratrol could also mimic insulin-like activity to decrease glucose levels and hence could be operating through both insulin-independent and insulin-dependent mechanisms [40]. Obesity is reported to be associated with elevated systolic blood pressure [41]. Our study also showed a diet-induced moderate increase in the blood pressure in both the OP and OR groups. Resveratrol treatment had no effect on elevated blood pressure in OP and OR groups. The lack of effect of resveratrol in reducing blood pressure is consistent with our earlier findings in other models of hypertension [17,18]. Although our studies show that resveratrol was ineffective at reducing adiposity and hypertension, some studies have shown otherwise. Rivera et al. [19] showed a decrease in blood pressure in obese Zucker rats treated with resveratrol, and Macarulla et al. [42] showed that resveratrol treatment reduced adipose tissue deposits in hypercaloric-diet-fed rats. The discrepancies observed in outcomes of these studies versus ours could be attributed to the higher dose and longer treatment with resveratrol in the other studies, as well as the difference in fat content of the diet and animal models used. Accordingly, our results indicate that resveratrol improved cardiac function and glucose levels but did not lower blood pressure.

Oxidative stress and inflammation are considered to be independent risk factors for pathological cardiac remodeling [43], leading to impairment of cardiac function. Evidence suggests that cardiac pathology associated with obesity could have a similar origin [44]. The positive outcomes of resveratrol in the treatment of disease are typically associated with its antioxidant and anti-inflammatory properties [15], and these aspects were examined in the current study. Elevated levels of TBARS in the plasma of OP rats observed in our study are consistent with the data from earlier studies showing an increase in markers of oxidative stress in obese animal models [45]; OR rats did not have increased adiposity or oxidative stress. This increase in TBARS in OP rats but not OR rats could be attributed to the difference between these strains. Circulating TG and LDL are factors contributing to oxidative stress and lipotoxicity in the myocardium [6]. Obese animals in this study had increased fasting serum TG levels which were normalized with resveratrol; these data suggest that resveratrol may have antihyperlipidemic properties. In this study, reduction in increased LDL levels with resveratrol treatment may have contributed to the alleviation of cardiac dysfunction in OP rats. However, LDL to HDL ratio remained unchanged in all the groups and could therefore undermine the fact that resveratrol exerts beneficial effects on the heart by increasing HDL levels. Elevated serum levels of IL-6 and TNF-α (typical markers of inflammation) in OP rats are consistent with earlier reports linking adipose tissue function, inflammation and cardiovascular disease in obesity [8,44]. Consistent with its antioxidant and anti-inflammatory properties, treatment with resveratrol reduced the diet-induced elevation in oxidative stress and levels of IL-6 in OP rats and TNF-α in OP and OR rats. The discrepancy in the effect of resveratrol in lowering the levels of inflammatory markers TNF-α and IL-6 in OR rats is interesting and is an observation to be explored later. A recent study has also reported that resveratrol targets adipose tissues preventing release of detrimental adipokines [46]. Accordingly, it is only appropriate to suggest that resveratrol exerts its cardioprotective effects by alleviating hyperglycemia, hyperlipidemia, oxidative stress and inflammation in obese animals. Nitric oxide [47], 5′ AMP-activated protein kinase [48] and sirtuin [36] are established cellular targets of resveratrol that mediate cardioprotective effects in different animal models of cardiac diseases. These molecules may play a significant role in the beneficial effects observed in our study which can only be confirmed with further studies.

In summary, we report for the first time that low-dose resveratrol reverses abnormalities in cardiac function in a model of DIO fed with HF, suggesting that these results could be explored further to affirm its potential in the treatment of cardiovascular impairments in obese patients. We also demonstrate for the first time that HF induces abnormalities in cardiac function in OR rats. The fact that OR rats in this study had impaired cardiac function accompanied with higher mortality supports the 'obesity paradox' theory, wherein obese phenotypes have better prognosis in cardiovascular diseases than the lean counterparts [35]. Beneficial effects of resveratrol being specific to OP and not OR rats could be attributed to the discrepancy in the origin of cardiovascular abnormalities in these two models as evident from the data presented here. The ineffectiveness of resveratrol in reversing HF-induced cardiac dysfunction in OR rats is an important subject to be investigated in future studies.

Supplementary materials related to this article can be found online at doi:10.1016/j.jnutbio.2011.06.010.

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