Resveratrol Arrests and Regresses the Development of Pressure Overload- but Not Volume Overload-Induced Cardiac Hypertrophy in Rats

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Abstract

Cardiac hypertrophy is a compensatory enlargement of the heart due to either volume overload (VO) and/or pressure overload (PO) that develops into heart failure if left untreated. The polyphenol resveratrol has been reported to regress PO-induced cardiac hypertrophy in rats. Our aim in this study was to assess the effectiveness of resveratrol on VO-induced cardiac hypertrophy. Sprague Dawley rats were subjected to aortocaval shunt and abdominal aortic banding surgeries to create VO and PO, respectively; sham-operated rats served as controls. To arrest the development of cardiac hypertrophy, daily resveratrol treatment (2.5 mg/kg body weight) was started 2 d postsurgery for 26 d and assessed by echocardiography at 2, 14, and 28 d postsurgery. Similarly, to regress cardiac hypertrophy resveratrol treatment was started after structural and functional abnormalities developed (14 d postsurgery) for 14 d and assessed by echocardiography at 14 and 28 d postsurgery. VO surgeries induced eccentric hypertrophy characterized by increased left ventricle internal dimensions (LVID) without wall thickening. Conversely, PO induced concentric hypertrophy with increased wall thickness without change in LVID. Lipid peroxidation, a marker for oxidative stress, was significantly elevated in both PO and VO rats. Resveratrol treatment arrested the development and regressed abnormalities in cardiac structure and function in PO but not VO rats. Treatment with resveratrol also significantly reduced oxidative stress in cardiac tissue of PO and VO rats. The results on cardiac structure and function demonstrate a potential for resveratrol in the treatment of cardiac hypertrophy due to PO but not VO.

Introduction

Heart failure is a multifactorial syndrome that is a leading cause of hospitalization and mortality worldwide (1,2). Heart failure is preceded by a stage called cardiac hypertrophy, which is an adaptive mechanism wherein the heart muscle enlarges in size to maintain adequate function in the presence of chronic pathological stress (3–6). This hypertrophic growth manifests in 2 ways: 1) concentric hypertrophy, which is caused by chronic pressure overload (PO) and leads to increased wall thickness; and 2) eccentric hypertrophy, which is caused by volume overload (VO), resulting in dilation of the heart (3–6). Although this myocardial enlargement is initially beneficial, prolonged hypertrophy has deleterious consequences that lead to heart failure.

To date, many pharmaceutical agents, such as angiotensin converting enzyme inhibitors, β-blockers, angiotensin receptor blockers, and diuretics, have been used to treat cardiac hypertrophy and early stages of heart failure. These therapies have proven reasonably effective; however, the incidence of mortality...
due to heart failure is on the rise (7–9). Consequently, there is an important need for alternative therapeutic strategies to prevent or reverse hypertrophy before it develops into heart failure.

The concepts of food and nutrition in the current scenario are changing; in the past, emphasis was placed solely on hunger satisfaction and survival. Today, certain foods are being used to promote better health and well-being, which in turn helps to reduce the risk of disease. This link between nutrition and health gave rise to the concept of nutraceuticals, which is defined as “part of a food that provides medicinal and health benefits” (10). The ability of nutraceuticals to positively influence cardiovascular risk factors presents an enormous opportunity in the future treatment of cardiovascular disease (11–13). The medical benefits of foods have been largely credited to components such as carotenoids, fatty acids, isothiocyanates, phenolic acids, plant sterols, polyols, vitamins, minerals, flavonoids, polyphenols, and sulfides/thiols. In the past few years, resveratrol (trans-3,5,4’- trihydroxystilbene), a phenolic phytoalexin present in grapes and berries and a major phenolic constituent of red wine, has been reported to have cardioprotective properties (14). A recent study from our laboratory demonstrated that treatment with resveratrol reversed chronic cardiac hypertrophy, along with its deleterious effects on cardiac function, in rats subjected to PO (15). In this study, we compared the effects of resveratrol on arresting or reversing cardiac hypertrophy due to VO and PO.

**Materials and Methods**

**Rats.** Male Sprague-Dawley rats weighing 150–200 g were obtained from Central Animal Care Services at the University of Manitoba and subjected to either aortocaval shunt or abdominal aortic banding surgery from Central Animal Care Services at the University of Manitoba and Male Sprague-Dawley rats weighing 150–200 g were obtained Rats.

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**Resveratrol treatment.** There were 2 major studies involved with resveratrol treatment. Study 1 tested the effects of resveratrol in arresting development of cardiac hypertrophy. Resveratrol treatment in study 1 started 2 d postsurgery and continued for 26 d. Study 2 tested the effects of resveratrol in reversing cardiac hypertrophy. Treatment in study 2 started 14 d postsurgery after hypertrophy had developed and continued for 14 d. In both studies, sham-operated control, aortocaval-induced VO, and aortic band-induced PO rats were randomly assigned to resveratrol-treated or untreated groups. Resveratrol (Sigma-Aldrich) was dissolved in 1 mL of 50% ethanol (vehicle) and 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 study (15), at the same time of day for each study. A preliminary study was conducted to assess the effect of vehicle on sham, PO, and VO surgery rats by administering 1 mL of 50% ethanol and the regime was the same as that for resveratrol in studies 1 and 2.

**Echocardiography.** Cardiac structure and function were analyzed in all animals using echocardiography. Rats starting treatment 2 d postsurgery were analyzed at 2, 14, and 28 d. Rats starting treatment 14 d postsurgery were analyzed at the 14 and 28 d time points. Both transcoracic 2-dimensionally guided M-mode and Pulse-Wave Doppler echocardiography were performed using a Sonos 5500 ultrasound system (Agilent Technologies) equipped with a 12 MHz (s12) transducer as described by us earlier (16). The following parameters were measured as described by the American Society of Echocardiography (17): percentage of left ventricular fractional shortening (FS), left ventricular ejection fraction (EF), cardiac output (CO), left ventricular mass, heart rate (HR), interventricular septal wall (IVS) thickness at systole and diastole, left ventricular posterior wall (LVPW) thickness at systole and diastole and left ventricle internal dimensions (LVID) at systole and diastole. Doppler measurements included: isovolumetric relaxation time (IVRt), aortic ejection time (AET), and early diastolic filling velocity (E wave).

**Blood pressure.** Systolic blood pressure was measured with a CODA multi-channel, computerized noninvasive blood pressure system (Kent Scientific) using a tail-cuff sphygmomonometer on a subset of conscious rats, as described previously (18).

**Oxidative stress.** The degree of lipid peroxidation was assessed by measurement of thiobarbituric acid reactive substances (TBARS) in the homogenized left ventricle (LV) tissue using the OxiSelect TBARS Assay kit (Cell Biolabs). The TBARS values were expressed as nmol/mg of protein.

**Statistical analysis.** All statistical analyses were performed using the SAS Statistical package (version 9.1; SAS Institute). Data were assessed for homogeneity of variance by Levene’s test and normality using the Shapiro-Wilk’s test. The effect of treatment (with or without resveratrol) and surgery (PO or VO surgery vs. respective sham surgery) on heart: body weight ratio (H:BW), all cardiac structure parameters, blood pressure measurements, and TBARS were assessed by 2-way ANOVA in both studies. The effects of treatment, surgery, and time on all cardiac function parameters were assessed by 3-way ANOVA in both studies. The significance level was P < 0.05 for main effects and P < 0.10 for interactions (to reduce the risk of missing interactions). For post-hoc testing, least-squares means with adjustment for multiple comparisons (Tukey-Kramer) was used. Values are expressed as mean ± SEM.

**Results**

**General observations.** Rats undergoing VO surgery had a greater H:BW ratio compared with sham-operated rats in study 1 (69% higher) and study 2 (52% higher). Resveratrol treatment did not affect the H:BW ratio in VO rats in both studies (Supplemental Fig. 1A,B). There was a significant interaction of surgery and treatment on the H:BW ratio in PO rats in studies 1 and 2. PO rats had a greater H:BW ratio compared with sham-operated rats in study 1 (29% higher) and study 2 (32% higher). Resveratrol treatment prevented an increase in the H:BW ratio in PO rats in study 1 (Supplemental Fig. 1C) and it reversed the increased H:BW ratio in PO rats in study 2 (Supplemental Fig. 1D). In both studies, sham rats treated with resveratrol did not have altered cardiac structure, function, or TBARS levels compared with untreated sham-operated rats. Vehicle treatment

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alone (oral gavage with 50% ethanol) did not affect any cardiac structure and TBARS levels compared with untreated rats (Supplemental Tables 1 and 2).

**Cardiac structure in study 1: resveratrol treatment commencing 2 d postsurgery.** Comprehensive assessment of cardiac structure and function were obtained by echocardiography for each rat. Data for cardiac structure are shown for the diastolic phase of the heart; the systolic phase showed similar trends (Supplemental Tables 3–6). In the prevention study (study 1), M-mode echocardiography did not significantly differ in cardiac structure with respect to wall thickness (IVS and LVPW) and LV internal dimensions in VO (Fig. 1A) and PO (Fig. 1B) rats compared with sham-operated controls at baseline (2 d after surgery). LVID was greater in VO rats at 14 d (13% greater) and 28 d (27% greater) postsurgery, with no significant differences in IVS and LVPW compared with sham-operated rats. Resveratrol treatment did not prevent the increase in LVID in VO rats (Fig. 1C, E). PO rats had greater cardiac wall thickness at 14 d (IVS, 36% greater; LVPW, 25% greater) and 28 d (IVS, 47% greater; LVPW, 45% greater) postsurgery, but LVID did not differ from sham-operated rats; resveratrol treatment prevented the increase in wall thickness at 14 and 28 d postsurgery in PO rats (Fig. 1D, F).

**Cardiac function in study 1: resveratrol treatment commencing 2 d postsurgery.** Baseline measurements 2 d postsurgery showed VO rats had an elevated HR (7%) compared with the sham rats. HR in VO rats normalized to sham rat levels at 14 and 28 d postsurgery but was significantly lower at d 14 and 28 compared with VO rats at 2 d post surgery (Table 1). CO was 26% higher at 2 d, 55% higher at 14 d, and 69% higher at 28 d postsurgery in VO compared with sham rats. Resveratrol treatment did not prevent the changes in CO in VO. Furthermore, CO significantly increased over time in VO and sham rats (Table 1). HR was not significantly altered by PO surgery and did not change over time, whereas CO increased over the time of the study (Table 2). Throughout the course of study 1, VO rats had lower IVRt compared with sham rats; this was not affected by resveratrol treatment (Table 1). VO rats also had a 16% higher E wave at 2 d, 29% higher at 14 d, and 28% higher at 28 d compared with sham rats. Early diastolic filling velocities were also increased at 14 and 28 d postsurgery in VO rats compared with VO rats at 2 d post surgery (Table 1). Resveratrol treatment had no effect on E wave in VO. Baseline measurements of IVRt in PO rats did not differ from sham rats. IVRt was, however, elevated 16% at 14 d and 37% at 28 d postsurgery in PO rats compared with sham rats. Resveratrol treatment in PO rats tended to prevent the elevation in IVRt at d 28.
14 and prevented it at d 28 postsurgery ($P = 0.06$) (Table 2). E wave in rats was not significantly altered by PO surgery and did not change over time (Table 2). EF and FS did not differ in VO (Table 1) and PO (Table 2) rats compared with respective sham-operated rats throughout the study. Similarly, AEt was also unaffected in both VO and PO rats (Tables 1 and 2).

**Cardiac structure in study 2: resveratrol treatment commencing 14 d postsurgery.** In the reversal study (study 2), rats undergoing VO surgery had 24% larger LVID but no differences in IVS and LVPW thickness compared with sham-operated rats at 14 d postsurgery (Fig. 2A). PO rats had a 18% larger IVS and 34% larger LVPW with no difference in LVID compared with sham-operated rats at 14 d (Fig. 2B). At 28 d postsurgery, resveratrol treatment did not reverse the increase in LVID in VO rats, which was 36% higher than in sham-operated rats (Fig. 2C). Rats undergoing PO surgery had 39% larger IVS and 42% larger LVPW compared with sham-operated rats at 28 d postsurgery. Resveratrol treatment significantly reduced both IVS and LVPW in PO rats at 28 d postsurgery (Fig. 2D).

**Cardiac function in study 2: resveratrol treatment commencing 14 d postsurgery.** HR did not differ between VO (Table 3) and PO (Table 4) rats and their corresponding sham-operated rats at baseline (14 d) and 28 d postsurgery. CO was 53% higher at 14 d and 88% higher at 28 d in VO rats compared with sham rats. Resveratrol did not prevent the changes in CO in VO rats. Furthermore, CO significantly increased over time in VO and sham rats (Table 3). In PO rats, CO significantly increased from 14 to 28 d postsurgery (Table 4). Throughout the course of study 2, VO surgery significantly lowered IVRt and elevated E wave compared with sham surgery in rats, but this was not affected by resveratrol treatment (Table 3). IVRt was elevated 17% at 14 d and 33% at 28 d in PO rats compared with sham rats. Resveratrol treatment significantly decreased the elevated IVRt in PO rats by 28 d postsurgery (Table 4). E wave was not significantly altered by PO surgery and did not change over time (Table 4). EF and FS were unchanged in VO (Table 3) and PO (Table 4) rats compared with respective sham-operated rats throughout the time course of this study. Similarly, AEt was also unchanged in both VO and PO rats (Tables 3 and 4).

**Blood pressure measurements.** PO rats developed significantly higher systolic blood pressure (18%) 28 d postsurgery compared with sham-operated rats (Supplemental Fig. 2). Resveratrol treatment did not reduce elevated systolic blood pressure in PO rats and also did not alter systolic blood pressure in sham rats (Supplemental Fig. 2).

**Oxidative stress.** As with cardiac structure and function, TBARS levels in the cardiac tissue were unaffected by vehicle treatment compared with untreated rats (Supplemental Table 2). The TBARS levels in rats undergoing VO surgery were 86% greater in both studies 1 and 2 compared with sham-operated rats (Supplemental Fig. 3A, B). Resveratrol treatment significantly prevented the increase in TBARS levels in VO rats in study 1 and reversed the increase in study 2 (Supplemental Fig. 3A, B). PO rats had greater TBARS levels in both studies compared with sham-operated rats (60% higher in study 1; 57% higher in study 2). In study 1, treatment with resveratrol significantly prevented the increase in TBARS levels in PO rats (Supplemental Fig. 3C) and reversed the elevated TBARS levels in study 2 (Supplemental Fig. 3D).

**TABLE 2** Effect of resveratrol treatment in arresting early changes in cardiac function during the development of PO-induced cardiac hypertrophy in rats at d 2, 14, and 28 postsurgery

<table>
<thead>
<tr>
<th>Variable</th>
<th>Sham</th>
<th>Sham + R</th>
<th>PO</th>
<th>PO + R</th>
<th>Sham</th>
<th>Sham + R</th>
<th>PO</th>
<th>PO + R</th>
<th>Sham</th>
<th>Sham + R</th>
<th>PO</th>
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<tr>
<td>FS, %</td>
<td>46.0 ± 2.4</td>
<td>46.3 ± 2.2</td>
<td>49.0 ± 1.8</td>
<td>47.4 ± 1.2</td>
<td>48.1 ± 1.9</td>
<td>47.0 ± 1.5</td>
<td>49.0 ± 2.2</td>
<td>50.9 ± 2.8</td>
<td>46.9 ± 1.5</td>
<td>46.2 ± 1.7</td>
<td>47.5 ± 3.2</td>
<td>47.8 ± 1.9</td>
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<tr>
<td>EF</td>
<td>0.010 ± 0.022</td>
<td>0.020 ± 0.020</td>
<td>0.040 ± 0.013</td>
<td>0.080 ± 0.001</td>
<td>0.034 ± 0.017</td>
<td>0.020 ± 0.014</td>
<td>0.040 ± 0.020</td>
<td>0.080 ± 0.016</td>
<td>0.026 ± 0.014</td>
<td>0.010 ± 0.016</td>
<td>0.020 ± 0.039</td>
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<tr>
<td>HR, bpm</td>
<td>367 ± 8</td>
<td>370 ± 7</td>
<td>361 ± 12</td>
<td>354 ± 11</td>
<td>348 ± 6</td>
<td>364 ± 13</td>
<td>368 ± 12</td>
<td>356 ± 12</td>
<td>348 ± 7</td>
<td>342 ± 5</td>
<td>363 ± 15</td>
<td>334 ± 6</td>
</tr>
<tr>
<td>CO, ml/min</td>
<td>246 ± 14</td>
<td>249 ± 11</td>
<td>248 ± 16</td>
<td>242 ± 17</td>
<td>366 ± 4</td>
<td>352 ± 24</td>
<td>352 ± 29</td>
<td>332 ± 8</td>
<td>422 ± 13</td>
<td>413 ± 20</td>
<td>459 ± 19</td>
<td>411 ± 17</td>
</tr>
<tr>
<td>IVRt, ms</td>
<td>18.7 ± 0.7</td>
<td>20.0 ± 0.7</td>
<td>20.9 ± 0.7</td>
<td>20.7 ± 0.8</td>
<td>18.6 ± 0.5</td>
<td>17.0 ± 0.5</td>
<td>21.5 ± 0.6</td>
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<td>19.4 ± 1.0</td>
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<td>Ewave, cm/s</td>
<td>105 ± 4</td>
<td>104 ± 3</td>
<td>100 ± 2</td>
<td>98.0 ± 3</td>
<td>100 ± 5</td>
<td>106 ± 5</td>
<td>112 ± 5</td>
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<tr>
<td>AEt, ms</td>
<td>64.9 ± 1.6</td>
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1 Data are mean ± SEM, n = 7–10. Symbols indicate that means differ, $P < 0.05$: *different from sham on the same day; †different from corresponding untreated group on the same day.
Discussion

We reported earlier that PO-induced cardiac hypertrophy and its deleterious consequences on heart function in rats were reversed with resveratrol treatment starting 14 d postsurgery (15). However, the effects of resveratrol at the early stages of PO-induced hypertrophy are not established. In addition, the effects of resveratrol on cardiac hypertrophy due to VO is unknown. Accordingly, our study addresses the potential of resveratrol in arresting the development of cardiac hypertrophy and regressing already-developed cardiac hypertrophy in rats subjected to both VO and PO.

Four weeks after aortocaval shunt surgery, rats developed VO-induced eccentric hypertrophy characterized by chamber dilation with no significant change in wall thickness. Conversely, 4 wk after abdominal aortic banding surgery, rats developed PO-induced concentric hypertrophy characterized by increased thickness of the IVS and LV posterior wall with no chamber dilation. Chamber dilation in VO hearts accommodated the increased venous return allowing for progressively increased CO and enhanced myocardial relaxation, whereas PO hearts had thickening of left ventricular walls leading to diastolic dysfunction. These results are consistent with our previous studies (15,16) and validate the experimental models used in this study.

The novel finding in this study is that daily treatment with resveratrol (2.5 mg/kg body weight) arrested the development of cardiac hypertrophy and regressed developed cardiac hypertrophy and associated alterations in cardiac function in rats subjected to PO, but not VO. It is important to point out that the concentration used in this study was very low compared with that used in the only other in vivo study carried out by Li et al. (19) on a similar model (50 mg/kg body weight). It is interesting to speculate that the antihypertrophic effects of resveratrol may in part be due to the removal of a specific type of stress placed on the heart and the targeting of specific antihypertrophic molecules in the heart.

Our results showing the arrest in development of PO-induced cardiac hypertrophy in resveratrol-treated aortic-banded rats are similar to that of Li et al. (19). In their study, Li et al. (19) showed that PO-induced cardiac hypertrophy was significantly higher in resveratrol-treated rats than in control rats. It is important to point out that the concentration used in this study was very low compared with that used in the only other in vivo study carried out by Li et al. (19) on a similar model (50 mg/kg body weight). It is interesting to speculate that the antihypertrophic effects of resveratrol may in part be due to the removal of a specific type of stress placed on the heart and the targeting of specific antihypertrophic molecules in the heart.

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cardiac remodeling and dysfunction due to PO in mice with eNOS overexpression (28). We have recently shown that 4 wk of abdominal aortic banding decreases eNOS protein levels in LV myocardial tissue, which is recovered upon treatment with resveratrol (15). Therefore, increased NO levels via resveratrol-induced upregulation of eNOS may play a major role in arresting or regressing the development of PO-induced alterations in cardiac structure and function in aortic-banded animals. Interestingly, eNOS protein level or activity is unaffected by cardiac hypertrophy due to VO (30); this may partly explain the lack of effect of resveratrol on VO-induced changes in cardiac structure and function in aortocaval-shunted animals. This aspect needs to be examined in future studies.

In conclusion, we have demonstrated that resveratrol is beneficial in both arresting and regressing cardiac hypertrophy due to PO, but not VO. Thus, resveratrol may have potential in the treatment of clinical situations of PO, such as hypertension and aortic stenosis.

Acknowledgments
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Literature Cited


