Preservation of diastolic function in monocrotaline-induced right ventricular hypertrophy in rats

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Lamberts RR, Caldenhoven E, Lansink M, Witte G, Vaessen RJ, St Cyr JA, Stienen GJ. Preservation of diastolic function in monocrotaline-induced right ventricular hypertrophy in rats. Am J Physiol Heart Circ Physiol 293: H1869–H1876, 2007. First published June 29, 2007; doi:10.1152/ajpheart.00294.2007.—During ischemic heart diseases and when heart failure progresses depletion of myocardial energy stores occurs. D-Ribose (R) has been shown to improve cardiac function and energy status after ischemia. Folic acid (FA) is an essential cofactor in the formation of adenine nucleotides. Therefore, we assessed whether chronic R-FA administration during the development of hypertrophy resulted in an improved cardiac function and energy status. In Wistar rats (n = 40) compensatory right ventricular (RV) hypertrophy was induced by monocrotaline (30 mg/kg; MCT), whereas saline served as control. Both groups received a daily oral dose of either 150 mg·kg−1·day−1 dextrose (placebo) or R-FA (150 and 40 mg·kg−1·day−1, respectively). In Langendorff-perfused hearts, RV and left ventricular (LV) pressure development and collagen content as well as total RV adenine nucleotides (TAN), creatine content, and RV and LV collagen content were determined. In the control group R-FA had no effect. In the MCT-placebo group, TAN and creatine content were reduced, RV and LV diastolic pressure-volume relations were steeper, RV systolic pressures were elevated, RV and LV collagen content was increased, and RV-LV diastolic interaction was altered compared with controls. In the MCT-R-FA group, TAN, RV and LV diastolic stiffness, RV and LV collagen content, and RV-LV diastolic interaction were normalized to the values in the control group while creatine content remained depressed and RV systolic function remained elevated. In conclusion, the depression of energy status in compensated hypertrophic myocardium observed was partly prevented by chronic R-FA administration and accompanied by a preservation of diastolic function and collagen deposition.

METHODS

Animals. Male Wistar rats were randomly assigned to four experimental groups (n = 10 per group). The animals had ad libitum access to chow and water and orally received a daily dose of 2 ml vanilla yogurt as a masking agent, with either dextrose (placebo, 150 mg/kg body wt) or with R-FA (150 and 40 mg/kg body wt, respectively) for 6 wk. After 2 wk, at a body weight of 175 g, animals received a single injection of saline (control) or 30 mg/kg monocrotaline (MCT). All protocols were in accordance to the American Physiological Society’s “Guiding Principles in the Care and Use of Animals” and with the necessary permits and approvals.

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Oxidative pentose phosphate pathway (PPP), is slow and a major limiting factor in the biosynthesis of ATP (45, 46). D-Ribose, a natural occurring pentose monosaccharide, bypasses the rate-limiting steps of the PPP by increasing PRPP levels and has been shown to improve total adenine nucleotide (TAN) levels after ischemia (45). Folic acid (FA) is mostly known for lowering increased plasma levels of homocysteine, a potential risk factor for vascular disease (32). However, a derivative of FA 10-formyl-H4PteGlu is an essential cofactor in the formation of ATP via the de novo purine synthesis (24).

In human and animals (14) it has been shown that the myocardial energy status is reduced in chronic (end-stage) heart failure. However, during the progression of heart failure, energy demand already increases, which may result in a reduction of the TAN pool (21, 33) and thereby accelerate diminution of myocardial function. Therefore, we assessed whether in a model of compensated hypertrophy, the energy balance was perturbed and whether this could be prevented by d-ribose/FA (R-FA). If effective, this might improve cardiac function and ultimately prevent or delay the transition to chronic heart failure.

To this end, the effects of daily dietary R-FA on cardiac energy status, cardiac function, and serum homocysteine levels were assessed in monocrotaline (MCT)-induced right ventricular (RV) hypertrophy. A single injection of MCT induces pulmonary hypertension and results in RV pressure overload, which causes compensatory RV hypertrophy in rats (8, 13, 16, 19, 20, 23, 38, 41). Recently, we (19) demonstrated in this model that the overall myocardial collagen content was increased and that both RV and LV diastolic function were depressed. To obtain insight in the processes involved, the effects of R-FA were also determined on collagen content, LV function, and on the RV-LV ventricular interaction.
Isolated Langendorff hearts. Four weeks after injection the animals were anesthetized with pentobarbital sodium (60 mg/kg), and cardiac function was assessed in a isolated Langendorff setup as described previously (19). In short, hearts were rapidly dissected, the aorta was Langendorff perfused at constant coronary perfusion pressure (100 mmHg) at 37°C, and hearts were paced at 5 Hz. Custom-made balloons were inserted in the RV and LV and isovolumic pressures were measured with a catheter tip manometer system. The modified Krebs-Henseleit solution contained (in mM) 118.5 NaCl, 4.7 KCl, 1.4 CaCl₂, 25 NaHCO₃, 1.2 MgCl₂, 1.2 KH₂PO₄, and 11 glucose and was continuously gassed with 95% O₂-5% CO₂ (pH 7.4). After the hearts were mounted, pressure development of the hearts stabilized in 20 min. Thereafter, the volume at maximal pressure development (Vₘₐₓ) of both ventricles was determined, and balloons were adjusted to 80% Vₘₐₓ, which in the control group resulted in end-diastolic pressures of ~5 mmHg.

Cardiac function. After the stabilization period and the Vₘₐₓ determinations, pressure-volume (P-V) relations and pressure-frequency (P-F) relations were determined. First, a P-V relation was determined in the RV by increasing RV volume from 70 to 95% Vₘₐₓ in 5% steps, whereas LV volume was kept at 80% Vₘₐₓ. Then a P-V relation from 70 to 95% Vₘₐₓ was obtained in the LV, whereas RV volume was kept at 80% Vₘₐₓ. Ventricular interaction was studied by measuring the effect of a change in RV volume on LV pressure and vice versa. Thereafter, RV and LV function was further characterized by studying P-F relations with both ventricular volumes adjusted to 80% Vₘₐₓ. The hearts were paced for 10 min at 3, 6, and 9 Hz.

RY and LV end-diastolic and peak systolic pressures were used as contractile parameters. The time from stimulus to half relaxation (tHR) and the minimum rate of pressure development during relaxation (−dP/dt) divided by developed pressure (Pdev) (−dP/dt/Pdev) were used as relaxation parameters. The range in volumes used (70–95% Vₘₐₓ) represents the physiological range of the in vivo heart under normal conditions (35).

After the P-V and P-F relations were recorded, the hearts of all four groups were assigned to two subgroups (both n = 5), subsequently paced for 60 min at low (3 Hz) or at high (9 Hz) frequency. Hereafter, with the use of a liquid nitrogen precooled Wollenberger clamp, the paced for 60 min at low (3 Hz) or at high (9 Hz) frequency. Hereafter, RV and LV function was further characterized by studying P-F relations with both ventricular volumes adjusted to 80% Vₘₐₓ. The hearts were paced for 10 min at 3, 6, and 9 Hz.

Energy status: homocysteine levels and collagen content. TAN content (TAN = ATP + ADP + AMP) and total creatine levels (phosphocreatine + creatine) were assessed in RV tissue by high-performance liquid chromatography. Values are expressed in nanomoles per gram of dry weight tissue (g dry wt) (44). Blood samples were taken immediately after dissection of the heart and were allowed to clot before centrifugation for 10 min at 3,000 rpm. Homocysteine levels were determined in the serum by high-performance liquid chromatography (18).

Collagen content was determined by measuring the amount of hydroxyproline in freeze-dried tissue as described previously (19). Cardiac tissue (~2 mg dry wt) was homogenized, lysated, and then hydrolyzed with 8 N HCl at 110°C. Hydroxyproline standard solutions and homogenates were oxidized by chloramine T and incubated with dimethylbenzaldehyde for red coloration, and then absorption was measured at a wavelength of 562 nm. Collagen content was estimated by multiplying hydroxyproline content with a factor of 8.2 (25).

Samples of freeze-dried tissue were dissolved in relaxing solution (in mM: 5.95 Na₂ATP, 6.04 MgCl₂, 2 EGTA, 139.6 KCl, and 10 imidazol, pH = 7.0) for 10 min at room temperature. After being embedded in gelatine, 5-μm thick sections were cut with a cryostat and stained for hematoxylin and eosin, and the cross-sectional area of at least 30 cardiomyocytes per sample were determined, as described previously (17).

Analysis and statistics. Macroscopic parameters and cardiac function measurements were tested with a two-way ANOVA (control vs. MCT and placebo vs. R-FA). Energy status data were tested with a three-way ANOVA (control vs. MCT, placebo vs. R-FA, and 3 Hz vs. 9 Hz) followed by a Bonferroni post hoc test. A value of P < 0.05 was considered significant. All data are expressed as means ± SE.

RESULTS

MCT-induced RV hypertrophy. On the day of the experiment (4 wk after the injection), both MCT-treated groups displayed slightly lower body weights and a moderate increase in lung weights compared with their respective controls (Table 1). The MCT-treated animals did not display a sudden loss of body weight or pleural effusion. No differences were found in RV and LV balloon volumes at Vₘₐₓ between control and MCT-treated animals or between RV and LV (Table 1). The cardiomyocytes in the MCT groups showed enlarged cross-sectional areas compared with those of the control groups (~65% increase, Table 1). All of these observations are indicative for compensated RV hypertrophy (8, 13, 19, 20, 41). R-FA did not influence any of the structural parameters between placebo and R-FA in the control or in the MCT groups (Table 1).

RV cardiac function. The averaged RV peak systolic and end-diastolic pressure-volume (P-V) relations are shown in the top panels of Fig. 1. The peak systolic pressures at corresponding volumes in the MCT placebo group were increased, and the end-diastolic P-V relation was steeper than those in the control placebo group. R-FA did not influence peak systolic pressure in neither the MCT nor in the control group. R-FA did not affect the end-diastolic P-V relation in the controls. The most striking observation was that the end-diastolic P-V relation in the MCT-R-FA group was similar to those found in control groups. The averaged relaxation parameters (tHR and (−dP/dt)/ Pdev) (Fig. 1, bottom) were prolonged in the MCT placebo group compared with control placebo, and both were not influenced by R-FA.

The averaged RV peak systolic and end-diastolic pressures at 80% Vₘₐₓ at stimulation frequencies of 3, 6, and 9 Hz are shown in the top panels of Fig. 2. The slope of the systolic P-F relation was not significantly different from 0 in the control placebo group but was negative in the MCT-placebo group. In the MCT group RV peak systolic pressures were increased at

<table>
<thead>
<tr>
<th>Table 1. Body weight, wet lung weight, lung weight-to-body weight ratio, and Vₘₐₓ on experimental day</th>
<th>Control</th>
<th>MCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>BW, g</td>
<td>331 ± 8</td>
<td>335 ± 8</td>
</tr>
<tr>
<td>LW, g</td>
<td>148 ± 0.05</td>
<td>155 ± 0.02</td>
</tr>
<tr>
<td>LW/BW (× 10⁻²)</td>
<td>4.5 ± 0.8</td>
<td>4.6 ± 0.7</td>
</tr>
<tr>
<td>RV Vₘₐₓ, μl</td>
<td>222 ± 12</td>
<td>234 ± 7</td>
</tr>
<tr>
<td>LV Vₘₐₓ, μl</td>
<td>227 ± 6</td>
<td>218 ± 11</td>
</tr>
<tr>
<td>CM-CSA, μm²</td>
<td>301 ± 50</td>
<td>314 ± 40</td>
</tr>
</tbody>
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Values are means ± SE, n = 10 per group. Total adenine nucleotide pool and total creatine content of isolated hearts. MCT, MCT-induced RV hypertrophy; R-FA, D-ribose-folic acid; BW, body weight; LW, lung weight; Vₘₐₓ, volume at maximal pressure development; RV, right ventricle; LV, left ventricle; CM-CSA, cardiomyocyte cross-sectional area. *P < 0.05 control vs. MCT. No significant differences between placebo vs. R-FA.
all frequencies compared with control. The diastolic pressure-frequency relation revealed an overall difference between the control and MCT group, which in the post hoc test was only significant at 9 Hz. R-FA did not modify the frequency-dependent alterations in systolic or diastolic pressure in each group. The relaxation parameters tHR and \( \frac{(dP}{dt}/P_{dev}) \) were prolonged in the MCT-placebo group compared with control placebo (Fig. 2, bottom), but the frequency dependence was not influenced by R-FA.

In summary, R-FA prevented the increase in end-diastolic pressure in the MCT group, whereas systolic function remained elevated and relaxation prolonged. In the control group, R-FA had no effect.

**Energy status and homocysteine levels.** The TAN content for all four groups at low and high frequencies is depicted in Fig. 3, top. The TAN content in the isolated Langendorff-perfused rat hearts were comparable to the literature (42). Three-way ANOVA revealed that the TAN content in the MCT-placebo group was reduced compared with control placebo at 3 Hz; an effect that was even more pronounced at 9 Hz. R-FA prevented the decrease in the TAN content at either frequency. Total creatine content (Fig. 3, bottom) was reduced in the MCT-placebo group to similar extents at low and high frequencies and was not preserved by R-FA.

The homocysteine levels in the serum samples were comparable to the literature (9), and no significant differences were
R-FA, in a two-way ANOVA. *P < 0.05 placebo vs. R-FA, †P < 0.05 3 Hz vs. 9 Hz in a Bonferroni post hoc test subsequent to a three-way ANOVA. Solid bars, control placebo (n = 5); dark shaded bars, control-R-FA (n = 5); light shaded bars, MCT-placebo (n = 4); and open bars, MCT-R-FA (n = 5).

found in serum homocysteine levels among all four groups (control placebo: 8.7 ± 0.3 μmol/l, n = 8; control R-FA: 7.8 ± 0.5 μmol/l, n = 8; MCT-placebo: 7.2 ± 0.5 μmol/l, n = 11; MCT-R-FA: 8.0 ± 0.5 μmol/l, n = 12, P > 0.05).

LV cardiac function and ventricular interaction. The averaged peak systolic LV pressures (Fig. 4) were neither affected by MCT treatment nor by R-FA. The LV end-diastolic P-V relation (Fig. 4) was steeper in the MCT-placebo compared with control placebo group. In the MCT group, R-FA tended (P = 0.08) to blunt the increase in LV end-diastolic pressure.

In the MCT-placebo group an increase in RV volume (70 – 95% V_{max}) caused an increase in LV diastolic pressure (Fig. 5, bottom) but not in the control placebo group. This indicates altered diastolic ventricular interaction in the MCT-placebo group. In the MCT R-FA group an increase in RV volume did not cause an increase in LV diastolic pressure. This indicates an effect of R-FA on diastolic ventricular interaction during RV hypertrophy. On the other hand, an increase in LV volume resulted in an increase in RV diastolic pressure, which was similar in the control placebo and MC-placebo groups. R-FA had no significant effects on these relations. An increase in RV or LV volume did not influence LV or RV peak systolic pressures nor the relaxation parameters [HR and (–dP/dt)/P_{ave}], in both the control placebo and MCT-placebo groups. R-FA did not influence these parameters at any of the volumes studied.

Collagen content. Figure 6 illustrates the relative collagen content expressed as collagen weight (in μg) per dry weight of cardiac tissue (in mg). In the MCT-placebo group, the relative collagen content was increased in the RV, the septum, and the LV compared with control-placebo group. R-FA prevented the increase in collagen content in the RV and LV in the MCT group. The septum values did not differ significantly (P = 0.09). R-FA did not alter the collagen content in the control group.

DISCUSSION

This study is the first to show that the cardiac energy status (TAN and total creatine) of the RV is reduced in MCT-induced compensatory hypertrophy to a similar extent as observed previously in the LV of failing hearts. In addition, this study showed that both RV and LV diastolic stiffness and collagen content were increased compared with control values. The changes in TAN content, diastolic stiffness, and collagen content in the MCT group were prevented by chronic oral R-FA administration.

Energy status and cardiac function during compensatory hypertrophy. It has been shown in human and animals (14) that the myocardial energy status is reduced in chronic heart failure. Our results show a reduction in TAN and total creatine levels (Fig. 3) in rat hearts with MCT-induced compensatory RV hypertrophy. This clearly indicates that the reduced energy status is not typical for (end stage) heart failure but that it may
already be present before the onset of heart failure. This notion is in agreement with findings reported in a pacing-induced model of heart failure in dogs (21, 33) where reduced ATP and creatine levels together with a loss in TAN content were observed during the progression of heart failure.

In MCT-treated animals, the slope of the RV systolic P-F relations was negative (Fig. 2) and RV relaxation was prolonged (Figs. 1 and 2). Both are hallmarks for hypertrophied and failing myocardium (3, 16, 19, 30). The negative P-F relation in diseased hearts has been attributed to changes in Ca^{2+}/H^{+} handling (30). The prolonged relaxation observed in this study is consistent with a deceleration of Ca^{2+} reuptake and Ca^{2+} extrusion by the sarcoplasmic reticulum (3, 30).

The RV-hypertrophied hearts showed a steeper RV diastolic P-V relation (Fig. 1), an increased collagen content (Fig. 6), a steeper LV diastolic P-V relation (Fig. 4), and an altered diastolic ventricular interaction (Fig. 5), which is in agreement with our previous findings (19). These alterations are all indicative of altered diastolic function of the hypertrophied hearts. Recently (13), in vivo measurements in rats with MCT-induced cardiac hypertrophy (30 mg/kg MCT) showed an increase in RV end-diastolic pressure, which was not found in rats with MCT-induced heart failure (80 mg/kg MCT), whereas in both MCT groups indexes of end-diastolic stiffness were unaltered. Moreover, in rats with MCT-induced heart failure (60 mg/kg MCT) (23), it was found that RV, but not LV, end-diastolic pressure was increased. In both studies, localization of fibrosis was determined using immunohistochemical techniques. Quantification of fibrosis in the histological coupes revealed that RV perivascular and interstitial fibrosis was unaltered (13), whereas the other study found that RV, but not LV, myocardial fibrosis was increased (23). Differences in MCT protocols, experimental conditions during hemodynamic measurements, and the fact that histological techniques are more suited for detection of collagen localization rather than for estimation of total collagen content, could be responsible for the differences.

Circulating neurohormonal factors might explain why an increase in collagen occurred in the nonstressed LV as well (7). In MCT-treated rats, plasma levels of positive inotropic factors like angiotensin II, endothelin-1, atrial natriuretic peptide, and norepinephrine have been reported to be elevated (6, 16, 23, 30).
improve the energy status in the acute setting of ischemia-reperfusion, it was found that two intravenous injections of D-ribose at 12-h intervals did not improve energy status (40). In our experiments, chronic (6 wk) oral R-FA normalized the TAN content at both frequencies. Together these observations suggest that short-term injections of D-ribose can deplete the TAN content at 9 Hz than at 3 Hz (Fig. 3), chronic R-FA normalized the TAN content at both frequencies. The increased systolic P-V relations, the negative P-F relations, and the prolonged relaxation of the RV in the MCT group (Figs. 1 and 2) were not affected by R-FA. In agreement with this preservation of systolic function, the RV hypertrophy in the MCT placebo group was not affected by R-FA administration, as indicated by the cross-sectional areas of the cardiomyocytes (Table 1). Interestingly, Omran et al. (27) did not find changes in systolic LV function in congestive heart failure patients receiving daily D-ribose for 3 wk. The preservation of the enhanced systolic RV function and the negative P-F relations with R-FA administration, as well as the lack of an effect of R-FA on lung weights and RV hypertrophy (Table 1), argues against an a specific effect of R-FA on the development of MCT-induced RV hypertrophy.

Our results showed that the normal RV diastolic P-V relation (Fig. 1) and the direct diastolic ventricular interaction (Fig. 5) were preserved with R-FA. The steeper LV diastolic P-V relation tended to be blunted, but the difference did not reach significance. In a dog model of global cardiac ischemia, diastolic function, as assessed from circumferential stress-strain measurements (37), was improved by short-term D-ribose for 24 h. The atrial contribution to LV filling in congestive heart failure patients receiving daily oral D-ribose for 3 wk was improved, thereby indirectly enhancing diastolic function (27). These observations most likely converge and indicate that long-term R-FA may be required for normalization of diastolic function, whereas the systolic alterations, which are not necessarily detrimental, remain.

The MCT-treated animals gained less weight than those of the control animals due to reduced food intake (16, 20), which could reduce the myofibrillar protein content of the myocardium and thereby theoretically the collagen content. However, R-FA administration resulted in normalization of the collagen content, whereas body weight was the same as in MCT-placebo group, indicating that in the MCT group alterations in collagen content cannot be attributed to reduced food intake.

**Link between energy status, diastolic function, and R-FA.** Our study clearly shows that R-FA administration can prevent the increase in collagen content in MCT-induced RV hypertrophy, resulting in increased diastolic stiffness. This could either be caused by D-ribose or by FA. It has been shown that diet-induced FA deficiency in rats caused a marked impairment in collagen synthesis in the skin (12). In addition, in vitro incubation with D-ribose (200–500 mM) caused nonenzymatic glycation of fibrous collagen in rat tail tendons (36) and human placenta tissue (31). However, to the best of our knowledge no literature is available on the link between D-ribose or FA and collagen content or diastolic stiffness in cardiac tissue.

A strong inverse relation has been observed between FA consumption and homocysteine levels (43). Yet, clinical trials showed variable outcomes regarding the effects of B vitamins on cardiovascular disease: after coronary interventions a reduction in the incidence of revascularization was found (32), whereas recently a trend to increased risk of recurrent cardiovascular complications was found after acute myocardial infarction (4). In animal studies, Joseph et al. (15) showed that 10 wk of hyperhomocysteinemia resulted in an increased diastolic stiffness and increased collagen deposition. However, the serum homocysteine levels in our study did not vary among groups, implying that R-FA does not exert its action on diastolic stiffness through changes in homocysteine levels.

In patients with coronary artery disease, a 6-wk FA treatment improved flow-mediated dilatation in the upper arm, independent of homocysteine levels (10). This effect might be linked to direct effects of 5-methyltetrahydrofolate, an active form of FA, on the enzymatic activity of endothelial NO synthase (34). However, as mentioned, FA provides an essential cofactor in the formation of ATP via the de novo purine synthesis (24) and therefore may contribute to the beneficial effect of D-ribose on the myocardial energy status, and thereby on cardiac function.

The relaxation rate of myocardium, a determinant of diastolic function, is in the rat predominantly determined by the Ca\(^{2+}\) reuptake by the sarcoplasmic reticulum (SR). Ca\(^{2+}\) reuptake is determined by the SR Ca\(^{2+}\)-ATPase (SERCA2a)
(2) and the intracellular free energy availability from ATP splitting (14). The amelioration of the energy status by R-FA through preserving TAN content did not result in an improvement of cardiac relaxation (Figs. 1 and 2). This suggests that the decreased mRNA/protein levels of SERCA2a, as found previously in the MCT model (16, 41), are the dominant factors in the observed slowing of relaxation.

In our study, R-FA preserved the TAN content in the MCT group, but total creatine remained depressed (Fig. 3). Moreover, the TAN content clearly depended on frequency, whereas total creatine did not. It has been suggested that the decreased creatine pool in failing hearts is caused by a reduction in creatine transporters (26) rather than by a mismatch between energy supply and demand. This may explain the difference in the effect of R-FA on TAN and total creatine.

The preserved energy status of the hypertrophied myocardium by R-FA administration might lower diastolic pressure through a reduction in passive tension of cardiomyocytes and thereby reduce the release of paracrine/endocrine substances by the myocardium, such as angiotensin II or endothelin-1. This would provide a link among energy status, collagen deposition, diastolic function, and R-FA. Therefore, it would be of interest to determine the effect of R-FA administration on the myocardial angiotensin II and endothelin-1 content.

Limitations and conclusions. This study demonstrates that the RV energy status is depressed in compensated RV hypertrophy. In addition, it shows that chronic R-FA administration exerts beneficial effects on TAN, diastolic stiffness, collagen deposition, diastolic function, and R-FA. Therefore, it would be of interest to determine the effect of R-FA administration on the myocardial angiotensin II and endothelin-1 content.

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Dr. J. A. St Cyr is consultant and holds stock options for Bioenergy Inc. All other authors have no disclosures.


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