Upregulated Neurohumoral Factors are Associated With Left Ventricular Remodeling and Poor Prognosis in Rats With Monocrotaline-Induced Pulmonary Arterial Hypertension

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Background Left ventricular remodeling might be involved in the pathophysiology of right ventricular hypertrophy/failure due to pulmonary arterial hypertension (PAH), while the left ventricle is considered not under pressure/volume overload.

Methods and Results Rats with monocrotaline-induced PAH were used in the present study to examine whether upregulated neurohumoral factors may induce left ventricular (LV) remodeling and/or contribute to prognosis. Morphological analysis revealed a significant increase in the weight of the free walls of both ventricles and the interventricular septum, indicating biventricular hypertrophy, although systemic blood pressure was not elevated. RNase protection assay demonstrated the activation of a fetal gene program in the cardiac muscle of the left and right ventricular free walls. Similar activation of the fetal gene program was observed in the LV of rats continuously infused with angiotensin (AT) II, although this was not the case for rats infused with isoproterenol. Measured plasma levels of ATII, noradrenaline, and brain natriuretic peptide (BNP) were all significantly elevated in the PAH rats. Furthermore, the plasma BNP level positively correlated with the ratio of heart weight to body weight and the plasma level of ATII. Not right but LV hypertrophy was significantly reduced by treatment with an AT II type 1 receptor blocker, valsartan, whereas the effect of an adrenergic β1 and β1,2 blocker, carvedilol, was borderline. Survival rate in the PAH rats was significantly improved when they were treated with valsartan or carvedilol.

Conclusions Upregulated neurohumoral factors seem to play an important role in LV remodeling without mechanical overload, and are associated with impairment of prognosis in rats with PAH. (Circ J 2006; 70: 1208–1215)

Key Words: Carvedilol; Hypertrophy; Monocrotaline; Pulmonary arterial hypertension; Valsartan

Pulmonary arterial hypertension (PAH) is a disorder induced by various causes, such as collagen or pulmonary obstructive/restrictive disease-associated vasculopathy, pulmonary artery embolism, hypoxia, and inflammatory diseases, as well as genetic abnormalities.1,2 Although the etiology of PAH is diverse, the essential pathophysiology is an elevation in the resistance of the pulmonary arteries characterized by vascular remodeling and smooth muscle spasm with continuous progression of luminal obliteration. Therefore, the strategy for treating PAH patients has focused on decreasing the resistance of the pulmonary arteries and/or preventing progression of pulmonary vascular remodeling. So far, vasodilatation therapy with Ca2+ antagonists and prostaglandin derivatives has been used for PAH patients, but the improvement of prognosis and/or quality of life (QOL) has been limited. Recently, several clinical trials have revealed that an endothelin (ET)-1 receptor blocker, bosentan, is the most promising drug for the treatment of PAH,3–5 and evidence for a beneficial effect of a phosphodiesterase V inhibitor, sildenafil, has accumulated6–9 with the Food and Drug Administration in the United States approving sildenafil as treatment for PAH in June 2005. However, these treatment strategies have not always been satisfactory for all PAH patients because of incomplete reversibility of the pulmonary vasculopathy, and the long-term benefits and side effects are not yet defined. The management of right ventricular failure should be considered together with treatment for pulmonary vasculopathy.

Many recent clinical mega-trials have clearly shown that angiotensin-converting enzyme (ACE) inhibitors/angiotensin (AT) II receptor blockers (ARB)10,11 and β-adrenergic-receptor blockers (BB)12–14 are beneficial drugs for patients with left-sided heart failure. Mechanical stress is an important factor in the progression of left ventricular (LV) hypertrophy/failure. In addition, circulating and/or locally produced ATII and catecholamines are now thought to directly contribute to LV remodeling and progression of hypertrophy/failure. However, it is a matter of debate whether the LV is affected by such neurohumoral factors in isolated right-sided heart failure due to PAH. The effect of ACE...
inhibitor/ARB or BB therapy on PAH has not been evaluated either clinically or experimentally. BB are currently thought to be contraindication for isolated right-sided heart failure due to PAH. Our purpose in the present study was by using a monocrotaline (MCT)-induced PAH model to examine whether the molecular mechanism for LV hypertrophy/failure is also involved in PAH-induced right-sided heart failure as a result of upregulated neurohumoral factors and, if so, whether ARB and/or BB have a beneficial effect on prognosis.

Methods

All protocols conformed with the guide for the Care and Use of Laboratory Animals (Washington, DC: Natl Acad Press, 1996).

MCT Model

Six-week-old male Wister rats, weighing 110–130 g, were used (n=225). MCT (WAKO Chemicals, Osaka, Japan) was dissolved in 1 mol/L HCl, neutralized with 0.5 mol/L NaOH, and then diluted with distilled water to pH 6.8–7.2 for use. Experimental animals were given a single subcutaneous injection of 60 mg/kg MCT, while 0.9% saline was used for control animals (Sham). The animals were then kept in their cages until use. The MCT-treated rats were divided into 3 treatment groups (valsartan (Val), carvedilol (Car), or vehicle (Veh)) 2 weeks after MCT injection. Val and Car were dissolved in the drinking water, the concentrations of which were 1.2 mg/ml and 0.4 mg/ml, respectively. Drinking water for all groups contained equal amounts of solvents, which were 0.006 mol/L NaOH with the correct amount of HCl for titration for the Val-containing solution, and 0.4% CH₃COOH. The probe specific for the rat ANP and rat Č skA protected a 195-bp fragment (246–428 nucleotides of M25297), respectively. The probe for rat SERCA2 mRNA; it protected a 300-bp fragment (3014–3347 nucleotides of RNAC02). The StyI-digested -MHC, and protected a 175-bp fragment (5656–5830 nucleotides of X15938). The probe for rat ANP and rat

ATII or Isoproterenol (ISO) Infusion Model

Twelve-week-old male Wistar rats weighing 260–300 g were continuously treated with Val or ATII (WAKO Chemical) or dl-ISO (WAKO Chemicals) by subcutaneously implanted osmotic pumps (Alzet mini osmotic pump, model 2ML4; Alza Corp). Val or ATII and dl-ISO were infused at a rate of 30 pg·kg⁻¹·h⁻¹ and 0.1 pg·kg⁻¹·h⁻¹, respectively. Age-matched rats subcutaneously implanted with an osmotic pump containing saline were used as the control group (Control). After 8-weeks’ infusion, samples were obtained as described below.

Sampling

After anesthesia with intraperitoneal injection of 50 mg/kg pentobarbital sodium, the animals were killed and their body weight (BW) measured. Blood samples were quickly obtained from the abdominal aorta and then the hearts were resected and the wet heart weight (HW) was measured. Immediately after, the ventricles were into 3 sections (right ventricular free wall, LV free wall and ventricular septal wall) and the weight of each (RVFW, LVFW, SepW, respectively) was measured. Each section was then kept in the correct amount of RNAlater Reagent (Ambion Inc) at -20°C. Next, the lung and liver weights (LungW, LiverW, respectively) were measured.

Table 1 Heart, Lung, and Liver Weights in the Sham and the MCT Groups

<table>
<thead>
<tr>
<th>Heart, Lung, and Liver Weights</th>
<th>Sham (n=26)</th>
<th>MCT (n=22)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HW/BW (mg/g)</td>
<td>2.97±0.05</td>
<td>5.08±1.19</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>RVFW/BW (mg/g)</td>
<td>0.43±0.01</td>
<td>1.19±0.08</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>SepW/BW (mg/g)</td>
<td>0.53±0.02</td>
<td>0.84±0.05</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LVFW/BW (mg/g)</td>
<td>1.49±0.03</td>
<td>2.12±0.06</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LungW/BW (mg/g)</td>
<td>4.3±0.1</td>
<td>9.4±0.5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LiverW/BW (mg/g)</td>
<td>35.4±0.5</td>
<td>45.2±1.4</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

MCT, monocrotaline; HW, heart weight; BW, body weight; RVFW, SepW, and LVFW, weights of right ventricular free wall, ventricular septal wall, and left ventricular free wall, respectively; LungW, lung weight; LiverW, liver weight.

Physiological Measurements

Blood pressure (BP) and pulse rate (PR) were simultaneously measured non-invasively without anesthesia. Animals were incubated at 37°C for 10–15 min and then BP was measured by tail-cuff method with BP-98A (Softrom Inc). The mean value of 3 consecutive measurements was used.

Plasma Brain Natriuretic Peptide (BNP), ATII, and Noradrenaline (NA)

The plasma fraction was extracted from the blood samples to be mixed with EDTA-2Na, and then kept at –20°C until the measurement of BNP, ATII, and NA. Because the amount of the blood sample was not always enough for all the measurements, the order was BNP, ATII, and then NA. All measurements were performed independently by SRL Inc. Briefly, BNP and ATII were first extracted from the plasma and then quantified by radioimmunoassay. The protein was removed from the residual plasma, and then dissolved NA was quantified with high-performance liquid chromatography.

Quantification of Expression of Myocyte-Specific mRNAs

Each section of heart was homogenized with TRIzol (GIBCO) and the extracted RNA was used in a RNase protection assay (RPAIII kit, Ambion Inc) with probes for sarcomplasmic reticulum Ca²⁺ ATPase (SERCA 2) Ca²⁺ ATPase (SERCA 2), Na/Ca exchanger (NCX), ÷-÷-myosin heavy chain (MHC), atrial natriuretic peptide (ANP), BNP, skeletal ÷-actin (÷-skA), plus glyceraldehyde 3-phosphate dehydrogenase (GAPDH) as an internal control. All plasmids for the riboprobes were sequenced, and linearized at the 3’-end of the antisense strand with appropriate restriction enzymes. Riboprobes were labeled with [³²P]-UTP using a Maxiscript kit (Ambion Inc). The probe specific for the rat SERCA2 gene protected a 333-bp fragment of SERCA2a (3014–3347 nucleotides of X15635), and the probe for NCX protected a 318-bp fragment of rat NCX1 (1820–2128 nucleotides of 60339).

The probe for rat MHC was complimentary to the 3’-end of ÷-MHC mRNA; it protected a 300-bp fragment (5626–5925 nucleotides of X15939), but also hybridized to ÷-MHC, and protected a 175-bp fragment (5656–5830 nucleotides of X15938). The probe for rat ANP and rat BNP protected 210-bp (96–307 nucleotides of E00443) and 180-bp (246–428 nucleotides of M25297) fragment, respectively. The probe for rat ÷-skA protected a 195-bp fragment (2841–3038 nucleotides of RNA02). The Chem-digested rat glyceraldehyde GAPDH probe (pTRI-GAPDH-Rat, Ambion Inc) protected a 134-bp fragment (complimentary
to nucleotides 369–503 of X02231). All labeled probe mixes were hybridized with 5 μg of total RNA. After incubation at 42°C overnight, the RNA-probe mix was digested with RNase A/T1 (1:25, RPAII, Ambion Inc) at 37°C for 30 min, and protected fragments were separated on a 6% denaturing polyacrylamide gel. In each gel lane, all specific signals, and GAPDH as the internal control, were quantified by InstantImager Electronic Autoradiography System (Packard Instrument). Myocyte-specific mRNA signals were normalized to GAPDH.

**Statistical Analysis**

Data are expressed as mean±SEM. Statistical analysis was performed with Excel Tokei software (version 5.0). Paired or unpaired t-test was used for the comparison between 2 groups. Survival rate is presented as a Kaplan Meier curve, and the logrank test was used to assess the statistical significance between groups. A p-value <0.05 was considered significant.
Results

Morphological Characteristics
The PAH rats exhibited a markedly hypertrophied right ventricle and mildly but significantly hypertrophied left ventricle as indicated by a significant increase in the ratios of RVFW to BW and of LVFW to BW (Table 1), although BW was less increased in the PAH rats (158±8 g, n=22 vs Sham 277±5 g, n=26, p<0.001) as has been reported for this model.16 The ratios of LungW to BW and of LiverW to BW were also increased in the PAH rats.

Fetal Gene Expression
It is well known that a series of fetal genes, such as ANP, ßMHC, and ß-skA, is upregulated in response to pathologic hypertrophic stimuli.17,18 The expression of BNP, NCX, SERCA, and the fetal genes was examined in the hearts of MCT rats using a RNase protection assay and as shown in Fig 1, ANP, BNP and ß-skA were all significantly upregulated in the free walls of both the ventricles in the PAH rats, compared with the Sham rats, whereas the expression of NCX and SERCA appeared to be augmented without statistical significance. As for MHC, ßMHC was downregulated, and ßMHC was upregulated in both the ventricles of the PAH rats, resulting in a significant decrease in the value of ß/ß, which is the expression ratio of ßMHC to ßMHC. These results strongly suggested that fetal genes were induced in both ventricles of the PAH rats. The fetal pattern was also observed in the interventricular septal wall of the PAH hearts (data not shown). Together with the data from the morphological analysis (Table 1), the biventricular hypertrophy in the PAH rats was not physiological but very likely pathological.

Effects of Upregulated Neurohumoral Factors
Up-Regulated Neurohumoral Factors in MCT-Induced PAH In contrast to the critical roles of ATII and NA in left-sided hypertrophy/failure, their roles in right-sided hypertrophy/failure in MCT rats or humans with PAH have been scarcely examined. In the current MCT model of PAH, the plasma levels of ATII and NA were significantly elevated as compared with those in the Sham rats (Fig 2a). The plasma level of BNP was also significantly elevated in the PAH rats and positively correlated with the ratio of HW to BW and that of ATII (Fig 2b).

Assessment of Direct Effects of ATII and ISO To elucidate whether the stimulation of ATII receptors or ß-adrenergic cascades activates the fetal gene program in vivo, rats were continuously treated with Val5-ATII or a non-selective ß agonist, ISO, for 8 weeks, and then the RNase protection assay was performed using the LVFW. As shown in Figs 3a,b, ATII infusion similarly activated the fetal gene program as was observed in both ventricles of the MCT rats, whereas the expression of SERCA was slightly but significantly augmented as compared with the Control rats. In contrast, the myosin isoform switch from ß to ß was not observed at all in ISO-infused rats (Figs 3c,d), suggesting that the fetal gene program was not turned on by continuous ß-adrenergic stimulation.

Effect of Blockade of ATII Type 1 (AT1) or ß-Adrenergic Receptor in MCT-Treated Rats Oral treatment with Car or Val was started in the MCT-treated rats 2 weeks after the MCT injection, and the effects on LVFW and RVFW were examined. The increase in LVFW/BW was significantly suppressed in Val-treated rats as compared with Veh-treated rats, whereas Car treatment showed the tendency (Fig 4). On the other hand, treatment with Val or Car did not affect RVFW/BW at all, suggesting that not right but LV hypertrophy is diminished by inhibition of ATII-associated signaling, and that ß1, ß2 receptor blockade might have some similar effects. To examine whether these drugs have an effect on the induction of the fetal genes, the RNase pro-

Fig 2. Plasma levels of humoral factors. (a) Brain natriuretic peptide (BNP), angiotensin (AT) II, and noradrenaline (NA) were measured in monocrotaline (MCT)-treated rats (n=22, 20, 11, respectively) and Sham rats (n=26, 26, 12, respectively). *p<0.01, **p<0.05. (b) The correlation between the concentration of BNP and the heart to body weight ratio (HW/BW) in the MCT-treated rats is shown in the Left panel and the correlation between the concentrations of BNP and ATII in the Right panel.
No change was detected in the expression of the fetal genes between the Veh- and the Val- or the Car- treated MCT rats (data not shown).

**Prognosis**  The prognosis of the MCT-treated rats was quite poor (Fig.5). To examine whether treatment with Val or Car would improve the prognosis, the MCT rats were divided into Veh, Val, and Car groups (n=27, 28, 28, respectively). BP and PR were measured in each group 4 weeks after MCT injection (=2 weeks after division into treatment groups) (Table 2). BP was not significantly changed in any of the groups. PR was significantly in-
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Increased in the Val-group, and significantly decreased in the Car-group, as compared with the Veh-group. PR in the Veh-group (equivalent to MCT-treated rats) was less than that in the Sham rats. The Kaplan-Meier survival curve and logrank analysis revealed that survival rate was significantly improved in the Val-group and Car-group as compared with the Veh-group, suggesting that Val and Car might have a beneficial effect on the prognosis of PAH.

Discussion

As a model for PAH, we have used the MCT-treated rat model, which has been well-established as representing PAH and severe right-sided hypertrophy/failure, and we have, for the first time, demonstrated activation of the fetal gene program in both ventricles. Because the LV was not affected by either pressure or volume overload, the hypertrophic responses in the LV seem to be derived from upregulation of neurohumoral factors. The plasma levels of ATII, NA, and BNP were significantly elevated in the MCT-treated rats, and the plasma level of BNP positively correlated with that of ATII and with the HW/BW ratio. Continuous infusion of ATII induced a similar pattern of fetal gene expression in LV muscle, whereas ISO infusion did not. Treatment with an AT1 receptor antagonist, Val, or an [1, 2 adrenergic blocker, Car, partially prevented LV hypertrophy in the MCT-treated rats without affecting systemic BP, and significantly improved their survival rate, suggesting that upregulated ATII and NA may be associ-

Table 2 BP and PR in the Sham and the Drug-Treated MCT Groups

<table>
<thead>
<tr>
<th></th>
<th>Sham (n=6)</th>
<th>MCT (n=5)</th>
<th>Veh (n=6)</th>
<th>Val (n=5)</th>
<th>Car (n=5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic BP (mmHg)</td>
<td>127±4</td>
<td>120±4</td>
<td>126±4</td>
<td>120±5</td>
<td>116±5</td>
</tr>
<tr>
<td>PR (beats/min)</td>
<td>467±16</td>
<td>447±12</td>
<td>402±9</td>
<td>402±9</td>
<td>330±15</td>
</tr>
</tbody>
</table>

BP, blood pressure; PR, pulse rate; MCT, monocrotaline; Veh, vehicle; Val, valsartan; Car, carvedilol.
*p<0.01, **p<0.05.
ated with LV hypertrophy and increase the risk for a poor prognosis for PAH.

LV Hypertrophy Without Mechanical Overload in PAH Rats

There have been several reports that the LV is affected in a similar model of PAH. Because the LV was not under pressure or volume overload, the increase in LVFW/BW can only be derived from the lower BW of the MCT-treated rats and therefore the LVFW/BW does not truly reflect the degree of hypertrophy. However, Seyfarth et al have already shown that the LV was hypertrophied even when BW was adjusted by feeding the Sham rats with the same amount of food eaten by the MCT rats. In addition, our data on the fetal gene activation have clearly indicated that pathological hypertrophic responses likely occurred in the LV as well as the RV. Taken together, the findings suggest that the LV is pathologically hypertrophied, most probably because of neurohumoral factors, independent of mechanical overload.

Role of Upregulated Neurohumoral Factors in Ventricular Hypertrophy in PAH Rats

Adrenergic Stimulation

Schott et al have speculated that the high level of catecholamines contributes to the increased expression of proteins for ATP synthesis in the LV of MCT-treated rats. Seyfarth et al have reported down-regulation of the \(\alpha_2\)-receptor-\(\alpha\) protein-adenyl cyclase system in both ventricles, although the change in the RV was more prominent than in the LV. As shown in Fig 2, and by Kögl et al, the plasma NA level was significantly increased in MCT-treated rats, suggesting that the down-regulation of the adrenergic \(\alpha\)-receptor may be in part due to catecholamine overload. Hence, overstimulation of \(\alpha\)-receptors by upregulated NA might be important for some aspects of LV hypertrophy. Although the inhibition of \(\alpha\)-adrenergic-associated signaling by Car tended to diminish the increase in LVFW/BW, continuous treatment with ISO did not cause the isoform switch of MHC, suggesting that \(\alpha\)-adrenergic stimulation might contribute to LV hypertrophy, but is not directly associated with the fetal gene activation. Different from the effect of ISO, NA activates \(\alpha_1\) adrenergic signaling, and therefore the effect of Car on LV hypertrophy may be the result of blockade of the \(\alpha\) receptor. Also, Kaddoura et al have shown that NA infusion can induce pathological hypertrophy, including fetal gene activation in part through secondarily upregulated ET-1.22 The overstimulation of the \(\alpha\)-adrenergic and/or an ET pathway(s) might play a role in the activation of the fetal program and/or pathological hypertrophy. Further investigation is necessary to elucidate why \(\alpha\)-adrenergic stimulation does not induce the isoform switch of MHC, and to evaluate the role of the \(\alpha_1\)-adrenergic pathway in LV hypertrophy in the MCT rat model.

Renin-AT System

Park et al have revealed with a method of reverse transcriptase-polymerase chain reaction that the expression of angiotensinogen was upregulated in both ventricles of MCT-treated rats, whereas the expression of AT1 and ATII type 2 (AT2) receptors was unchanged. Both Brunner et al and we have shown that the plasma concentration of ATII was increased. In our study, the inhibition of AT1 receptor-associated signaling by Val significantly prevented the increase in LVFW/BW, while RVFW/BW was unaffected. Therefore, LV hypertrophy in MCT-treated rats is likely, but only partially, associated with ATII-dependent signaling.

Several key enzymes leading to pathological hypertrophy have been recognized: MAP kinase, protein kinase C, calmodulin kinase, and calcineurin. Pathological hypertrophy is thought to be the result of overactivation of these kinases. ATII is widely known to activate all these enzymes and induce fetal genes. From this viewpoint, it is reasonable that ATII infusion would cause the typical pathological hypertrophy that we have shown in the present study. However, we have noted that the inhibition of ATI signaling by Val had no apparent effect on the activation of the fetal gene program in either ventricle of the MCT-treated rats, which implies that the activation of fetal gene program might be the result of complex upregulation of neurohumoral factors, leading to activation of the kinases, or that it is independent of ATI-dependent signaling. ET-1, which has similar intracellular signaling to ATII, has already been reported as upregulated in similar models and may be a candidate for fetal gene activation in the LV of MCT-treated rats. Further experiments are necessary to elucidate which neurohumoral factor is the key to induction of the fetal gene program and LV hypertrophy in the MCT rat model.

Is Blockade of the Upregulation of Neurohumoral Factors Important for the Prognosis of PAH?

ATII and NA are widely accepted as playing a critical role in the progression of left-sided (and bi-ventricular) heart failure. However, in patients with PAH-related right-sided hypertrophy/failure, especially those without clinically detectable left-sided hypertrophy/failure, there has been no report showing that blockade of ATII and/or \(\alpha\) adrenergic signaling improves prognosis. We believe that our study is the first to show that treatment with an AT1 blocker, Val, or an \(\alpha_1\)-blocker, Car, significantly prolonged the survival of PAH rats. From the Kaplan-Meier survival curve, it appears that the prolongation of survival was apparent after 30 days of the drug treatment, implying that the effect was not exerted acutely, but chronically. This is reasonable, because these drugs are well-known to improve ventricular function, prognosis, and QOL in patients with left-sided heart failure, which is not an acute, but rather a chronic effect. Although our study was limited in its ability to clarify this point, PAH-related right-sided heart failure also seems to be improved by these drugs.

Compared with the benefits from treatment with ET-1 blockers or a phosphodiesterase V inhibitor, sildenafil reported in MCT-treated rats, the improvement in prognosis by Val or Car is relatively minor. Furthermore, combination therapy with sildenafil and beraprost, which was reported by Ito et al dramatically improved the prognosis of MCT-treated rats. These reports strongly suggest that treatment of pulmonary arterial vasculopathy may be primarily important for PAH. Nonetheless, it can be noted that factors that progress left-sided heart failure are also likely to contribute to the progression of right-sided hypertrophy/failure associated with PAH. In addition, these factors might be involved in progressing LV hypertrophy and/or leading to the poor prognosis of MCT-treated rats, because treatment with Val significantly diminished LV hypertrophy, and treatment with Car had a similar effect. Further investigation is necessary to elucidate whether the improvement in prognosis by these drugs is due to reduction of LV hypertrophy, but it is worth paying attention to LV remodeling as well as right ventricular hypertrophy/failure and pulmonary vascular remodeling in PAH rats.

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Conclusion

Without direct mechanical overload on the LV, circulating and/or locally upregulated neurohumoral factors could induce pathological hypertrophic responses in the LV, in addition to the pressure-overloaded right ventricle in a rat model of PAH. Blockade of upregulated ATII or NA improved the survival of PAH rats, suggesting that upregulated neurohumoral factors might play an important role in the pathophysiology of PAH.

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References