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Valsartan attenuates cardiac and renal hypertrophy in rats with experimental cardiorenal syndrome possibly through down-regulating galectin-3 signaling

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Abstract. – OBJECTIVE: Aortocaval fistula (AV) induced chronic volume overload in rats with preexisting mild renal dysfunction (right kidney remove: UNX) could mimic the type 4 cardiorenal syndrome (CRS): chronic renocardiac syndrome. Galectin-3, a β-galactoside binding lectin, is an emerging biomarker in cardiovascular as well as renal diseases. We observed the impact of valsartan on cardiac and renal hypertrophy and galectin-3 changes in this model.

MATERIALS AND METHODS: Adult male Sprague-Dawley (SD) rats (200-250 g) were divided into S (Sham, n = 7), M (UNX+AV, n = 7) and M+V (UNX+AV+valsartan, n = 7) groups. Eight weeks later, cardiac function was measured by echocardiography. Renal outcome was measured by glomerular filtration rate, effective renal plasma flow, renal blood flow and 24 hours albuminuria. Immunohistochemistry and real-time PCR were used to evaluate the expressions of galectin-3 in heart and renal.

RESULTS: Cardiac hypertrophy and renal hypertrophy as well as cardiac enlargement were evidenced in this AV shunt induced chronic volume overload rat model with preexisting mild renal dysfunction. Cardiac and renal hypertrophy were significantly attenuated but cardiac enlargement was unaffected by valsartan independent of its blood pressure lowering effect. 24 hours urine albumin was significantly increased, which was significantly reduced by valsartan in this model. Immunohistochemistry and real-time PCR evidenced significantly up-regulated galectin-3 expression in heart and kidney and borderline increased myocardial collagen I expression, which tended to be lower post valsartan treatment.

CONCLUSIONS: Up-regulated galectin-3 signaling might also be involved in the pathogenesis in this CRS model. The beneficial effects of valsartan in terms of attenuating cardiac and renal hypertrophy and reducing 24 hours albumin in this model might partly be mediated through down-regulating galectin-3 signal pathway.

Key Words:
Cardiorenal syndrome, Galectin-3, Angiotensin II receptor blocker, TGF-β, ERK.

Abbreviations

α-SMA = α-smooth muscle actin; TNF-α = tumor necrosis factor alpha; CRP, C-reaction protein; TGF-beta = transforming growth factor-β; ELISA = enzyme-linked immunosorbent assay; RT-PCR = real-time polymerase chain reaction; ERK = extracellular signal-regulated kinases.

Introduction

Clinical and experimental studies have demonstrated that cardiac dysfunction could induce renal injury and, conversely, impaired renal function could also be a risk factor for cardiovascular diseases[1]. Cardiac and renal dysfunction may worsen each other, which is usually referred to as the cardiorenal syndrome (CRS). It has been proposed that mechanisms of this organ crosstalk occur at multiple levels, including hemodynamics, dysregulation of salt and fluid balance, endothelial dysfunction, inflammation, and activation of regulatory systems such as the renin-angiotensin aldosterone system (RAAS) and the sympathetic nervous system (SNS)[2]. The exact pathophysiological mechanisms underlying the CRS are not fully understood yet.

Previously, we showed that aortocaval fistula (AV)-induced cardiac remodeling was aggravated in rats with preexisting mild renal dysfunction post right kidney remove (UNX), a model mimicked the type 4 CRS: chronic renocardiac syndrome[3,4].

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Galectin-3 is a macrophage product member of the lectin family, which is found on a wide variety of cells and tissues surfaces[5]. Previous studies[6,7] demonstrated that galectin-3 was related to the inflammatory cascade and myocardial fibrosis following cardiac injury, as well as pathways in regulating cardiac contractility. It was shown that increased circulating galectin-3 belonged to the strongest correlate of decreased renal function both in general population and patients with heart failure[8-12]. Sharma et al[5] found that galectin-3 could bind directly to cardiac fibroblasts, increase collagen production and reduce left ventricular systolic function. Bogrov et al[13] demonstrated that RAAS activation, as seen in the cases of hypertrophy, heart failure and renal disease, could induce subsequent pro-fibrotic factor release including galectin-3, TGF-β and endogenous cardiac steroids. Till now, the contribution of galectin-3 to the pathogenesis of CRS is not fully understood.

The purpose of the present study is to explore the potential contribution of galectin-3 to the disease pathogenesis of CRS, and we observed the changes of galectin-3 expression in the UNX+AV rat model and the impact of angiotensin II receptor blocker valsartan on circulating and tissue galectin-3, cardiac and renal function as well as inflammation fibrosis markers.

Materials and Methods

Experimental Animals and Study Groups

Experiments were approved by the Tongji Medical College Council on the Animal Care Committee of Huazhong University of Science and Technology (Wuhan, China). Animals were maintained in accordance with the Guide for the Care and Use of Laboratory Animals published by the US National Institute of Health (NIH Publication No. 85-23, revised 1996). All surgeries were performed under sodium pentobarbital anesthesia, and all efforts were made to minimize suffering. Male Sprague-Dawley (SD) rats (weighing 200 to 250 g) were housed under standard conditions with free access to food and drinking water. Rats received a normal salt diet (0.3% NaCl) throughout the study. Rats were randomly divided into S (Sham, n=7), M [UNX (right kidney remove)+AV (AV established between the levels of renal arteries and iliac bifurcation at one week after UNX), n=7] and M+V [UNX+AV+valsartan (valsartan initiated at the time of AV with a dose of 20 mg/kg/day per gavage), n = 7]. Eight weeks later, survived rats were placed in individual metabolic cages. After 5 days of adaptation, twice consecutive 24-hour urine was collected from each rat. Echocardiography was performed two days followed the metabolic cage studies. After echocardiography examination, rats received renal function measurements[3]. A blood sample was obtained from the vena cava post above measurements. Finally, all rats were killed under deep anesthesia (70 mg/kg sodium pentobarbital intraperitoneally), and organs were removed, weighed, and processed for histological quantification and molecular examinations.

Echocardiography Examination

Echocardiography examination was performed by an investigator blinded to the study protocol. Left parasternal and left apical echocardiographic images of light anesthetized (1% pentobarbital sodium salt, 40 mg/kg, intraperitoneal injection) rats lying in a supine position were obtained with an echocardiographic system (GE, Fairfield, CT, USA) equipped with an 11.4 MHz transducer. A two-dimensional short-axis view of the left ventricle was obtained at the level of the papillary muscles.

Renal Function Measurements

The jugular vein catheter was connected to a syringe and each rat was given an i.v. bolus (2 ml/kg) of the inulin/para-amino hippurate (PAH) (TCI, Hashimoto CHO, Tokyo, Japan) solution, followed by an i.v. infusion (25 μl/min) of the inulin/PAH solution via an infusion pump as described previously[3]. The inulin/PAH solution contained 3% inulin and 2% PAH in saline. An additional infusion of saline (25 μl/min) into the jugular vein catheter was also performed and was continued for the duration of the experiment. Following a one-hour equilibration period, hemodynamics and renal function were determined for 90 min (three 30 min clearance periods). Urine was collected in pretreated vials at 30 min intervals through the bladder catheter. Arterial blood samples (500 μl) were drawn through the carotid artery catheter at the midpoint of each urine collection period into prechilled heparinized tubes. The blood sample was taken into microhematocrit tubes for measurement of hematocrit. The urine samples were measured gravimetrically for

urine volume. Urine samples were then refrigerated until they were assayed. Plasma samples were separated by centrifugation and kept at -80°C freezer until analysis.

Blood and Tissue Collection

After blood sampling from vena cava, the rats were sacrificed under additional deep anesthesia (70 mg/kg sodium pentobarbital intraperitoneally). Total heart, right ventricular and left ventricular weight including the septum were measured. Kidney, liver and lung were also removed from all animals and immediately placed in ice-cold saline to wash out the blood; wet weights were measured. Then parts of heart and kidney were fixed by immersion for 48 hours in 4% neutral formaldehyde. Subsequently, they were processed for paraffin embedding according to standard procedures. 4 μm tissue sections were stained with immunohistochemistry methods and images were then captured with a Leica microscope (Wetzlar, Germany).

Biochemistry Measurements

The 24-hour urine albumin was measured by using a sensitive enzyme-linked immunosorbent assay (ELISA) kit (Abcam, Cambridge, UK). The plasma galectin-3 was measured with the ELISAs kit (Elabscience Biotechnology Co., Wuhan, Hubei, China) following manufacturer's instructions. The absorbance was recorded at 450 nm. An enzymatic method was used for the determination of inulin, and a calorimetric method was used for determination of PAH in the plasma and urine samples. The GFR was estimated as the clearance of inulin (urine volume urine inulin/plasma inulin). The effective renal plasma flow (ERPF) was estimated as the clearance of PAH (urine volume urine PAH/plasma PAH). The renal blood flow was calculated as ERPF/(1-hematocrit). The renal vascular resistance was calculated as mean arterial pressure divided by the renal blood flow. The fractional excretion of sodium was calculated as the clearance of sodium divided by the GFR.

Immunohistochemistry

Immunohistochemistry staining was made on heart and kidney tissue sections. Galectin-3 was identified with rabbit polyclonal galectin-3 antibody (1:200, GeneTex, Alton Pkwy, CA, USA). Galectin-3 was evaluated by assessing the percent positive area of the picture.

Real-time Polymerase chain Reaction Measurements for mRNA Expression of Cytokines in Heart and Kidney

Total RNA was extracted from heart and kidney using RNA Tissue Mini Kit (Takara, Dalian, Liaoning, China) according to the manufacturer's instructions. Reverse transcription and cDNA synthesis were accomplished using PrimeScript RT Master Mix Perfect Real Time (Takara, Dalian, Liaoning, China). Real-time polymerase chain reaction was performed to detect the expression of various cytokines by QuantiFast SYBR Green PCR Kit (Qiagen, Dusseldorf, Germany) and Bio-Rad CFX96 (Bio-Rad, Hercules, CA, USA) according to the manufacturer's instructions. The conditions of amplification reaction were 95°C for 30 sec, 95°C for 5 sec, 60°C for 30 sec, and PCR was done for 40 cycles. PCR primers are shown in Table I. Relative gene expression was calculated using the $2^{-\Delta\Delta CT}$ method.

Western Blot

Total proteins were extracted from the heart, protein concentrations were determined through bicinchoninic acid (BCA) method. After electrophoresis (SDS-PAGE), transmembrane, blocking (milk protein), incubation with primary anti-galectin-3 polyclonal antibody (GeneTex, Alton Pkwy, CA, USA), anti-ERK polyclonal

Table I. RT-PCR forward/reverse (F/R) primers sequences.

F/R	Sequence (5′-3′)
GAPDH	F CAACGGGAAACCCATCACCA
	R ACGCCAGTAGACTCCACGACAT
Galectin-3	F GAGAACAACAGAAGAGTCATCGTG
	R GACCTGTATTTTGAATGGTTTGCC
α-SMA	F CTCCCAGCACCATGAAGATCAA
	R GGGCGTGACTTAGAAGCATTTG
Collagen I	F TTTAATGGATAGGGACTTGTGTGAA
	R GAGAGAGAGAGAAGCTGAGGGTAGG
Collagen III	F GGTTTGGAGAATCTATGAATGGTGG
	R GCTGGAAAGAAGTCTGAGGAAGG
TGF-β	F CTAATGGTGGACCGCAACAAC
	R CACTGCTTCCCGAATGTCTGA
CRP	F AAGCCTTCACTGTGTGTCTCTATGC
	R TTCAGGCCCACCTACTGCAATA
Fibronectin	F GAGGCACAAGGTCCGAGAAGAG
	R GAAACCGTGTAAGGGTCAAAGCA
TNF-α	F AGCAAACCACCAAGCGGAGG
	R CAGCCTTGTCCCTTGAAGAGAAC

GAPDH: glycerinaldehyd-3-phosphate-dehydrogenase; α-SMA: α-smooth muscle actin; TGF-β: transforming growth factor beta; CRP: C-reactive protein; TNF-α: tumor necrosis factor-α.

antibody (Abcam, Cambridge, UK), anti-p-ERK polyclonal antibody (CST, Boston, MA, USA) and secondary antibody (KPL, Washington, DC, USA), and coloration, immunoreactive bands were obtained. Then the images were captured and semi-quantitatively analyzed by Quantity One (Bio-Rad, Hercules, CA, USA).

Statistical Analysis

Data were shown as mean ± SD. One-way ANOVA and Tukey's post hoc test or Games-Howell test was used to test the difference between the means of various groups and $p < 0.05$ was considered as statistically significant.

Results

Survival and Body and Organ Weights, Blood Pressure and Heart Rate

One moribund rat was euthanized under anesthesia (40 mg/kg sodium pentobarbital intraperitoneally) before echocardiography measurement in M+V group due to breathing difficulty, post-mortem examination revealed hypertrophied heart, congested liver and lung, suggesting that overt congestive heart failure might be the cause of breathing difficulty in this rat. Three rats (1 in S group, 1 in M group and 1 in M+V group) were excluded from the final analysis because of the lack of mixing of venous and arterial blood in the vena cava as visualized before sacrifice. Finally, data from 6 rats in S and M groups, 5 rats in M+V group were analyzed. Ascites and pleural effusion were not seen on the rats survived to study end. Body weight (BW) and organ weights as well as systolic and diastolic aortic blood pressure, mean arterial pressure and heart rate of rats from various groups are presented in Table II. Eight weeks post various procedures, body weight was similar among groups. Heart weight (HW) and HW/BW ratio, LVW, LVW/BW, RVW, RVW/BW, left kidney weight and left kidney weigh/BW were significantly increased in M group compared to S group. HW/BW, RVW and RVW/BW ratios were significantly lower in M+V group compared to M group. Systolic and diastolic aortic blood pressure, mean arterial pressure and heart rate were similar among various groups.

Echocardiography Measurements

As shown in Figures 1 and 2, LVIDD and LVISD were significantly higher while LVEF and LVFS values were significantly lower in the M and M+V groups than in S group.

Biochemistry and Renal Function Parameters

GFR tended to be lower in M and M+V group compared to S group; ERPF and RBF were significantly reduced in M group and tended to be lower in M+V group compared to S

Table II. Body weight and organ weights, blood pressure and heart rate.

	S (n = 6)	M (n = 6)	M+V (n = 5)
BW (g)	431 ± 29	440 ± 36	477 ± 20
HW (mg)	1484 ± 357	2280 ± 114**	1962 ± 221*
HW/BW (mg/g)	3.45 ± 0.82	5.22 ± 0.57**	4.11 ± 0.44†
LVW (mg)	1044 ± 279	1493 ± 100**	1366 ± 163*
LVW/BW (mg/g)	2.43 ± 0.64	3.41 ± 0.28**	2.86 ± 0.31
RVW (mg)	300 ± 58	528 ± 57**	402 ± 39*††
RVW/BW (mg/g)	0.70 ± 0.13	1.22 ± 0.22**	0.84 ± 0.08††
Lung Wt (mg)	2863 ± 772	2810 ± 416	2859 ± 565
Lung Wt/BW (mg/g)	6.68 ± 1.84	6.45 ± 1.28	6.04 ±1.45
Liver Wt (mg)	13392 ± 2171	13837 ± 2014	16463 ± 1642
Liver Wt/BW (mg/g)	31.22 ± 5.31	31.63 ± 5.30	34.61 ± 4.28
Left kidney Wt (mg)	1779 ± 311	2235 ± 180*	2161 ± 148*
Left kidney Wt/BW (mg/g)	4.14 ± 0.73	5.10 ± 0.44*	4.53 ± 0.23
Systolic pressure (mmHg)	109 ± 15	116 ± 9	106 ± 19
Diastolic pressure (mmHg)	71 ± 12	73 ± 6	66 ± 25
MAP (mmHg)	83 ± 13	88 ± 7	79 ± 23
Heart rate (bmp)	259 ± 10	253 ± 64	266 ± 49

Values are mean ± SD. S, sham; M, unilateral nephrectomy+aortocavalfistula; M+V, M+valsartan. BW, Body weight; HW, Heart weight; LVW, left ventricular weight; RVW, right ventricular weight; Wt, wet weight; MAP, mean arterial pressure. *$p < 0.05$ *vs.* S group, **$p < 0.01$ *vs.* S group, $^{\dagger}p < 0.05$ *vs.* M group, $^{\dagger\dagger}p < 0.01$ *vs.* M group.

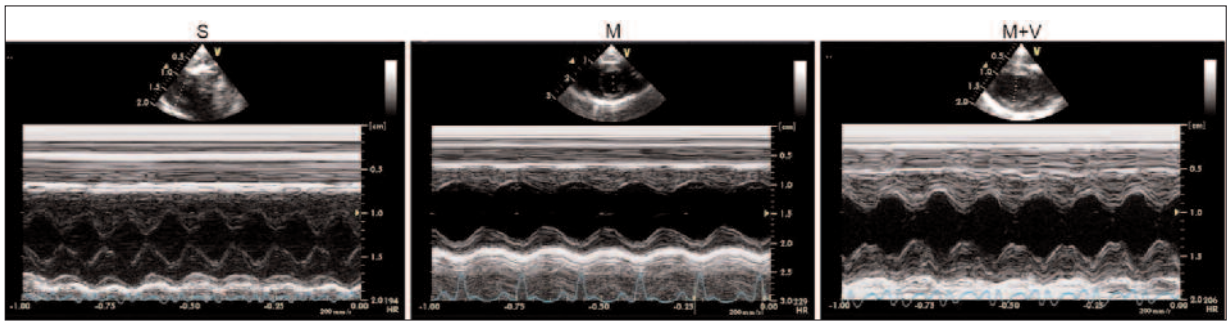

Figure 1. Transthoracic echocardiography Representative B- and M-mode images of the rats from S, M and M+V groups.

group. 24 hours albuminuria was significantly increased in M group compared to S group, which could be significantly reduced in M+V group (Figure 3).

Immunohistochemistry Results of Heart and Kidney and Plasma Galectin-3

Galectin-3 might be involved in the pathogenesis of the chronic volume overload-induced cardiac remodeling and cardiac and renal function changes in rats. Galectin-3 immunohistochemistry staining results on heart and kidney showed that galectin-3 positive area (Figure 4A, B, C, D) and plasma galectin-3 value (Figure 4E) were significantly higher in M group compared to S group and which could be significantly reduced in M+V group ($p < 0.05$ *vs*. M).

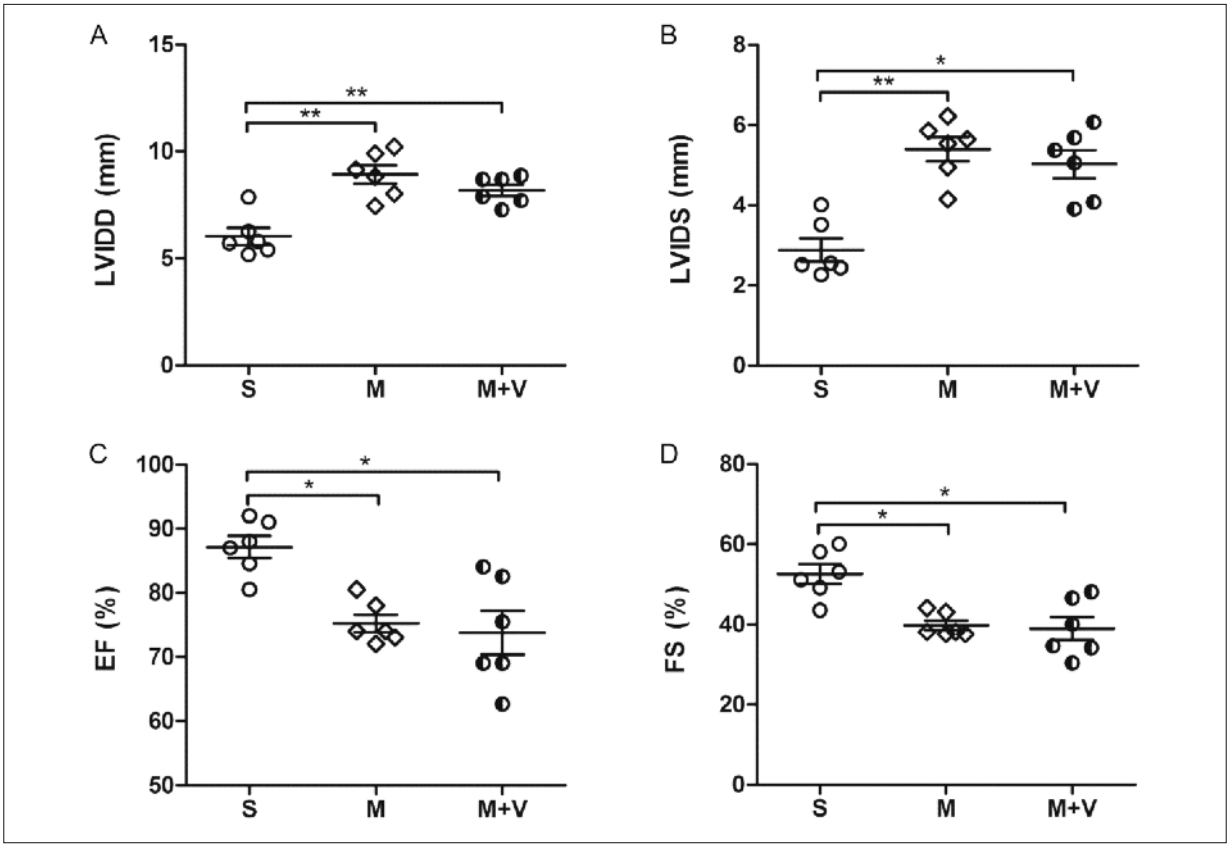

Figure 2. Transthoracic echocardiography analysis. ***A,*** LVIDD, left ventricular internal diameter at end-diastole. ***B,*** LVIDS, left ventricular internal diameter at end-systole. ***C,*** EF, ejection fraction. ***D,*** FS, fractional shortening. *$p < 0.05$, **$p < 0.01$.

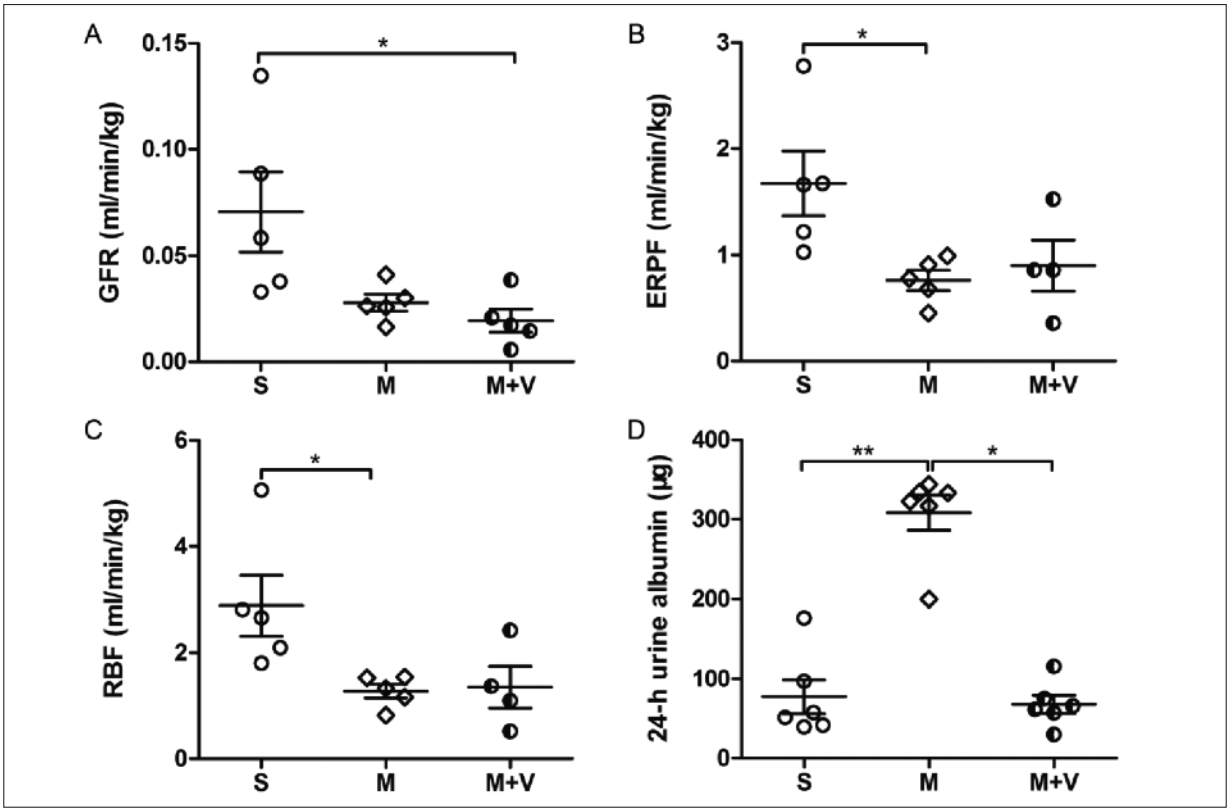

Figure 3. Renal function analysis. ***A,*** GFR, glomerular filtration rate. ***B,*** ERPF, effective renal plasma flow. ***C,*** RBF, renal blood flow. ***D,*** 24-h urine albumin. *$p < 0.05$, **$p < 0.01$.

Cytokine mRNA Expression in Heart and Kidney

Inflammation and cardiac fibrosis are known factors contributing to the pathogenesis of volume overload induced heart failure and renal dysfunction. As shown in Figure 5, CRP expression in heart (Figure 5A) and the expression of galectin-3 in heart (Figure 5A) and kidney (Figure 5C) were significantly increased, while TGF-β, TNF-a and α-SMA expression in the heart tended to be higher in M group compared to S group, and this trend could be slightly reversed by valsartan treatment (Figure 5A and B). Collagen I expression tended to be higher in M group compared to S group (Figure 5B). Compared to S group, TGF-β and fibronectin expression in kidney was significantly increased in M group, and this trend could be slightly attenuated by valsartan treatment (Figure 5C).

Protein Expression of Galectin-3, ERK and p-ERK in Heart Tissue

TGF-β/ERK activation might be one of the mechanisms responsible for remodeling and functional changes in the heart in this model. We thus detected the protein expression of galectin-3, ERK and p-ERK in the heart by Western blot. Protein expression of galectin-3 (Figure 6A and B), ERK (Figure 6A and C) and p-ERK (Figure 6A and D) in heart tended to be higher in M group compared to S group, which was significantly lower in M+V group than in S group.

Discussion

The major finding of the present study is as follows: (1) Cardiac hypertrophy and renal hypertrophy as well as cardiac enlargement were evidenced in this AV shunt induced chronic volume overload rat model with preexisting mild renal dysfunction, cardiac and renal hypertrophy was significantly attenuated but cardiac enlargement was unaffected by valsartan independent of its blood pressure lowering effect. (2) 24 hours urine albumin was significantly increased in this model and which was significantly reduced by

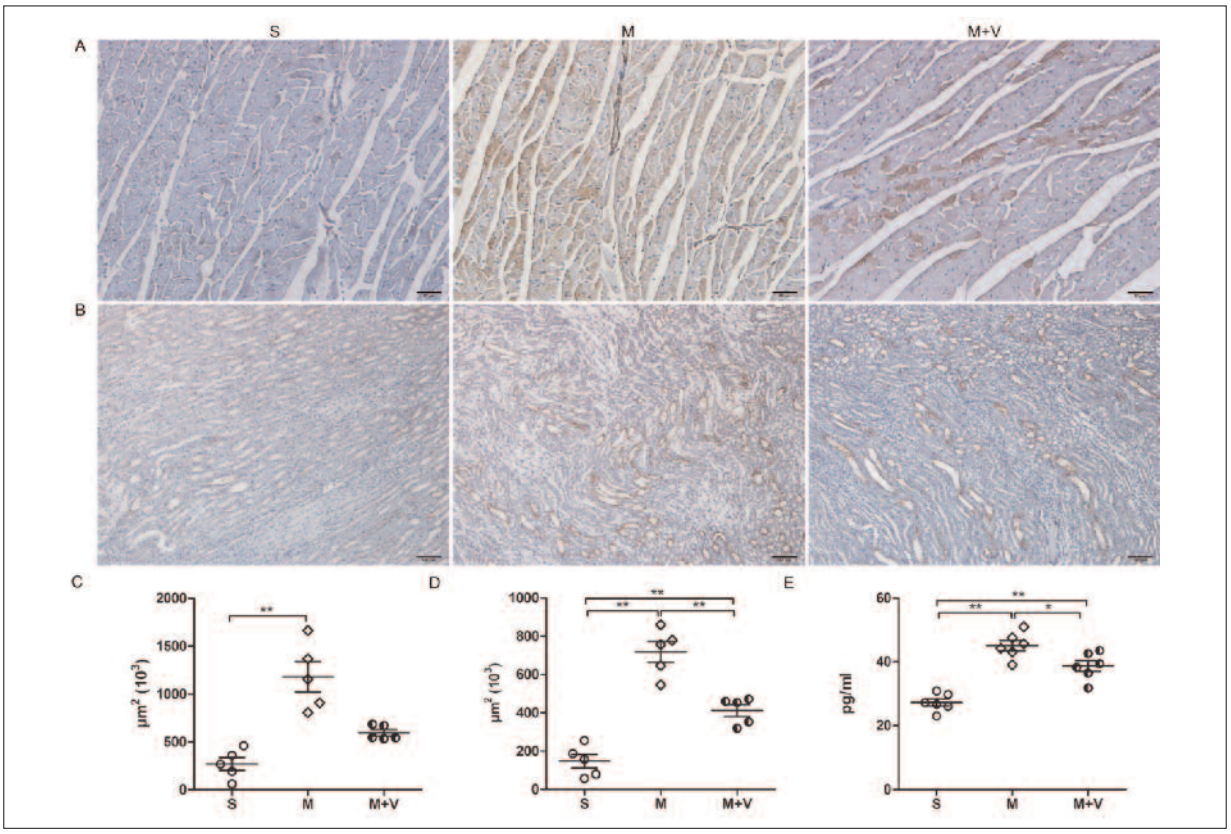

Figure 4. Galectin-3 expression detected by immunohistochemistry in heart ***(A*** and ***C)*** and kidney ***(B*** and ***D)*** were up-regulated in M group and decreased in M+V group ***(E)***. *$p < 0.05$, **$p < 0.01$.

valsartan. (3) Immunohistochemistry and real-time PCR evidenced significantly up-regulated galectin-3 expression in heart and kidney and borderline increased myocardial collagen I expression, which tended to be lower post valsartan treatment. (4) Cytokines expression in the heart (TGF-β, TNF-α, CRP, α-SMA) and kidney (TGF-β, Fibronectin) tended to be up-regulated in M group and was slightly reduced by valsartan. (5) These changes were accompanied by non-significant up-regulated myocardial protein expression of ERK and phosphorylation-ERK in M group, and myocardial protein expression of ERK and phosphorylation-ERK was significantly lower in M+V group than in M group.

Galectin-3, Inflammation, Fibrosis and Cardiorenal Dysfunction

Our results showed that chronic volume overload after mild renal dysfunction is related to up-

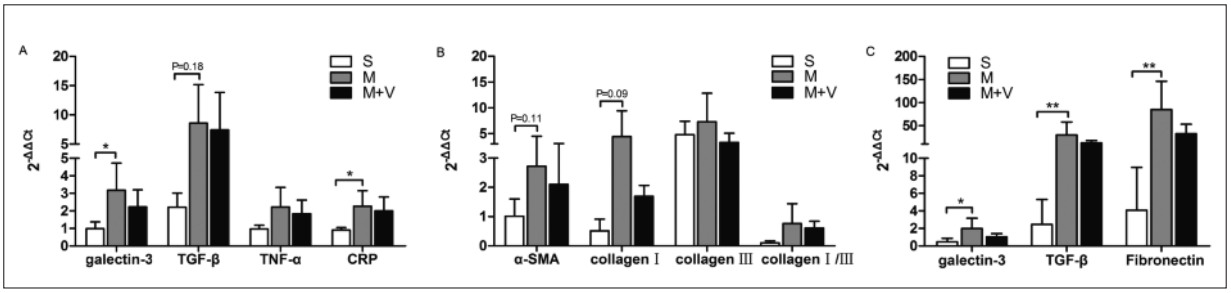

Figure 5. Galectin-3 was associated with increased pro-inflammation and cardiac fibrosis cytokine mRNA expression in heart ***(A*** and ***B)*** and kidney ***(C)*** in M group. *$p < 0.05$, **$p < 0.01$.

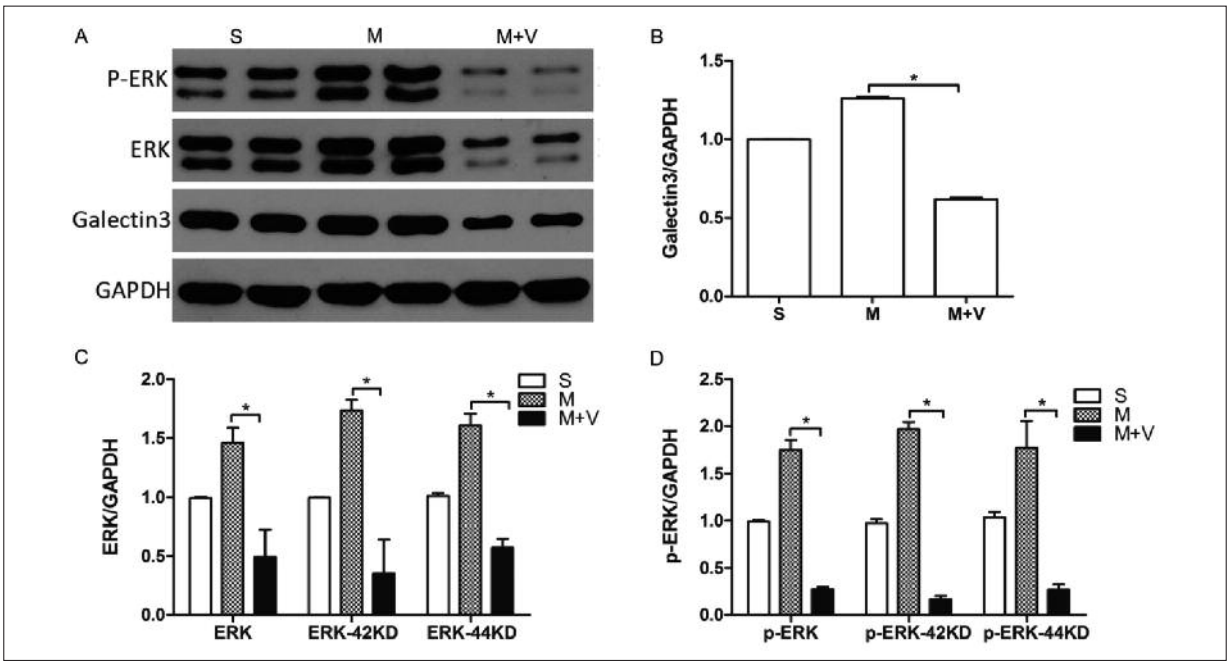

Figure 6. Galectin-3 induced ERK protein expression and phosphorylation in heart. ERK protein expression and phosphorylation in heart and their quantification ***(A, C*** and ***D)***. The protein expression of galectin-3 in heart ***(A*** and ***B)***. *$p < 0.05$.

regulated galectin-3 expression in this model. Previous clinical studies[10,12,14,15] demonstrated that increased galectin-3 is associated with heart failure and renal dysfunction. Studies[6,7,14,16] also suggested that elevated galectin-3 levels were associated with a poor prognosis in patients with heart failure. The present work revealed that tissue galectin-3 expression and plasma galectin-3 level were already increased in hypertrophied rats with preserved cardiac function, suggesting galectin-3 signaling is involved in the hypertrophy pathogenesis in this model. This hypothesis is supported by previous observations in that galectin-3 was known to regulate cardiac fibrogenesis, inflammation, tissue repair and cell proliferation[16]. Till now, the action of galectin-3 in renal function is controversial. Previous studies demonstrated that galectin-3 was significantly associated with impaired kidney function. But, Okamura et al[17] performed unilateral urethral obstruction (UUO) surgery on galectin-3 deficient male mice. Their results suggested that galectin-3 did protect renal tubules from chronic injury by limiting apoptosis and led to enhanced matrix remodeling and fibrosis attenuation. In the present study, we showed increased plasma and tissue galectin-3 in this model with renal hypertrophy and dysfunction, suggesting a rather negative effect of galectin-3 in case of renal dysfunction. Future studies are warranted to verify the role of galectin-3 in renal dysfunction.

The Ang II Receptor blocker and Cardiorenal Syndrome

As a blocker in Ang II receptor, the potential effects of valsartan have been widely investigated in the disease process of different organs, including liver fibrosis, kidney injury and cardiovascular injury[18]. In line with the previous study[19,20], we showed that valsartan attenuated cardiac and renal hypertrophy in this model with preserved cardiac function. Similar as the previous beneficial renal effects of valsartan in a rat model of cardiometabolic syndrome[21], we showed that valsartan also significantly reduced the 24 hours urine albumin secretion in this model. It is to note that down-regulated plasma and tissue galectin-3 was observed post valsartan treatment in this model, although it remains unclear whether and to which extent of the down-regulation of galectin-3 contributed to the observed beneficial effects of valsartan in this model, it is reasonable to speculate that the observed effects of valsartan might at least partly attributed to the valsartan induced down-regulation of

galectin-3. Future studies are needed to verify the mechanistic relationship between the galectin-3 modulation and the beneficial effects of valsartan in this model.

Potential Role of Galectin-3, TGF-β/ERK on Cardiorenal Syndrome

The cardiorenal syndrome is a multifactorial, pathological process and heart-kidney interaction diseases. The previous researches[22] suggested a potential involvement of galectin-3 in TGF-β-induced lung fibrosis. In the present study, we demonstrated that galectin-3 might also be involved in the pathogenesis of TGF-β-related cardiac and renal fibrosis in this model. Galectin-3 is known to a macrophage-derived mediator, Gong et al[23] established a critical biological role for TGF-β signaling in promoting the alternative activation of macrophages. It was shown that TGF-β could activate ERK phosphorylation and regulate nuclear transcription factor[24,25]. Thus, both TGF-β signaling and galectin-3, as well as their interactions, might play a crucial role in the pathogenesis of cardiorenal syndrome. We observed up-regulated myocardial, renal and plasma galectin-3 expression in this rat model, TGF-β and ERK were also up-regulated in myocardial tissue accompanied with up-regulated ERK phosphorylation. It is possible that galectin-3 might induce cardiac fibrosis and inflammation via the ERK phosphorylation signaling in the circumference of activated TGF-β activation in this model. We observed a trend of reduced TGF-β expression and fibrosis and inflammatory cytokine expressions post valsartan treatment in this model, and valsartan also significantly reduced the myocardial protein expression of ERK and phosphorylated ERK. Although, the present work did not supply evidence demonstrating the mechanistic link between beneficial effects of valsartan and down-regulated TGF-β, ERK and phosphorylated ERK, it is possible that down-regulated TGF-β, ERK and phosphorylated ERK might serve as part of the underlying working mechanisms of valsartan in this model.

Conclusions

Chronic volume overload on the basis of mild renal dysfunction is associated with cardiac and renal hypertrophy, cardiac remodeling and renal dysfunction, these changes are linked with increased inflammatory and fibrosis responses in this rat model. Up-regulated galectin-3 signaling might also be involved in the signal pathway in this model, together with activated TGF-β, ERK and ERK phosphorylation. Valsartan can partly attenuate above changes and the beneficial effects of valsartan might at least partly mediate through down-regulating galectin-3 signal pathway in this model.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

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