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Effects of Baicalin on Blood Pressure and Left Ventricular Remodeling in Rats with Renovascular Hypertension

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Background: This study aimed to explore the effect of baicalin, which is a kind of bioactive flavonoid, on blood pressure and left ventricular remodeling in rats with renovascular hypertension.

Material/Methods: A total of 40 male Wistar rats were randomly assigned into sham-operation (n=10) and renal hypertension model groups (2-kidney-1 clip; 2K-1C, n=30). The rats in the renal hypertension model group were randomly subdivided into 2K-1C (n=13) and 2K-1C/Baicalin groups (n=14). The cardiac function indexes were determined after 4 weeks. The morphological changes in the myocardial tissue were observed using hematoxylin and eosin and Masson staining. The myocardial apoptosis was detected using the terminal deoxynucleotidyl transferase deoxyuridine triphosphate nick-end labeling method, and the expression of C/EBP homologous protein and caspase-3 was monitored by Western blot. The expression of GRP78 and GRP94 in myocardial cells of rats was detected by qPCR and Western blot technology.

Results: No significant change in blood pressure was observed in the 2K-1C/Baicalin group compared with the 2K-1C group, but the indexes of left ventricular remodeling significantly improved. Pathological myocardial fibrosis and expression of fibrosis-related factors significantly decreased in the 2K-1C/Baicalin group compared with the 2K-1C group. The expression of glucose-regulated protein (GRP)78, GRP94, CHOP, and caspase-3, and apoptosis of cardiomyocytes also decreased in the 2K-1C/Baicalin group.

Conclusions: Baicalin has no significant antihypertensive effect, but reduced pathological changes in the myocardium, alleviated endoplasmic reticulum stress, and reduced myocardial apoptosis, reverting left ventricular remodeling in rats with renovascular hypertension.

MeSH Keywords: Cystic Fibrosis • Endoplasmic Reticulum Stress • Hypertension, Renovascular

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Background

Hypertension (persistent elevated blood pressure) is the most important risk factor for death and disability worldwide, affecting more than 1 billion individuals and causing an estimated 9.4 million deaths every year [1]. A large number of observational studies have reported the relationship between blood pressure values and cardiovascular diseases, renal morbid, and fatal events [2]. A meta-analysis indicated that a reduction of 10 mm Hg in systolic blood pressure could reduce the risk of major cardiovascular disease events by 20%, coronary heart disease by 17%, stroke by 27%, heart failure by 28%, and all-cause mortality by 13% [1]. Nevertheless, no radical cure exists for hypertension yet. Drugs such as diuretics, beta-blockers, calcium antagonists, angiotensin-converting enzyme inhibitors (ACEIs), and angiotensin receptor blockers (ARBs) are suitable for the initiation and maintenance of antihypertensive treatment. Of these drugs, only ACEIs and ARBs are known to improve left ventricular remodeling induced by continuous high blood pressure [3]. However, ACEIs can cause an irritating cough [4] and kidney damage under special conditions [5] and even angioedema [6]. Although ARBs are considered suitable due to their outstanding tolerability [7], a number of studies have reported that ARBs are associated with a modestly increased risk of developing a new cancer [8]. Thus, finding an antihypertensive drug that can attenuate ventricular remodeling with fewer adverse effects would help provide a useful therapeutic alternative for treating hypertension.

Traditional Chinese medicines have been recently recognized as a new source of treatment of cardiovascular diseases [9,10]. Baicalin, an herb-derived flavonoid compound, has been previously shown to induce apoptosis and growth inhibition in cancer cells through multiple pathways [11,12]. However, the potential role of baicalin in left ventricular remodeling and preventing cardiovascular diseases remains unexplored. The aim of the present study was to explore the function of baicalin in a renovascular hypertension model to determine its therapeutic status.

Material and Methods

Reagents and instruments

Reagents and instruments used were as follows: Baicalin (Jiangbei Medicine, China); MP150 multilead physiological record analyzer (BIA PAC, USA); optical microscope (Olympus, Japan); NO-501 nitric oxide detector (IMN, Japan); WD-9405B horizontal shaker (Six One Company, China); antibodies: anti-growth-regulated protein (GRP)78, anti-GRP94, anti-CHOP, anti-caspase-3, and anti-glyceraldehyde-3-phosphate dehydrogenase (Abcam, Shanghai, China); one-step terminal deoxynucleotidyl transferase deoxyuridine triphosphate (dUTP) nick-end labeling (TUNEL) Apoptosis Assay Kit (Beyotime, China); Exicycler 96 fluorescence quantitative polymerase chain reaction (PCR) instrument (Bioneer, Korea); and WD-9413B gel imaging system (Six One Company, China).

Animals and treatments

This study complied with the guidelines of the Faculty of Kunming Medical University, and the animals were handled according to the guiding principles published by the National Institutes of Health. A total of 40 male Wistar rats (220±15 g), obtained from the Experimental Animal Center of Basic Medicine, Kunming Medical University, were maintained on a 14-h light/8-h dark cycle at 22°C with free access to rat chow and water. Surgery was performed after adaptive feeding for 1 week. This study was approved by the Ethics Committee of The Second People's Hospital of Yunnan Province.

2K-1C hypertension was induced by clipping the left renal artery with an acupuncture needle (0.25 mm) to construct a rat model of hypertension [13]. Sham-operated rats underwent the same surgical procedure (anesthesia with ketamine 100 mg/kg and xylazine 10 mg/kg intraperitoneally) except for the needle placement (n=10). Penicillin sodium (3×10^4 U/d) was used for preventing infection through an intraperitoneal injection 3 days after surgery. Blood pressure increased to 20 kPa 6 weeks after surgery. The rats were randomly assigned to 1 of 3 groups: those in the 2K-1C and sham-operation groups received 0.9% NaCl solution, and those in the 2K-1C group received equal amounts of 2 mL of 100 mg/kg baicalin with 0.9% NaCl solution (indicated as 2K-1C/Baicalin). The treatments were maintained for 4 weeks, once a day.

Blood pressure measurement

Tail systolic blood pressure (SBP) was assessed 3 times a week with a noninvasive blood pressure meter when the rats were placed in a familiar environment. SBP of each rat was measured before surgery, after surgery, and after treatment.

Cardiac echocardiography

Transthoracic echocardiography was performed on each group of rats using a GE Vivid E9 color ultrasound imaging device after the 4-week treatment. After the rats were anesthetized with 10% chloral hydrate at a concentration of 0.2 g/kg, the interventricular septal thickness at diastole (IVSd), left ventricular internal diameter at end-diastole (LVIDd), and left ventricular posterior wall depth diastole (LVPWd) at the left thoracic long-axis section were recorded using two-dimensional ultrasonography.

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Immunohistochemical analysis

Freshly excised heart from each rat was obtained after transthoracic echocardiography. Briefly, the rats were sacrificed by cervical dislocation. The left rib cage of the rats was cut out in an aseptic state with an ophthalmic scissor. The heart was then fully exposed and extracted carefully, followed by fixing with 4% paraformaldehyde solution, embedding in paraffin, and sectioning at 10 mm. The sections were stained with hematoxylin and eosin and Masson stains to observe the myocardial pathological changes in each group using a light microscope. Image J 6.0 software was used to analyze the collagen volume fraction (CVF) of myocardial tissue in each figure. CVF=collagen area/total area.

Analysis of apoptosis

For detecting apoptosis, the sections were treated with 2% H_2O_2 to quench endogenous peroxidase and permeated with 0.1% Triton X-100 for 10 min, followed by 10 mg/mL proteinase K (Sigma, USA) for 20 min at room temperature. After washing, the sections were incubated with the TUNEL reaction solution, containing terminal deoxynucleotidyl transferase and fluorescein-labeled dUTP, at 37°C for 60 min in the dark. Then, DAPI was added for staining. Finally, the sections were sealed with anti-fluorescence quenching sealed tablets after washing 3 times with phosphate-buffered saline. The number of apoptotic cells was counted using a high-power light microscope when reddish brown cells were observed under adjacent 10 fields. Apoptotic index (AI)=number of positive cells/total number of cells ×100%.

ELISA analysis

Matrix metalloproteinase (MMP)-9, MMP-2, connective tissue growth factor (CTGF), and transforming growth factor-beta (TGF-β) in the ventricular homogenate of rats were measured with a commercial enzyme-linked immunosorbent assay (ELISA) kit (WAK-Chemie, Bad Soden, Germany) as described by the manufacturer.

RNA extraction and quantitative real-time PCR

Total RNA from samples was isolated by TRIzol reagent (Invitrogen, USA) according to the manufacturer's protocol and reverse transcribed to cDNA using a reverse transcription kit. The total volume of the reaction system was 20 μL, and the conditions were as follows: 16°C (30 min), 45°C (30 min), and 85°C (5 min). The qRT-PCR reactions on diluted cDNA were performed using Power SYBR Green PCR Master Mix in triplicate. The data were analyzed using a Roche Lightcycler 480 Real-Time PCR System under the following conditions: 2 min of pre-denaturing at 95°C and 40 cycles at 95°C (15 s) and at 60°C (60 s). Relative miRNA and mRNA expression levels were determined using the $2^{-\Delta\Delta Ct}$ method and normalizing to β-actin. The primer sequence of each mRNA is shown in Table 1.

Table 1. Primer sequence of each mRNA.

Names	Sequence
GRP78	F: 5'-GATAATCAGCCCACCGTAA-3'
	R: 5'-TTGTTTCCTGTCCCTTTGT-3'
GRP94	F: 5'-GATGTGGATGGCACGGTAG-3'
	R: 5'-GTTCCCTTATTTGTGATGCA-3'
β-actin	F: 5'- CTACAATGAGCTGCGTGTGG-3'
	R: 5'-CGGTGAGGATCTTCATGAGG-3'

Western blot analysis

Heart tissues were homogenized in homogenization buffer and centrifuged at 10 000 revolutions per min for 10 min. The protein concentration in the supernatant was determined using a bicinchoninic acid protein assay kit. Equal amounts of proteins were added for sodium dodecyl sulfate-polyacrylamide gel electrophoresis and blotted onto polyvinylidene difluoride membranes. The membranes were probed with antibodies against GRP78, GRP94, CHOP, and caspase-3 overnight at 4°C followed by incubation with secondary antibody for 1 h at room temperature. The specific proteins were detected using an enhanced chemiluminescence detection system (Millipore, Merck, Germany) as described by the manufacturer.

Statistical analyses

Statistical analyses were performed using SPSS18.0 software (SPSS, IL, USA). The differences between groups were analyzed using the *t* test (when only 2 groups were compared) or the Student-Newman-Keuls test (when more than 2 groups were compared). The significance level was $P<0.05$.

Results

Survival rate of renovascular hypertension

Unfortunately, 1 rat died due to postoperative infection in the sham-operation group, and 2 rats died due to deep anesthesia and 1 due to postoperative infection at week 3 after surgery in the 2K-1C group. In the 2K-1C/Baicalin group, 1 rat died due to deep anesthesia and 2 died after surgery. The details are shown in Table 2.

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Table 2. Success rate of surgery of rats.

Group	Number	Surgery	Molded quantity	Success rate of surgery (%)	Modeling (%)
Sham-operation	10	9	9	90	90
2K-1C	15	13	10	86.67	66.66
2K-1C/Baicalin	15	14	11	93.33	73.33

Table 3. Change in blood pressure in each group (X±s).

Group	Before surgery (kPa)	After surgery (kPa)	After treatment (kPa)
Sham-operation	16.53±0.43	16.32±0.64	16.82±1.04
2K-1C	16.47±1.85	22.54±1.33**	23.53±1.94**
2K-1C/Baicalin	15.91±1.32	23.53±2.42	22.67±0.76

* $P<0.05$, ** $P<0.01$ versus sham group.

Baicalin had no effect on blood pressure in rats with renovascular hypertension

Table 3 shows that the blood pressure of rats was significantly higher in the 2K-1C and 2K-1C/Baicalin groups than in the sham-operation group ($P<0.05$). However, the blood pressure in the 2K-1C/Baicalin group slightly dropped, but with no statistical difference compared with the 2K-1C group.

Results of high-frequency cardiac ultrasonography

The IVSd and LVPWd were significantly thickened, and the LVIDd was distinctly larger in the 2K-1C group compared with the sham-operation group ($P<0.05$), suggesting that rats with renovascular hypertension had experienced ventricular remodeling with thickened ventricular muscle and dilated ventricular cavity. Interestingly, cardiac ultrasonography in the 2K-1C group indicated that the thickening of IVSd and LVPWd was alleviated, and an improvement was seen in the LVIDd (Figure 1). The specific values are shown in Table 4.

Baicalin mitigated left ventricular remodeling of rats with renovascular hypertension

General changes in hearts in each group were recorded. When hearts were exposed, no obvious abnormalities were observed in the sham-operation group. On the contrary, despite no change in color, the ventricle was significantly dilated, with the hard texture of ventricular muscle and poor elasticity, in the 2K-1C group. The aforementioned changes in the 2K-1C group remarkably improved in the 2K-1C/Baicalin group. On the basis of these findings, we further explored whether pathological alterations occurred. HE-stained sections were observed under a light microscope, and the results suggested that the ventricular muscle fibers were thickened, the intervals were widened accompanied by infiltration of masses of lymphocytes, and the nuclei of cells were disorderly arranged in the 2K-1C group compared with the sham-operation group. However, myocardial fibers in the 2K-1C/Baicalin group were arranged closely in neat rows, and the intercellular space was small with karyopyknosis in few cardiomyocytes (Figure 2). Furthermore, Masson staining indicated that few fibrous tissues were evenly distributed between ventricular muscle tissues of rats in the sham-operation group, with a CVF value of (3.74±0.41)% (Figure 3A). A large number of fibrous tissues were observed around the blood vessels and myocardial cells in the 2K-1C group, and the CVF of these tissues was (13.76±1.37)%. Severe fibrosis in the ventricular tissues was observed in the 2K-1C group compared with the sham-operation group ($P < 0.05$). Interestingly, myocardial fibrosis was significantly reduced in the sham-operation group compared with the 2K-1C group when treated with baicalin, with the CVF value of (8.63±0.47)% ($P<0.05$) (Figure 3C).

Baicalin reduced the apoptosis of ventricular muscle cells

Only a few apoptotic ventricular myocytes were observed in the sham-operation group [apoptotic index (AI)=2.78±1.14) (Figure 4). Unfortunately, a large number of apoptotic cells were found in the 2K-1C group compared with the sham-operation group (AI=21.98±2.1, $P<0.01$). However, apoptotic ventricular muscle cells were significantly reduced on treating 2K-1C rats with a certain concentration of baicalin (AI=7.43±0.72, $P<0.01$) (Figure 4C). Taken together, the data suggested that baicalin could reduce the apoptosis of ventricular muscle cells *in vivo*.

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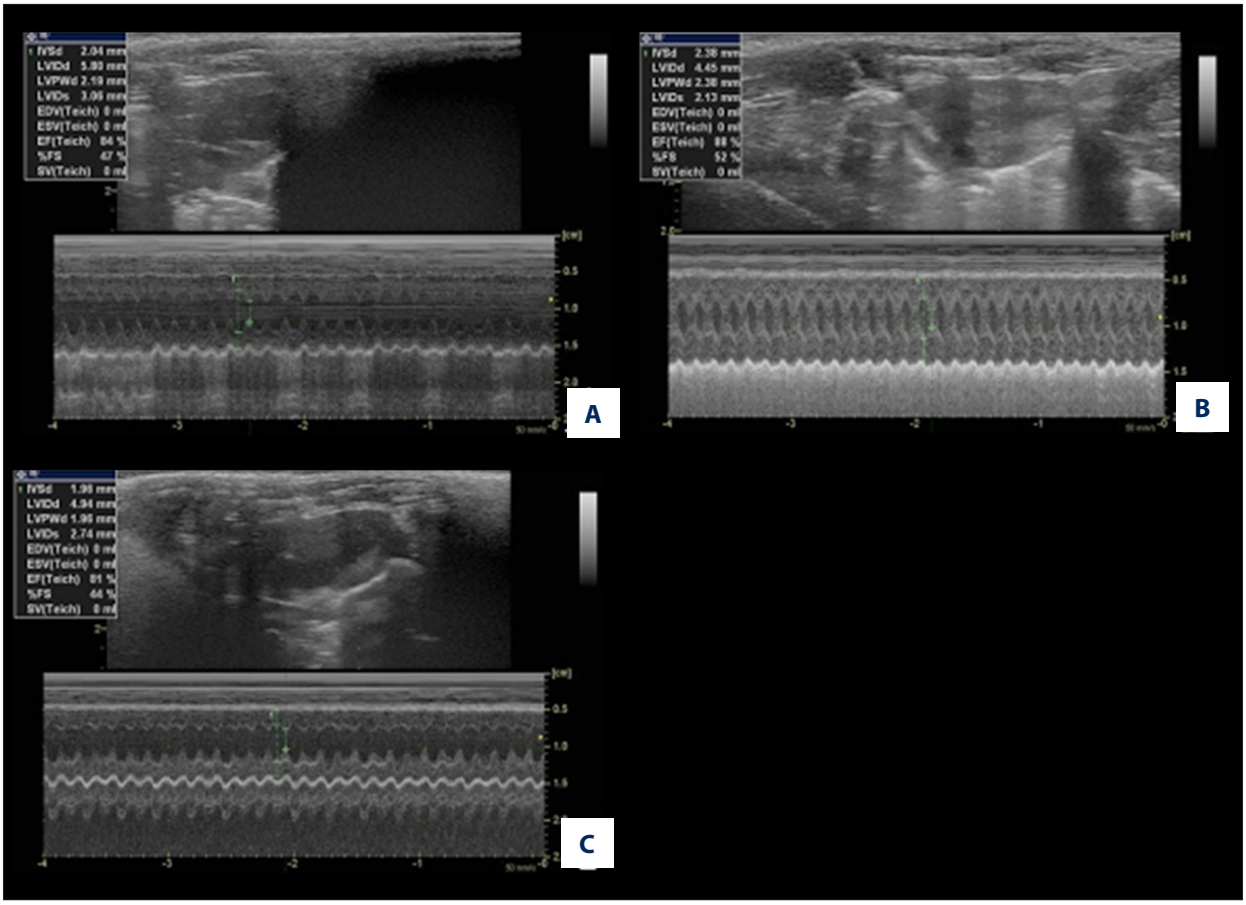

Figure 1. Results of cardiac ultrasonography in each group. (**A**) Sham group; (**B**) 2K-1C; (**C**) 2K-1C/Baicalin.

Table 4. Change in cardiac ultrasonography of rats in each group (X±s).

Group	n	IVSd (mm)	LVPWd (mm)	LVIDd (mm)
Sham operation	9	1.93±0.01	1.85±0.04	4.85±0.28
2K-1C	10	2.54±0.02$^{\#\#}$	2.37±0.13$^{\#\#}$	5.64±0.31$^{\#\#}$
2K-1C/Baicalin	11	2.05±0.08$^{\#\#,**}$	2.03±0.09$^{\#\#,**}$	5.03±0.39**

* P<0.05, ** P<0.01 versus sham group; $^{\#}$ P<0.05, $^{\#\#}$ P<0.01 versus 2K-1C group.

Baicalin suppressed the expression of fibrosis-associated factors in ventricular muscle cells

The relative expression of MMP-9, MMP-2, CTGF, and TGF-β1 was detected by ELISA tests to investigate whether baicalin affected fibrosis in ventricular muscle cells. The results showed that the expression of fibrosis-associated factors significantly increased in the 2K-1C group compared with the sham-operation group (P<0.01). When the rats in the 2K-1C/Baicalin group were given baicalin through gavage, the relative expression of MMP-9, MMP-2, CTGF, and TGF-β1 was suppressed. The relative expression of these fibrosis-associated factors is shown in Table 5.

Baicalin attenuated endoplasmic reticulum stress in rats with renovascular hypertension

The relative expression of GRP78 mRNA and GPR94 mRNA, reported as a chaperone protein of endoplasmic reticulum stress (ERS), was investigated by RT-PCR to explore whether baicalin could attenuate ERS in rats with renovascular hypertension. The relative expression of GRP78 mRNA and GPR94 mRNA was markedly upregulated in the 2K-1C group compared with the sham-operation group (P<0.01) (Figure 5 and Table 6). The expression was partly downregulated in the 2K-1C/Baicalin group (P<0.01). Furthermore, the expression of GRP78, GRP94, CHOP, and caspase-3 protein was evaluated

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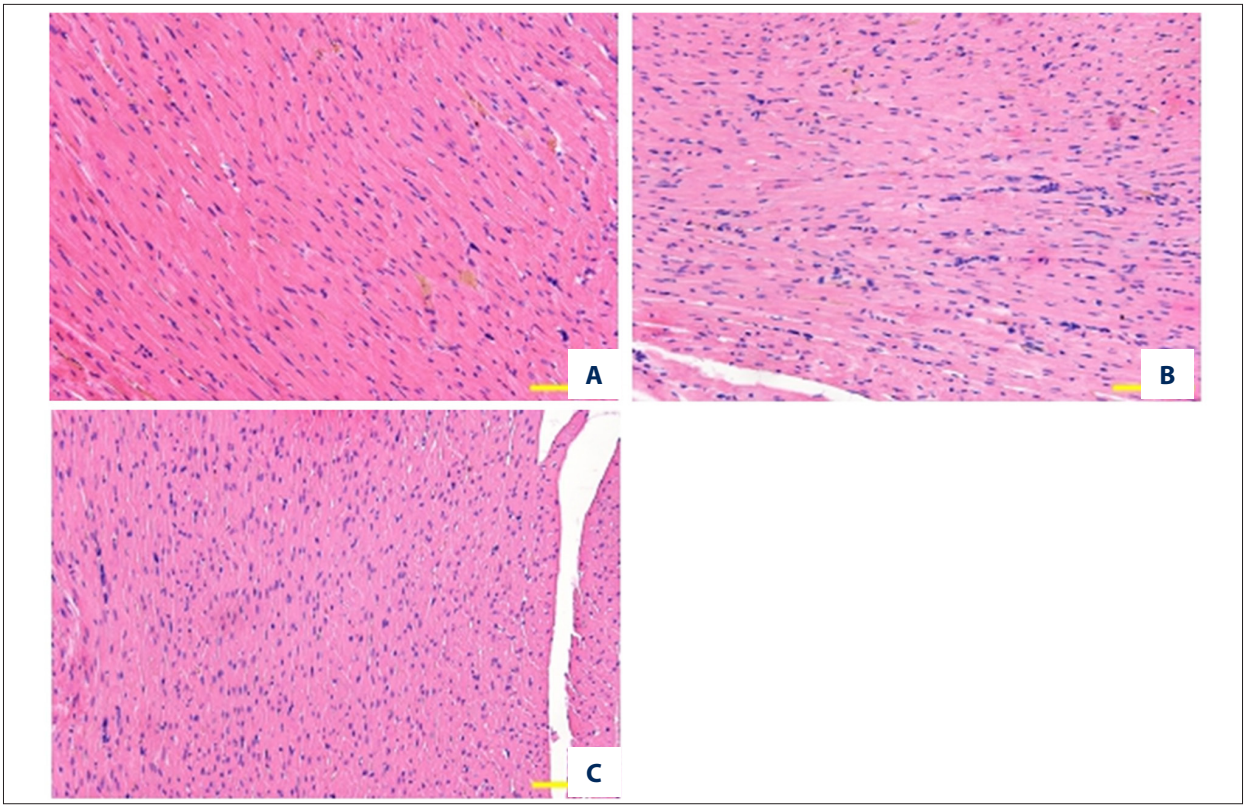

Figure 2. Results of HE staining under a light microscope (×200). (**A**) Sham-operation; (**B**) 2K-1C; (**C**) 2K-1C/Baicalin.

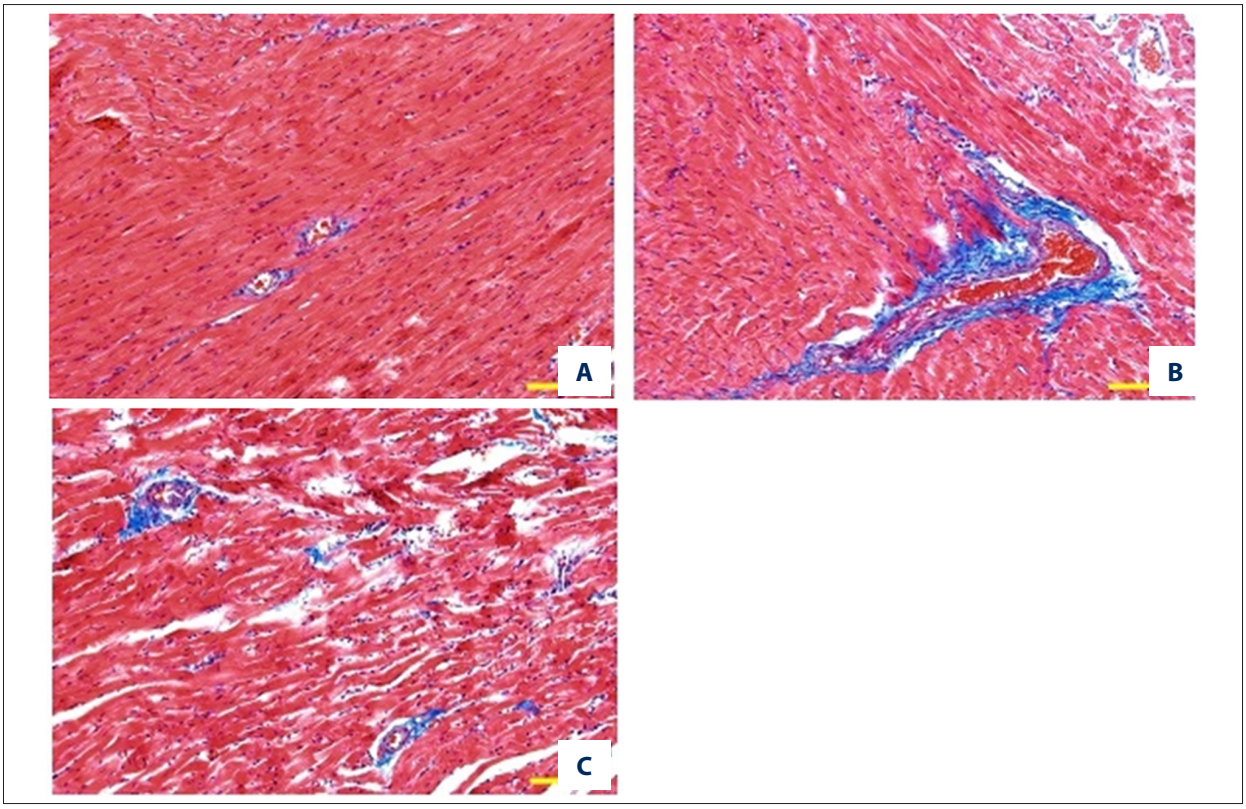

Figure 3. Results of Masson staining under a light microscope (×200). (**A**) Sham-operation; (**B**) 2K-1C; (**C**) 2K-1C/Baicalin.

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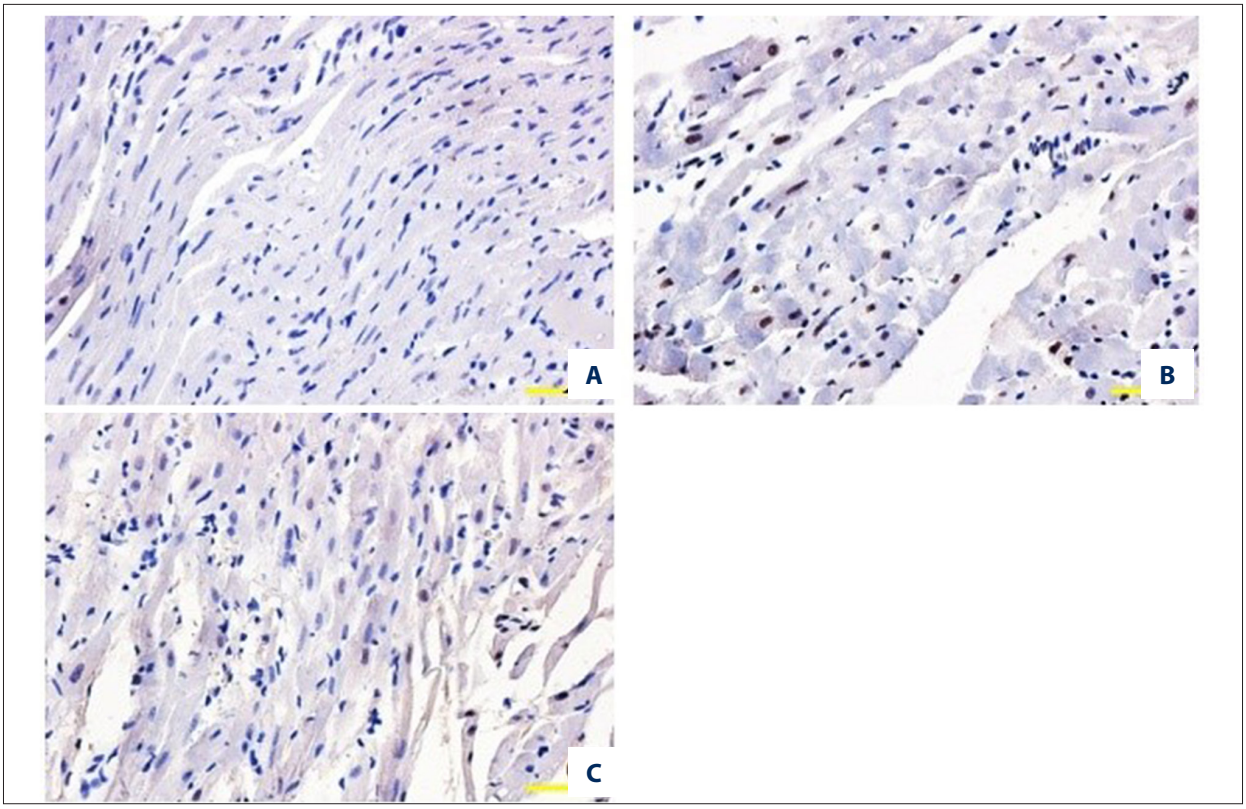

Figure 4. Ventricular muscle cell apoptosis was observed by TUNEL method (×400). (**A**) Sham-operation; (**B**) 2K-1C; (**C**) 2K-1C/Baicalin.

Table 5. Relative expression of MMP-9, MMP-2, CTGF, and TGF-β1 (X±s).

Group	MMP-9 (ng/mL)	MMP-2 (ng/mL)	CTGF (pg/mL)	TGF-β1 (pg/mL)
Sham operation	107.53±8.31	135.37±10.63	376.22±24.61	294.31±19.66
2K-1C	365.06±21.75**	254.31±27.46**	742.45±46.32**	643.96±53.01**
2K-1C/Baicalin	158.64±9.77##	139.53±7.54##	458.52±31.91##	375.04±28.48##

* $P<0.05$, ** $P<0.01$ versus sham group; # $P<0.05$, ## $P<0.01$ versus 2K-1C group.

by Western blot. Figure 6 and Table 7 indicate that GRP78, GRP94, CHOP, and caspase-3 protein expression levels were significantly higher in the 2K-1C group than in the sham-operation group ($P<0.01$). On the contrary, the expression of these proteins decreased when rats with renovascular hypertension were treated with baicalin ($P<0.01$).

Discussion

Hypertension is an important public health challenge worldwide because of its high frequency and concomitant risks of cardiovascular and kidney diseases. The prevalence of hypertension in the Asian population is 20–30% higher compared with Western countries [14]. Due to elevated blood pressure in patients with hypertension, the resistance of periphery blood vessels and the load of the heart increase, resulting in compensatory myocardial hypertrophy and left ventricular remodeling. Once decompensation occurs, heart failure is inevitable, reducing the quality of life of patients and even causing adverse events [15]. Thus, attenuating left ventricular remodeling has become an important treatment of hypertension [16,17].

Baicalin is an effective component of traditional Chinese medicine *Scutellaria baicalensis*. It has various pharmacological actions, including antiviral, antioxidative, antitumor, antiapoptosis, and antihypertensive effects. Wei et al. reported that baicalin significantly attenuated angiotensin II – induced endothelial dysfunction and oxidative stress [18]. Liu et al. investigated acute myocardial infarction in rats pretreated with different concentrations of baicalin and found that baicalin significantly reduced the infarct size and levels of myocardial enzymes

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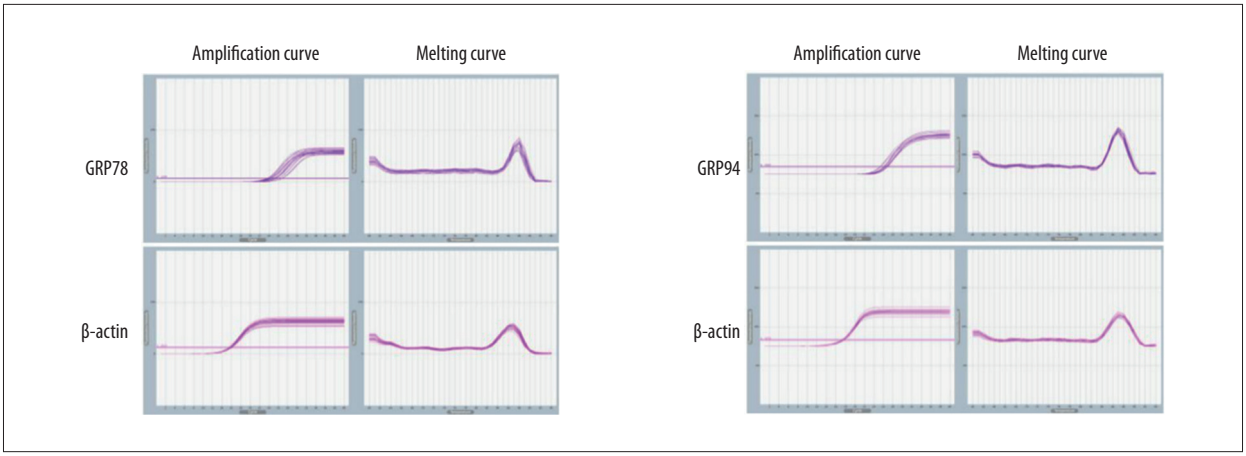

Figure 5. Amplification and melting curves of GRP78 and GRP94 mRNA.

Table 6. Relative expression of GRP78 and GRP94 mRNA ($2^{-\Delta\Delta Ct}$ X±s).

Group	After surgery (kPa)	After treatment (kPa)
Sham operation	1.00±0.01	1.00±0.02
2K-1C	2.59±0.12**	1.45±0.11**
2K-1C/Baicalin	1.85±0.08##	1.17±0.06#

* *P*<0.05, ** *P*<0.01 versus sham group; # *P*<0.05, ## *P*<0.01 versus 2K-1C group.

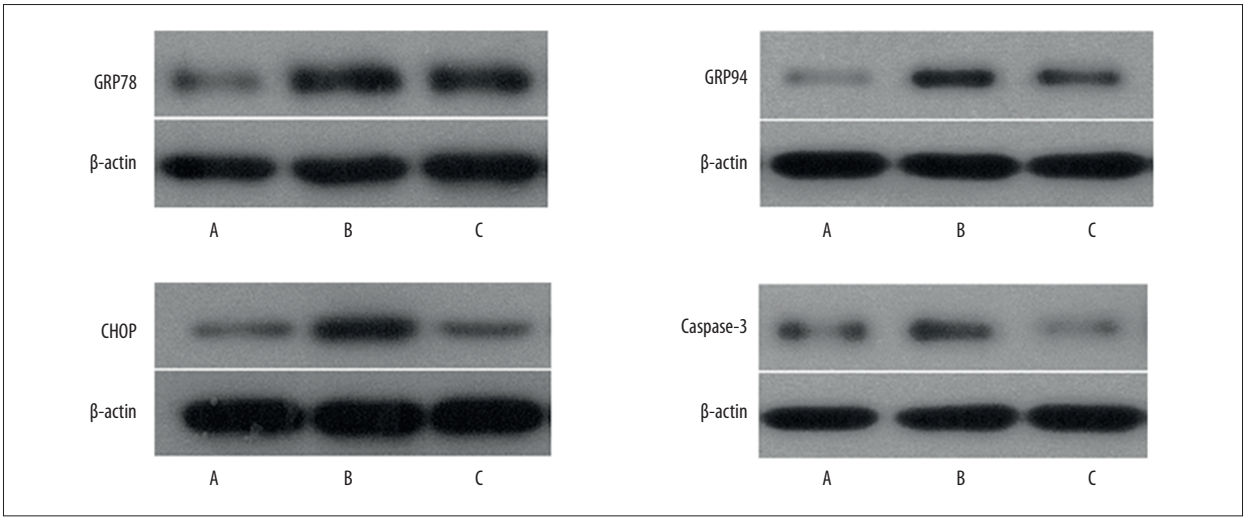

Figure 6. Relative expression of GRP78, GRP94, CHOP, and caspase-3 proteins. A. Sham-operation; B. 2K-1C; C. 2K-1C/Baicalin.

Table 7. Relative expression of GRP78, GRP94, CHOP, and caspase-3 (X±s).

Group	GRP78/β-actin	GRP94/β-actin	CHOP/β-actin	Caspase-3/β-actin
Sham operation	1.00±0.05	1.00±0.01	1.00±0.01	1.00±0.03
2K-1C	3.69±0.25**	2.36±0.18**	2.84±0.09**	1.93±0.02**
2K-1C/Baicalin	1.95±0.22##	1.54±0.08##	0.94±0.02##	0.86±0.15##

* *P*<0.05, ** *P*<0.01 versus sham group; # *P*<0.05, ## *P*<0.01 versus 2K-1C group.

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[creatine kinase (CK), CK-MB, lactate dehydrogenase, and cardiac troponin T], suppressed the activity and protein expression of caspase-3, and mediated mitogen-activated protein kinase cascades, suggesting that baicalin could be a promising cardioprotective agent for treating acute myocardial infarction [19]. Importantly, a study investigated the role of baicalin in the ERS-induced apoptosis of cardiomyocytes, and the results indicated that baicalin significantly reduced apoptosis induced by the ERS-inducer tunicamycin in cardiomyocytes via regulating the CHOP/endothelial nitric oxide synthase/NO pathway [20].

Ventricular remodeling refers to alterations in anatomical and histological structures of ventricles due to elevated pressure, insufficient blood supply, and damage caused by drugs. It is involved in lesion repair, ventricular compensation, and secondary pathophysiological response to damage [21]. Studies have confirmed a close correlation of myocardial apoptosis and fibrosis with ventricular remodeling [22,23], but the underlying mechanism is complex. Many studies have reported that the activation of ERS in the heart was closely related to myocardial apoptosis [24], hypertrophy [25], and fibrosis [26], the pathological processes common in the development of ischemic and hypertrophic heart diseases. The ER is an intracellular organelle in which most of the secretory and membrane proteins are synthesized, post-translationally modified, and folded into their correct conformations. ERS is a result of an imbalance between protein load and folding capacity [27]. A moderate degree of ERS can be alleviated by upregulating the expression of molecular chaperones GRP78 and GRP94, inhibiting protein synthesis and accelerating degradation of misfolding and unfolding proteins [28]. However, persistent or severe ERS can trigger apoptotic signals, induce the expression and activation of pro-apoptotic factors such as CHOP and caspase-3, and cause the apoptosis of cells [24,29]. MMPs are proteinases that participate in extracellular matrix remodeling and degradation [30]. Evidence suggests that the levels of MMP-2 and MMP-13 are elevated after myocardial infarction. MMP-9 also increases after myocardial infarction and is correlated with heart failure progression and severity [31]. TGF-β1 is involved in the regulation of cell growth and differentiation. It is known to induce myofibroblastic activation, increased collagen deposition, and wound contraction [32]. It also appears to play a vital role in fibrogenesis and fibroproliferative disorders [33,34]. It is a key mediator of fibrosis in myocardial injury [35] and has been confirmed to contribute to unresolved cardiac pro-fibrotic remodeling [36]. CTGF, a member of the CCN (ctgf/cyr61/nov) gene family, has been demonstrated to play an important role in promoting mitosis, proliferation of cardiac fibroblasts, and stimulation of extracellular matrix formation, thus contributing to switching of fibroblasts to myofibroblasts and promoting myocardial fibrosis [37,38]. Moreover, CTGF is suggested to play a role in the extracellular matrix deposition as an important downstream mediator of TGF-β [39].

In this study, rats with renovascular hypertension were treated with a certain concentration of baicalin. An antihypertensive effect of baicalin was observed, but with no statistical significance. This result could not rule out the limitation of the small sample size or lower drug concentration. The indicators of IVSd, LVPWd, and LVIDd significantly improved in the 2K-1C/Baicalin group compared with the 2K-1C group. The results of the pathological examination indicated that baicalin can reverse the disordered arrangement of myocardial fibers in rats with renovascular hypertension, reduce degenerative or necrotic cardiomyocytes, attenuate interstitial fibrosis, and downregulate the expression of MMP-9, MMP-2, CTGF, and TGF-β1. Also, the expression of GRP78, GRP94, CHOP, and caspase-3 was suppressed by baicalin, suggesting that it can attenuate ERS in rats with renovascular hypertension, reduce the apoptosis of ventricular muscle cells, and inhibit left ventricular remodeling.

Conclusions

In summary, this novel study demonstrated the effect of baicalin on the reversal of left ventricular remodeling in rats with renovascular hypertension. However, further studies are required to determine how baicalin inhibits the ERS-related apoptotic signaling pathway or other apoptosis pathways. Baicalin may serve as a useful therapeutic alternative for treating cardiovascular diseases.

Conflict of interest

None.

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