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Impacts of a Specific Cyclooxygenase-2 Inhibitor on Pressure Overload–Induced Myocardial Hypertrophy in Rats

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ABSTRACT

Objective: The aim of this study was to observe the impacts of the specific cyclooxygenase-2 inhibitor celecoxib on cardiac structures, functions, and inflammatory factors during the process of pressure overload–induced myocardial hypertrophy.

Methods: Twenty-four male Sprague Dawley rats were randomly divided into 3 groups: the sham operation group, the surgery group, and the celecoxib group. The model was established according to the abdominal aortic coarctation method.

Results: At 16 weeks, rats in the celecoxib group were fed a celecoxib-mixed diet (10 mg/kg) for 8 consecutive weeks. At week 24 after model establishment, the cardiac structures and functions were observed; changes in the levels of tumor necrosis factor (TNF)-α, transforming growth factor (TGF)-β, prostaglandin E2 (PGE2), C-reactive protein (CRP), and uric acid (UA) were detected; and the contents of Smad1/2/3 proteins (Smad1, Smad2, and Smad3) were determined. Left ventricular mass index, the heart weight/body weight ratio, and TNF-α, TGF-β, PGE2, CRP, and UA levels of the celecoxib group were all significantly decreased relative to those of the surgery group ($P < .05$); moreover, the cardiac functions were significantly improved compared to those of the surgery group ($P < .05$).

Conclusions: These results show that inflammatory factors are involved in the myocardial hypertrophy process and that celecoxib may reverse myocardial hypertrophy through a variety of pathways.

INTRODUCTION

Myocardial remodeling is the basic mechanism underlying the occurrence and development of chronic congestive heart failure [Jugdutt 2009]. Myocardial remodeling involves 2 main components: (1) myocardial hypertrophy (MH), which is the most important component and is mainly considered from the aspect of myocardial cells, and (2) myocardial fibrosis (MF), which is mainly considered from the aspect of the extracellular matrix and is the main factor contributing to extracellular matrix remodeling [Buja 2008]. Ventricular remodeling is not only the initiating factor leading to heart failure but also an important pathological process underlying various other cardiovascular diseases and is the strongest risk factor associated with a variety of cardiovascular and cerebrovascular events. Accordingly, developing strategies for reversing MH and MF has become a major hot spot of cardiac remodeling research in recent years. Many factors are involved in the process of myocardial remodeling, with 2 playing the most important roles: neuroendocrine factors (eg, adrenaline and the renin-angiotensin-aldosterone system) and cytokines [Bujak 2008]. More than 10 kinds of cytokines have been identified to be involved in myocardial remodeling to date, including Toll-like receptors, nuclear factor (NF)-κB, tumor necrosis factor (TNF), and transforming growth factor (TGF). Inflammatory factors might play a role in the myocardial remodeling process through cascade effects of the inflammatory cytokines themselves, as well as inductions from interactions among them. Previous studies have shown that inflammatory cytokines are involved in the whole process of chronic heart failure [Tsutamoto 2001; Janczewski 2003; Voloshenyuk 2011] and play important roles in both its occurrence and development [Parish 2008]. Despite the numerous studies on these

Table 1. Left Ventricular Mass Index (n = 8)

Groups	LVMI (mg/g)	HW/BW (mg/g)
Sham operation	1.680 ± 0.072	2.213 ± 0.079
Surgery	1.954 ± 0.104*	2.556 ± 0.162*
Celecoxib	1.721 ± 0.033†	2.22 ± 0.074†

Compared with the sham operation group, *$P < .05$; compared with the situations on the postoperative 24th week, †$P < .05$.

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Table 2. Myocardial Structures of the Experimental Groups on the Postoperative 24th Week (n = 8)

Groups	IVSd (mm)	IVSs (mm)	LVDd (mm)	LVDs (mm)	LVPWd (mm)	LVPWs (mm)
Sham operation	1.75 ± 0.13	2.99 ± 0.11	6.55 ± 0.90	3.61 ± 0.88	1.66 ± 0.27	3.17 ± 0.26
Surgery	2.27 ± 0.41*	3.49 ± 0.57†	7.38 ± 0.44†	4.36 ± 1.21	2.17 ± 0.28*	3.58 ± 0.28†
Celecoxib	2.12 ± 0.34	3.33 ± 0.30	7.10 ± 0.62	4.08 ± 0.74	2.04 ± 0.11‡	3.37 ± 0.33

Compared with sham operation group †$P < .05$, *$P < .01$; compared with the situations on the postoperative 24th week, ‡$P < .05$, §$P < .01$; compared with the surgery group, ‡$P < .05$.

Table 3. Cardiac Functions of the Experimental Groups (n = 8)

Groups	CO (L/min)	SV (L/min)	EF (L/min)	LV-FS (L/min)
Sham operation	0.29 ± 0.01	0.71 ± 0.05	0.83 ± 0.05	0.50 ± 0.04
Surgery	0.18 ± 0.02*	0.54 ± 0.08†	0.70 ± 0.10†	0.38 ± 0.08†
Celecoxib	0.24 ± 0.02‡	0.70 ± 0.06§	0.81 ± 0.04§	0.46 ± 0.04‡

Compared with sham operation group *$P < .05$, †$P < .01$; compared with the situations on the postoperative 24th week, ‡$P < .05$, §$P < .01$.

roles of inflammatory cytokines, there is still some dispute about the role of cyclooxygenase (COX). In particular, there is controversy as to whether or not a COX inhibitor could be used to intervene with the process of myocardial remodeling and whether it could change the degree of risk for cardiovascular events, including disputes about its adverse effects [Chan 2006] and positive effects on the cardiac vessels [Chao 2013]. Because many inflammatory factors are involved in the process of heart failure and because there are the conflicting results from previous work, it is necessary to further clarify the role of COX on the heart.

In our previous study [Wang 2014], we showed that the specific COX-2 inhibitor celecoxib had positive effects on heart protection and could inhibit MH and MF, thus exhibiting overall positive effects for the heart. However, the relationships between the time and dose of celecoxib treatment with the extent of improvement in MH are not yet clear. In addition, there is a general lack of information on the clinical effects and impacts of the long-term use of celecoxib on MH and heart failure. Therefore, in this study, the effects of the long-term use of celecoxib on MH were investigated with a rat model to evaluate the possibility of using celecoxib in the clinical treatment of MH.

MATERIALS AND METHODS

Model Preparation

The model of abdominal aortic coarctation was established according to the methods described by Anversa et al [Anversa 1973]. The rats were fed the same diet for 1 week for environmental adaptation, and surgery was performed when the physiological status was deemed to be stable. A total of 24 specific-pathogen-free (SPF) male Sprague Dawley rats, weighing 100–120 g, were obtained from the State Key Laboratory of Respiratory Diseases (SPF laboratory), Guangzhou. The rats had fasting for 12 hours before the surgery, with free access to water. The rats were anesthetized by using 10% chloral hydrate (0.3 mL/100 g body weight), and the abdominal skin was exposed and sterilized. One longitudinal incision was made at about 1 cm to the left of the center of the subxiphoid, and then the abdominal cavity was entered layer by layer; the abdominal aorta could be found upward along the left renal artery. One 0.7-mm blunt needle was then placed along the direction of the left renal arterial branch of the abdominal aorta, which was sutured with a no. 0 suture. The needle was then slowly pulled out so that a 0.7-mm lumen was left in the abdominal aorta to form the abdominal aortic stenosis. After the flow inside the stenotic abdominal aorta was confirmed, the abdomen was closed layer by layer. The same surgery was performed for the sham operation group, except that no ligation was made after puncturing the abdominal aorta. After the surgery, the rats were strictly raised according to the requirements for SPF animals, including tight control of the living conditions such as temperature, humidity, and noise, which were maintained by qualified staff of the animal laboratory. This study was carried out in strict accordance with the recommendations in the Guide for the Care and Use of Laboratory Animals of the National Institutes of Health. The animal use protocol has been reviewed and approved by the Institutional Animal Care and Use Committee (IACUC) of Guangzhou Red Cross Hospital.

Animal Grouping

The rats were randomly divided into 2 main groups: the sham operation group (n = 8) and the surgery group (n = 16). The surgery group was then randomly divided into the

Table 4. Inflammatory Cytokine Levels among the Experimental Groups (n = 8)

Groups	TNF-α	TGF-β	PGE2	CRP	UA
Sham operation	0.56 ± 0.04	0.55 ± 0.06	1351.25 ± 58.90	7.79 ± 2.02	46.51 ± 6.18
Surgery	2.73 ± 0.42*	0.74 ± 0.07	2265.00 ± 159.04*	38.75 ± 17.75†	93.93 ± 28.79†
Celecoxib	0.63 ± 0.13‡	0.49 ± 0.08§	1256.25 ± 102.17‡	7.88 ± 0.72§	35.49 ± 1.06‡

Note: Compared with sham operation group †$P < .05$, *$P < .01$; compared with the surgery group, §$P < .05$, ‡$P < .01$.

surgery group (n = 8) and the celecoxib group (n = 8). On postoperative week 16, 3 rats of each group were randomly selected for the cardiac B-ultrasound examination to confirm the formation of MH, and then the rats in the celecoxib group were administered 10 mg/kg celecoxib (Pfizer Inc., New York, NY, USA), which was uniformly mixed with the standard diet for 8 consecutive weeks. The rats in the other 2 groups were fed with the additive-free SPF-grade diet. On the last day of postoperative week 24, blood was sampled from the rat's left ventricle to detect the inflammatory markers.

Echocardiogram

After 8-week feeding of celecoxib, namely at postoperative week 24, echocardiogram (GE Vivid7, General Electric Co., Ltd., New York, NY, USA) was performed on the rats to evaluate the cardiac structures and functions. The specific frequency was flexibly chosen to be able to clearly exhibit the left ventricular structures. After the rats were anesthetized, the detection was measured by the 2D ultrasound-guided M-curve. Each recorded value was taken as the average from the values of 3 consecutive cardiac cycles. The following parameters were measured and calculated: interventricular septal thickness (IVS), left ventricular posterior wall thickness (LVPW), left ventricular end-diastolic diameter (LVDD) and left ventricular end-systolic diameter (LVSD), left ventricular fractional shortening (LV-FS), ejection fraction (EF), cardiac output (CO), and stroke volume (SV).

Specimen Processing

After 8-week celecoxib feeding, the rats were routinely anesthetized and weighed. After skin preparation and sterilization, thoracotomy was performed to quickly remove the heart, which was then lavaged with icy saline, cleaned of residual blood, and weighed (HW). The atrium and ventricle were then dissected; the left ventricle (including the interventricular septum) was weighed (LVW); and the cardiac index (LVI) was calculated. Partial left ventricular myocardial tissues were then fixed in 10% neutral formalin for the pathological examination.

Detection of Inflammatory Markers

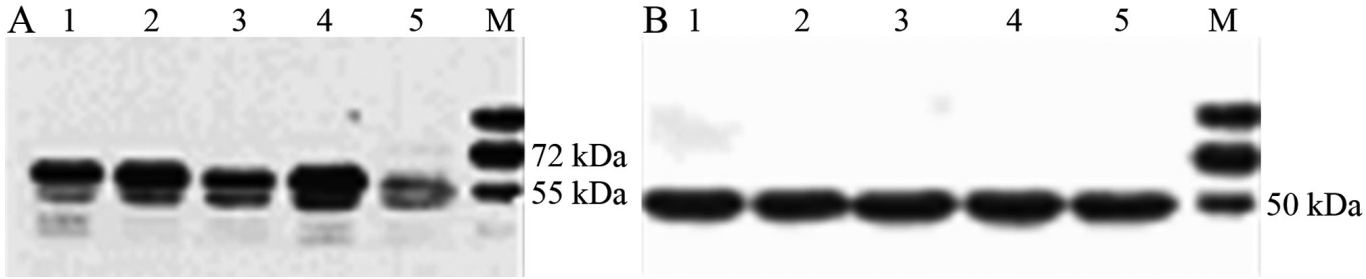
After the thoracotomy, 5 mL of blood was sampled by puncturing the left ventricle, centrifuged at 3000 rpm for 7 min; and then the serum was separated and stored at –80°C for further testing. Enzyme-linked immunoassays were conducted for TNF-α, TGF-β (Matsa Biotechnology Co., Ltd., Shanghai, China), prostaglandin E2 (PGE2; Matsa Biotechnology Co., Ltd.), and C-reactive protein (CRP; Shenzhen Neobioscience Biological Technology Co., Ltd., Shenzhen, China) in strict with the manufacturer instructions. An automatic biochemical analytical instrument was used to detect the concentration of serum uric acid (UA).

Western Blot

To detect the expression of nuclear Smad1/2/3 protein (Smad1, Smad2, and Smad3), the Nuclear Isolation Kit (Invitrogen, Thermo Fisher Scientific, Waltham, MA, USA) was used to extract the nuclear fraction, which was resuspended in the 0.1% Triton X-100 and phosphatase inhibitor–containing cell lysate for 5-second ultrasound clearage; the step was repeated 5 times; the supernatant was extracted; and the protein concentration in the supernatant was measured by the bicinchoninic acid method. An equal amount of protein was taken, mixed with 5× sodium dodecyl sulfate (SDS) sample buffer, and boiled for 5 minutes. The samples were then subjected to SDS–polyacrylamide gel electrophoresis and electrically transferred onto a polyvinylidene fluoride (PVDF) membrane. After incubating at room temperature for 1 hour, the primary antibodies rabbit anti-rat Smad1/2/3 (Cell Signaling Inc., Danvers, MA, USA) and β-actin (Cell Signaling Inc., Danvers, MA, USA) were added dropwise and incubated overnight at 4°C. After washing of the membrane, the secondary antibody horseradish peroxidase–labeled goat anti-rabbit IgG (Santa Cruz Inc., CA, USA) was added for 2-hour incubation at room temperature. The PVDF membrane was incubated with enhanced chemiluminescence reagent in a dark room for 5 minutes, followed by x-ray exposure, image visualization, and fixation. The gel imaging system was then used for absorbance scanning and analysis, and the ratio of measured optical densities of the sample and internal reference (β-actin) was used to express the relative expression level.

Statistical Analysis

The measurement data of each group are expressed as mean ± standard deviation, and the averages among multiple groups were compared through analysis of variance following the test of homogeneity; pairwise comparisons were made using the SNK method. All data were statistically analyzed by the SPSS13.0 statistical package (SPSS Inc., Chicago, IL, USA), with $P < .05$ considered to indicate statistical significance.



Expressions of Smad1/2/3 proteins inside the myocardial tissues of the experimental groups. <<Q29>>

RESULTS

Left Ventricular Mass Index

The left ventricular mass index (LVMI) and HW to body weight (BW) ratio (HW/BW) of the surgery group were significantly increased relative to those of the sham group ($P < .05$); such an increase indicated that the model had been successfully established. However, LVMI and HW/BW of the celecoxib group were significantly lower than those of the surgery group ($P < .05$, Table 1).

Myocardial Structures

On postoperative week 24, IVSd and LVPWd of the surgery group were significantly higher than those of the sham operation group ($P < .01$). IVSs, LVDd, and LVPWs of the surgery group were significantly higher than those of the sham operation group ($P < .05$), whereas there was no difference in the LVDs when compared with that of the sham operation group. Except for LVPWd, there was no significant difference in other indexes between the celecoxib group and the surgery group ($P < .05$, Table 2).

Cardiac Functions

On postoperative week 24, the comparison of cardiac functions among experimental groups revealed that SV, EF, and LV-FS of the surgery group were significantly lower than those of the sham operation group ($P < .01$), whereas CO was significantly lower than that of the sham operation group ($P < .05$). SV and EF of the celecoxib group were significantly higher than those of the surgery group ($P < .01$), whereas CO and LV-FS were significantly higher than those of the surgery group ($P < .05$, Table 3).

Inflammatory Cytokines

At postoperative week 24, there was a significant difference in TNF-α and PGE2 levels between the surgery group and the sham group ($P < .01$); CRP and UA levels were also significantly different ($P < .05$) between these groups, whereas TGF-β levels were similar ($P > .05$). TNF-α, PGE2, and UA levels of the celecoxib group were highly significantly different from those of the surgery group ($P < .01$), whereas CRP and TGF-β were significantly different ($P < .05$, Table 4).

Expression Levels of Smad1/2/3 Proteins

The expression levels of Smad1/2/3 proteins were significantly increased in the surgery group relative to those of the sham operation group. In addition, Smad1/2/3 protein levels of the celecoxib group were significantly decreased relative to those of the surgery group (Table 5, Figure).

DISCUSSION

A variety of inflammatory factors are involved in the occurrence and development of MH. Therefore, in this study, the effects of the long-term use of the COX-2 inhibitor celecoxib on MH were investigated. Consistent with our expectation, the results showed that celecoxib could inhibit MH, exerting a protective effect to the heart by improving heart function and reversing the effects of MH. In the rat model of aortic stenosis, the heart weight increased, and cardiac function decreased. At the same time, TNF-α, TGF-β, PGE2, CRP, and UA levels were increased. After celecoxib intervention, the heart weight decreased; cardiac function improved; and the MH was abated. The level of each inflammatory factor was also reduced.

COX is well known to be involved in the occurrence and development of heart failure. Although the effects of COX on the heart remain controversial, its involvement in the processes of MH and cardiac remodeling are undisputed. Castro et al [Castro 2013] studied the relationship between MH and COX-2 during exercise training in Atlantic salmon. Although the impacts of COX-2 on the heart were not studied in detail, they found that with an increase in physical activity, the levels of inflammatory cytokines such as TNF-α, NF-κB, and IL-1 progressively increased during the MH process. Moreover, Cochain et al [Cochain 2012] found that the chemokine decoy receptor D6 was capable of specifically binding to the CC-chemokine in a mouse model of myocardial infarction, thereby inhibiting inflammatory activities and myocardial remodeling after myocardial infarction. By contrast, obvious infiltration of neutrophils in the ischemic areas was observed in D6 gene–deficient mice, and the expression levels of matrix metalloproteinases-2 and -9 were increased along with upregulated COX-2 expression. In addition, Morales et al [Morales 2012] investigated the relationships between COX and vessel function by using a rat model of heart failure and found that the expression level of COX-2 was higher than that of COX-1 and that COX-2 also had a greater effect on the cardiac vessels. Further experiments revealed that the increase in COX-2 levels in the rats with heart failure was accompanied by a simultaneous increase in the sensitivities of the renal sympathetic nervous system and

Table 5. Expressions of Smad1/2/3 Proteins inside the Myocardial Tissues of the Experimental Groups (n = 8)

Groups	Smad1/2/3 Proteins
Sham operation	0.99 ± 0.11
Surgery	1.50 ± 0.23*
Celecoxib	0.75 ± 0.39†

Note: Compared with the sham operation group, *$P < .01$; compared with the surgery group, †$P < .01$.

aortic baroreceptors; in particular, the energy required to produce 0.5-kg muscle tension was only 50% of the original level [Morales 2012]. These findings proved that COX expression increases during the progression of heart failure, which then plays a role in the process of myocardial remodeling, consequently increasing blood pressure and enhancing cardiac output to a certain extent. A series of tests conducted by the same experimental group confirmed this hypothesis.

Various studies have also produced different results with respect to the negative effects of COX on the heart. Krum et al [Krum 2012] conducted a large-scale multicenter clinical trial to analyze the effects of the long-term (18 month) administration of a nonsteroidal anti-inflammatory drug (diclofenac) or COX-2 inhibitor (etoricoxib) and found no effect on blood pressure or cardiac output. Although this trial did not show a negative effect of COX or its inhibitor on the cardiac vessels, a previous study conducted by Abbate et al [Abbate 2007] using a rat model of ischemic heart failure showed that the expression level of COX was positively correlated with disease severity and that treatment with the COX-2 inhibitor parecoxib significantly improved the LV-FS, indicating obvious improvements in cardiovascular events. In addition, in the experiment described above by Morales et al [Morales 2012], although the increase in the sensitivities of the renal sympathetic nervous system and aortic baroreceptors during the process of heart failure could improve the cardiac output and raise the blood pressure in a short period, the downside of this apparently positive effect is that the continuation of the pathological process—especially the long-term high-stress status of the sympathetic nervous system and the increased cardiac work—would result in an increased load, with ultimate negative effects on the cardiac muscles. Fujisawa et al [Fujisawa 2014] injected dioxin (2,3,7,8-tetrachlorodibenzo-p-dioxin [TCDD]) into chicken eggs and found that the hatched chicks exhibited heart failure and that the H/B ratio and mRNA expression level of atrial natriuretic factor were increased. However, these effects were reversed if both TCDD and the selective COX-2 inhibitor NS398 were simultaneously injected into the eggs, and the probability of heart failure in the chick was reduced; thus, the cardiac toxicity of COX-2 was confirmed. The present study demonstrated that COX-2 began to be expressed at 16 weeks at the latest, when the pressure load was increased, producing negative effects on the heart (eg, increased heart volume, MH, and decreased cardiac functions), and that blocking COX-2 could reverse these effects to various degrees. This phenomenon might be related to a direct effect of COX itself or to the release of inflammatory factors induced by COX.

In addition, this experiment revealed nonsynchronization between the different effects of the COX-2 inhibitor on the heart. First, after 8 weeks of treatment, the cardiac functions recovered to various degrees, but the cardiac structures recovered to a lesser extent, especially with respect to the degree of improvement in left ventricular hypertrophy. In particular, the improvements of MH were not in line with the degree of recovery of cardiac functions. The possible reason for this phenomenon might be that before structural recovery, ie, the process of heart failure reversal, the heart functions could be more easily recovered, whereas more time was required for the process of myocardial remodeling. Thus, the synchronic recoveries of functions and structure might be expected to be observed over a longer duration.

The present experiment confirmed that COX-2 is indeed involved in the myocardial remodeling process, and further revealed that COX-2 might affect the progression of MH and heart failure via inflammatory cytokines. However, the precise mechanisms underlying the effects of COX-2 on inflammatory cytokines are still not clear. The results suggest that one potential mechanism could be via the Smad protein pathway, which is strongly related to the roles of TGF-β. This pathway could be a valuable focus of future research to provide important experimental evidence for initiating clinical trials on the potential for COX-2 inhibitors to treat heart conditions and improve heart functions. The main focus of this experiment was to determine the effects of the COX-2 inhibitor at a certain time point in treatment. However, MH and heart failure are chronic processes, and thus the drug treatment course is inevitably long. We have no experience in using the COX-2 inhibitor for more than 8 weeks, and there has been no in-depth study conducted on the dose. Therefore, further studies are needed to determine the relationship between MH and the celecoxib dose.

The incidences and mortality rates of cardiovascular diseases are high worldwide, irrespective of gender, and heart failure was found to be the leading cause of death among cardiovascular diseases [Regitz-Zagrosek 2011]. There has been great progress in medical science for other types of organ failure, such as developments in kidney and liver transplantation with very good effects on improving organ function in advanced stages of failure, thereby improving patient quality of life. However, research progress in treating heart failure remains unsatisfactory, and the functions of transplanted organs are still not sufficiently strong. Studies on heart failure have revealed numerous underlying mechanisms, including roles of the adrenaline system and the renin-angiotensin-aldosterone system [Bisping 2014], as well as apoptosis [Javadov 2014]. However, studies related to the effects of inflammatory factors on cardiovascular diseases are increasing at an unprecedented rate, and in-depth studies of inflammatory cytokines have revealed that inflammatory responses are involved throughout the disease process (from occurrence to development) for several cardiovascular diseases such as

dyslipidemia, acute coronary syndrome, arrhythmia, hypertension, and heart failure [Deftereos 2014]. The results of the present study provide the strongest evidence put forward to date that inflammatory factors are involved in the development of MH and heart failure. These results clearly show that continued research on the role of the inflammatory response in cardiovascular diseases, especially heart failure, has important significance and a profound impact for clinical practice.

CONCLUSION

Inflammatory factors are involved in the MH process, and the specific COX-2 inhibitor celecoxib may reverse MH through a variety of pathways.

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