

Effects of meloxicam and etoricoxib on blood pressure and vascular reactivity in rats

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Background : *Treatment with selective cyclooxygenase-2 (COX-2) inhibitor is associated with increased risk of cardiovascular events. Inhibition of COX-2 reduces vascular prostacyclin synthesis without disrupting COX-1-derived thromboxane synthesis, which may alter vascular tone and responsiveness.*

Objective : *To examine the effects of two COX-2 inhibitors, meloxicam and etoricoxib, on blood pressure and vascular reactivity in rats.*

Methods : *Unconscious blood pressure was obtained from Sprague Dawley rats by a tail-cuff method, and then the rats were divided into 3 groups (n = 9 in all groups): 1) non-treated control, 2) meloxicam 1 mg/kg/d, 3) etoricoxib 3 mg/kg/d. Drugs were orally administered 4 times/week in a consecutive day for 6 weeks. At the end of the treatments, unconscious blood pressure and pulse wave velocity (PWV, an index of arterial compliance) were determined. Thoracic aorta was isolated for the assessment of vascular responses to phenylephrine (PE, α -adrenoceptor agonist; 10^{-10} – 10^{-6} M), isoproterenol (Iso, β -adrenoceptor agonist; 10^{-8} – 10^{-4} M), and acetylcholine (Ach, muscarinic receptor agonist; 10^{-9} – 10^{-5} M).*

- Results** : *Etoricoxib caused a more pronounced effect on body weight gain than meloxicam, suggesting its greater effect on body fluid. Both COX-2 inhibitors did not alter PWV, indicating no change in arterial compliance. The systolic pressure, diastolic pressure and mean arterial pressure of etoricoxib group, but not meloxicam group, showed non-significantly higher than those of control group. The responsiveness of aortic rings to PE and Ach were not altered by either meloxicam or etoricoxib treatment. However, both drug treatments caused a significantly greater vasorelaxation responses to Iso ($P < 0.05$).*
- Conclusions** : *These results show that etoricoxib, but not meloxicam, has a non-significant increasing blood pressure which may be associated with body fluid retention. Both COX-2 inhibitors enhance β -adrenoceptor vasodilation.*
- Keywords** : *COX-2 inhibitor, blood pressure, vascular reactivity, adrenoceptor response, endothelial function.*

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- ปัญหาวิจัย** : การรักษาด้วยยากลุ่มที่มีฤทธิ์ยับยั้งเอนไซม์ cyclooxygenase-2 (COX-2) อย่างจำเพาะมีความสัมพันธ์กับการเพิ่มความเสียหายในการเกิดโรคหัวใจหลอดเลือด การยับยั้ง COX-2 มีผลลดการสังเคราะห์ prostacyclin โดยไม่มีผลต่อการสังเคราะห์ thromboxane จากเอนไซม์ COX-1 อาจมีผลเปลี่ยนแปลงแรงตึงและการตอบสนองของหลอดเลือด
- วัตถุประสงค์** : เพื่อศึกษาผลของยายับยั้ง COX-2 2 ชนิด คือ meloxicam และ etoricoxib ต่อความดันเลือดและการตอบสนองของหลอดเลือดในหนูขาว
- วิธีการ** : วัดความเลือดของหนูขาวสายพันธุ์ Sprague Dawley ในภาวะสลบด้วยวิธีการวัดความดันเลือดทางหาง จากนั้นแบ่งหนูขาวออกเป็น 3 กลุ่ม (กลุ่มละ 9 ตัว) คือ 1) กลุ่มควบคุมไม่ได้ให้สารใด ๆ 2) กลุ่มที่ให้ meloxicam 1 mg/kg/d 3) กลุ่มที่ให้ etoricoxib 3 mg/kg/d ให้ยาโดยการป้อนทางปากสัปดาห์ละ 4 วัน ติดต่อกันเป็นเวลา 6 สัปดาห์ เมื่อครบกำหนดจะสลบหนูขาวแล้ววัดความดันเลือดและ pulse wave velocity (PWV, เป็นดัชนีชี้วัดการผ่อนคลายของหลอดเลือด) จากนั้นแยก thoracic aorta เพื่อประเมินการตอบสนองของหลอดเลือดต่อ phenylephrine (PE, α -adrenoceptor agonist; 10^{-10} - 10^{-6} M), isoproterenol (Iso, β -adrenoceptor agonist; 10^{-8} - 10^{-4} M), และ acetylcholine (Ach, muscarinic receptor agonist; 10^{-9} - 10^{-5} M).
- ผลการศึกษา** : etoricoxib มีผลให้น้ำหนักตัวของหนูขาวเพิ่มได้มากกว่า meloxicam แสดงว่า etoricoxib อาจมีผลต่อการคั่งของสารน้ำในร่างกายมากกว่า ยาทั้งสองไม่มีผลต่อ PWV แสดงว่าไม่มีผลเปลี่ยนแปลงการผ่อนคลายของหลอดเลือด ในหนูขาว กลุ่มที่ได้รับ etoricoxib มีค่า systolic pressure, diastolic pressure และ mean arterial pressure สูงกว่ากลุ่มควบคุมอย่างไม่มีนัยสำคัญทางสถิติ ซึ่งไม่พบในหนูขาวกลุ่มที่ได้รับ meloxicam นอกจากนี้ยังพบว่ายาทั้งสองไม่มีผลเปลี่ยนแปลงการตอบสนองของหลอดเลือด aorta ต่อ PE และ Ach แต่มีผลเพิ่มการตอบสนองต่อ Iso โดยหลอดเลือดขยายตัวมากขึ้นอย่างมีนัยสำคัญทางสถิติ ($P < 0.05$)

- สรุป** : ผลการทดลองแสดงให้เห็นว่า ยา *etoricoxib* มีผลเพิ่มความดันอย่างไม่มีนัยสำคัญซึ่งอาจมีความสัมพันธ์กับการคั่งของน้ำในร่างกาย แต่ไม่พบในยา *meloxicam* ยาทั้งสองมีผลเพิ่มการขยายตัวของหลอดเลือดที่เกิดจากการกระตุ้น β -adrenoceptors
- คำสำคัญ** : ยายับยั้งเอนไซม์ COX-2, ความดันเลือด, การตอบสนองของหลอดเลือด, การตอบสนองของ adrenoceptor, การทำงานของ endothelium.

Cyclooxygenases (COX) are the key enzymes for the biosynthesis of prostaglandins (PGs) from arachidonic acid.^(1,2) Two isoforms of COX have been identified. COX-1, a house keeping enzyme, is constitutively expressed throughout the body, whereas COX-2, an inducible enzyme, is markedly expressed in response to inflammatory stimuli.⁽³⁾ The traditional nonsteroidal anti-inflammatory drugs (NSAIDs) are nonspecific inhibitors of both COX-1 and COX-2 which cause gastrointestinal side effects. The new class of NSAIDs, the selective COX-2 inhibitors, has been shown to have less adverse GI effects and are selected for long-term treatment of chronic inflammation.^(2, 4)

Although COX-2 is thought to induce under inflammatory responses, there is evidence that COX-2 is constitutively expressed in the vascular endothelium.⁽⁵⁾ Previous study demonstrated that COX-2 inhibition suppressed prostacyclin biosynthesis in healthy volunteers, suggesting that COX-2 is the source of PGI₂ production in human under physiological conditions.⁽⁶⁾ A study in mice deficient prostacyclin receptor emphasizes an important role of PGI₂ in mediating inflammation and in preventing thrombosis.⁽⁷⁾ Moreover, the observation that celecoxib, a selective NSAIDs, reversed the aspirin-induced inhibition of coronary thrombosis.⁽⁸⁾ These raise concerns regarding an increased risk of cardiovascular events of COX-2 inhibitors. Also growing evidence has suggested the increased cardiovascular risk associated with COX-2 inhibitors.⁽¹⁻³⁾

It has been postulated that selective inhibition of COX-2 may block the synthesis of the vasoprotective prostacyclin, without inhibiting the

COX-1-related formation of thromboxane A₂ (TxA₂). Therefore, selective COX-2 inhibitors may facilitate thrombosis and blood pressure elevation.^(9,10) An experimental animal model revealed that either COX-2 inhibition or COX-2 gene deficiency exaggerated the pressor effect of angiotensin II, suggesting an important role of COX-2-derived vasodilator in blood pressure regulation.⁽¹¹⁾ A recent meta-analysis of trial has reported the greater blood pressure rising effect of selective COX-2 inhibitors compared to nonselective NSAIDs, but this pressor effect seems heterogeneous among the selectivity of the COX-2 inhibition.⁽¹²⁾ However, it remains uncertain whether COX-2 inhibitor would cause an alteration in vascular tone leading to increased blood pressure and may modulate vascular responses to vasoactive substances, as a result of the imbalance of vasoconstrictor TxA₂ and vasodilator PGI₂. Therefore, the aim of this study was to investigate the effects of two COX-2 inhibitors, meloxicam and etoricoxib, on blood pressure and vascular reactivity in normotensive rats.

Material and Methods

1. Animal and treatment

Male Sprague Dawley rats, 7-8 weeks old, were obtained from the National Laboratory Animal Center, Mahidol University. Rats were housed two per cage in the animal facility of Burapha University. Rats were fed with a standard rat chow ad libitum and maintained at 25°C under a 12-hour light/dark cycle.

Unconscious blood pressure were obtained from 27 rats by a tail-cuff method. The rats were divided into 3 groups (n=9 in all groups): 1) non-treated control, 2) meloxicam treatment 1 mg/kg/d, 3)

etoricoxib treatment 3 mg/kg/d. The selected doses of both drugs were showed to exert an effectively anti-inflammatory action in rats.^(13,14) Drugs were given by gavage in a consecutive day 4 days per week for 6 weeks. Each animal weight was examined before starting the treatment and every 2 weeks during the treatment period. At the end of the treatments, unconscious blood pressure, pulse wave velocity, and vascular reactivity were assessed.

2. Blood pressure measurement

Animal was anesthetized with thiopental sodium 45 mg/kg by intraperitoneal injection. The body temperature was maintained at $37 \pm 0.2^{\circ}\text{C}$ with a lamp and continuously monitored with a rectal temperature probe connected to a computer-based recording system (model MP100, BIOPAC Inc., Santa Barbara, CA). An automatically inflated-deflated cuff pressure with a plethysmography (IITC Life Sciences; Woodland, CA) was placed around the proximal portion of the tail for detection of arterial pulsation. The tail-cuff was also connected to an interface for computer data acquisition. Systolic blood pressure (SBP) was identified at the first appearance of arterial pulse during the deflation of the tail-cuff. The first maximum amplitude of arterial pulse was taken as the mean arterial pressure (MAP), and diastolic pressure (DBP) was calculated from MAP equation: $\text{MAP} = \text{DBP} + 1/3\text{pulse pressure}$.

3. Measurement of pulse wave velocity

Pulse wave velocity (PWV) has been widely used to reflect arterial compliance or distensibility.⁽¹⁵⁾ PWV of all rats were assessed at the end of the treatments by a noninvasive method modified from

the method of Fitch.⁽¹⁶⁾ Rat was anesthetized with 45 mg/kg thiopental sodium (i.p.) and body temperature was controlled at $37 \pm 0.2^{\circ}\text{C}$. Electrocardiogram (ECG) lead electrodes were placed on the right front leg and the left hind leg for monitoring ECG, and a plethysmography was placed around the proximal tail for detection of arterial pulse. Both ECG and tail pulse were simultaneously recorded with a computer data acquisition unit (Biopac AC Inc.). Pulse transit distance was measured from aortic notch to the position of tail pulse sensor. Pulse transit time was the time delay between the peak of R-wave and the peak of the related pulse. PWV was calculated from the equation: $\text{PWV (m/s)} = \text{pulse transit distance/pulse transit time}$.

4. Evaluation of vascular reactivity

One day after BP and PWV assessment, rat was anesthetized with thiopental sodium 45 mg/kg (i.p.). The descending thoracic aorta was dissected, cut into small rings (3 mm), and suspended in an organ bath containing Krebs' solution of the following composition (mM): NaCl 118, KCl 4.6, KH_2PO_4 1.2, MgSO_4 1.2, NaHCO_3 25, CaCl_2 1.8, and glucose 11. The bathing solution was gassed continuously with 95% O_2 and 5% CO_2 and maintained at 37°C and pH 7.4. The isometric tension was measured by a force transducer connected to a computer data acquisition system (MP100, BIOPAC Inc.). The aortic rings were stretched to an optimal basal tension of 1 g and allowed to equilibrate for 60 min with the bath solution being changed every 15 min. The vasoconstrictor responses were assessed by phenylephrine (PE), α -adrenoceptor agonist, at cumulative doses of 10^{-10} - 10^{-6} M. The aortic rings were washed and left to

equilibrate in Krebs' solution for another 45 min. After that the rings were pre-contracted with PE at doses of producing 70% responses, the vasodilator responses were determined with isoproterenol (Iso, 10^{-8} - 10^{-4} M), β -adrenoceptor agonist. The responses to acetylcholine (Ach, 10^{-9} - 10^{-5} M), muscarinic receptor agonist, were also performed as an evaluation of endothelium-dependent relaxation.

5. Chemicals and drugs

Chemicals and drugs used and their sources were: Phenylephrine, acetylcholine, and isoproterenol from Sigma, thiopental sodium from Abbott, meloxicam from Boehringer Ingelheim, and etoricoxib from MSD.

6. Calculation and statistical analysis

Results are presented as mean and SEM. The contractile responses to PE are expressed as the percentage of the maximum contractile response. The relaxant responses to iso and Ach are expressed as the percent decrease of the peak contraction induced by PE. The maximum response (E_{max}) was the greatest response obtained with the agonist. The concentration

of the agonist producing 50% of the maximum effect (EC_{50}) was determined from each dose-response curve, and then the pD_2 values ($= -\log EC_{50}$) was obtained. The statistic analyses were performed using one-way ANOVA for comparison of more than two groups followed by Tukey HSD test. The concentration response curves were compared by using two-way ANOVA. The significance level considered in all test was ≤ 0.05 .

Results

Effects of COX-2 inhibitors on body weight and blood pressure

The pre-treatment body weight of each animal group was not significantly different (control 439.4 ± 8.25 g, meloxicam 445.8 ± 12.38 g, etoricoxib 420.6 ± 11.72 g). The changes in body weight during 6 week treatment time are showed in table 1. The body weight gain of meloxicam group showed slightly lower than that of control except at week 4 of treatment. Etoricoxib was associated with the highest body weight gain compared to the other two groups, and significant difference from control was found at week 4 of treatment ($P < 0.05$).

Table 1. Effects of meloxicam and etoricoxib on body weight gain during the treatment period. * $P < 0.05$ vs control in the same period, $n=9$ in all groups

Treatment time	% Body weight gain		
	Control	Meloxicam	Etoricoxib
2 weeks	1.83 ± 0.47	1.72 ± 0.15	2.30 ± 0.49
4 weeks	3.24 ± 0.55	4.96 ± 0.45	$5.98 \pm 0.82^*$
6 weeks	7.67 ± 0.69	7.17 ± 0.68	9.19 ± 0.77

The average SBP, DBP and MAP of all animal groups before the treatment were not significantly different. The effects of meloxicam and etoricoxib on blood pressure and arterial compliance parameters after 6 week period of drug administration are summarized in table 2. Although the significant differences in SBP, DBP and MAP between groups did not exist, all the blood pressure parameters of etoricoxib group were the highest among the three groups. Etoricoxib treated animals also showed the greatest average blood pressure elevation from the pre-treatment values (SBP 53, DBP 13, MAP 27 mmHg). In comparison, the control group had 37, 2 and 14 mmHg increase in SBP, DBP and MAP respectively. Meloxicam group exhibited the lowest average elevation in SBP and MAP from the pre-treatment blood pressure (36 and 9 mmHg respectively), whereas the DBP was slightly decreased (3 mmHg).

The arterial compliance as indicated by PWV was also assessed in all animal groups. Consistent with the blood pressure, the PWV of all groups were

not significantly different, and etoricoxib group showed the greatest PWV (table 2).

Effects of COX-2 inhibitors on vascular reactivity

The vasoconstrictor responses to PE were determined in isolated aortas derived from control, meloxicam-treated and etoricoxib-treated rats as described in Figure 1A and Table 3. The contractile responses to PE were similar in the aortas from all three groups (Fig 1A). The sensitivity and responsiveness to PE were also not significantly different as indicated by pD_2 and E_{max} respectively (Table 3). In contrast, the aortas from meloxicam and etoricoxib groups exhibited significantly greater vasodilator responses to Iso (Fig 2B). The E_{max} were increased by 12% and 15% in the meloxicam and etoricoxib groups respectively (Table 3). Endothelial-dependent vasorelaxation to Ach was not altered by either meloxicam or etoricoxib treatment (Fig 3C), and the pD_2 and E_{max} of all groups were comparable (Table 3).

Table 2. Blood pressure and arterial compliance parameters after treatment with meloxicam and etoricoxib for 6 weeks. n = 9 in all groups

Parameter	Control	Meloxicam	Etoricoxib
SBP (mmHg)	154 ± 5.4	158 ± 6.9	168 ± 3.2
DBP (mmHg)	67 ± 6.5	71 ± 4.7	79 ± 8.7
MAP (mmHg)	96 ± 4.9	100 ± 3.2	109 ± 6.9
PWV (m/s)	1.892 ± 0.04	1.898 ± 0.04	1.903 ± 0.04

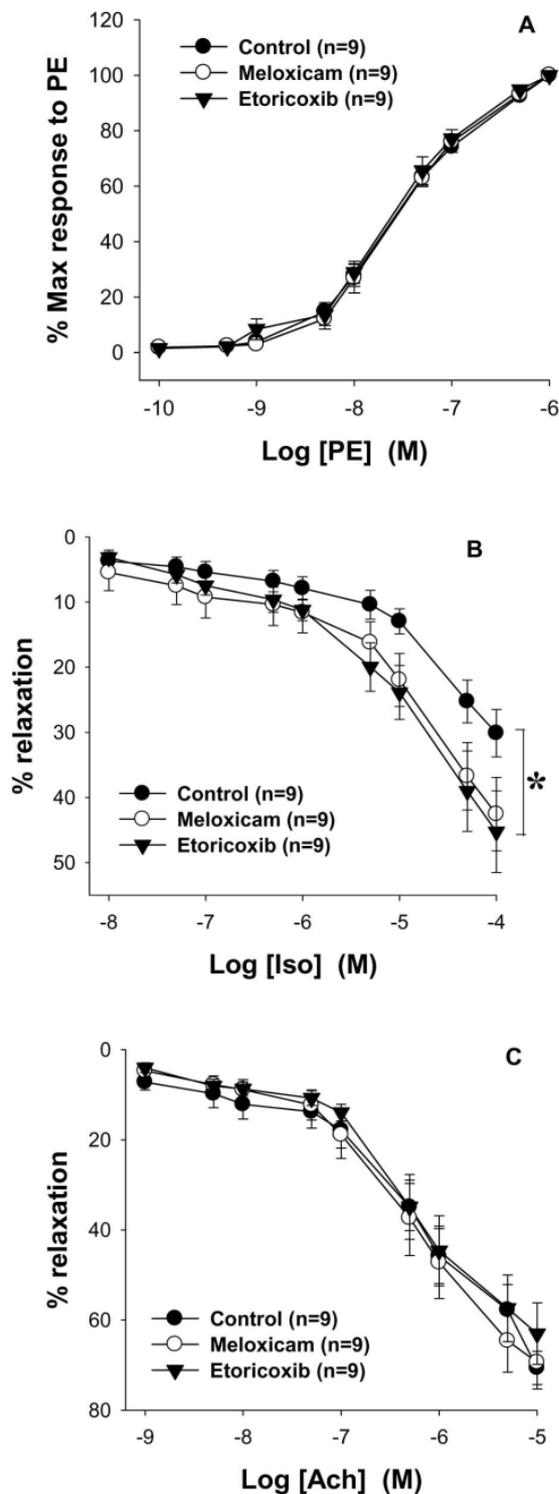


Figure 1. Cumulative dose-response curves to phenylephrine (A), isoproterenol (B), and acetylcholine (C) in isolated aortas derived from control, meloxicam, and etoricoxib groups. Symbols represent mean \pm S.E.M. * $P < 0.05$ vs control, two-way ANOVA.

Table 3. Dose-response parameters for the actions of pheylephrine, isoproterenol, and acetylcholine on isolated aorta derived from control, meloxicam, and etoricoxib groups. * $P < 0.05$ vs control, $n = 9$ in all groups.

Dose response parameter	Control	Meloxicam	Etoricoxib
Phenylephrine			
E_{max} (g)	1.96 ± 0.16	2.16 ± 0.21	2.56 ± 0.20
pD_2	7.66 ± 0.04	7.67 ± 0.05	7.71 ± 0.06
Isoproterenol			
E_{max} (%)	30.11 ± 3.43	$42.56 \pm 5.26^*$	$45.26 \pm 6.27^*$
Acetylcholine			
E_{max} (%)	70.62 ± 3.26	73.39 ± 4.43	70.28 ± 6.28
pD_2	5.79 ± 0.24	$6.01 \pm .23$	5.80 ± 0.25

Discussion

The present study demonstrated that after 6-week treatment period, both meloxicam and etoricoxib did not significantly alter PWV, indicating no change in arterial compliance. Moreover, etoricoxib treated rats exhibited a non-significant increase in blood pressure, which was associated with the greatest in body weight gain, compared to control and meloxicam treated groups. These findings suggest that etoricoxib is correlated with body fluid retention, which may contribute to the slight elevation of blood pressure observed in these rats. The results also showed that inhibition of COX-2 with either meloxicam or etoricoxib enhanced the isoproterenol vasorelaxation in isolated rat aortas, suggesting that COX-2 pathway may be implicated in vascular β -adrenoceptor responses.

COX-2 inhibitor and blood pressure

It has been postulated that selective COX-2

inhibitor may reduce vasodilator PGI_2 synthesis without disrupting vasoconstrictor TxA_2 derived from COX-1,^(9,10) which may cause an increase in vascular tone and blood pressure. A previous study has been reported an association of NSAIDs treatment and increased aortic stiffness.⁽¹⁷⁾ In the present study we assessed the arterial compliance or distensibility in rats treated with meloxicam and etoricoxib for 6 weeks by measuring the PWV. The finding showed non-significant differences in PWV compared to control, indicating that based on the doses and duration of the treatments in this study, both meloxicam and etoricoxib do not alter arterial tone. The results also imply that the slightly higher blood pressure observed in etoricoxib treated rats may not be related to the increase in arterial tone.

Growing evidence has pointed the correlation of COX-2 inhibitors and blood pressure elevation. In clinical study, coxibs appeared to produce greater

hypertension than non-selective NSAIDs.⁽¹²⁾ Furthermore, celecoxib treatment for 3 weeks significantly increased systolic blood pressure in both normotensive and hypertensive rats.⁽¹⁸⁾ Of particular interest was the observation that either COX-2 inhibition or COX-2 gene knockout augmented the pressor effect of angiotensin II, an important mediator in hypertensive state.⁽¹¹⁾ However, the effect on blood pressure appears to differ across the individual drugs within the COX-2 inhibitor class.^(12,19) Therefore, this study examined the blood pressure rising effect of two different classes of COX-2 inhibitors, meloxicam (COX-2 preferential inhibitor) and etoricoxib (COX-2 specific inhibitor). Both drugs differ not only in their selectivity for COX-2, but also in their site of action on this enzyme.⁽³⁾ One possible mechanism that COX-2 inhibitors increase blood pressure may be attributed to their effects on the kidney by decreasing glomerular filtration rate leading to fluid retention.^(3,9,10) In the present study, meloxicam treated rats exhibited lower blood pressure elevation, which was consistent with their lower weight gain, suggesting its less effect on body fluid. Correspondingly, previous study showed that meloxicam did not alter renal perfusion and function in experimental animals.^(20,21) In comparison, etoricoxib treatment was associated with the greatest blood pressure elevation and body weight gain, indicating its more pronounced effect on body fluid. Clinical study also provided a consistent evidence that etoricoxib, compared to placebo, caused a higher risk for renal adverse effects, including hypertension, lower-extremity edema, and elevated serum creatinine concentration.⁽²²⁾ Taken together, it appears that etoricoxib, but not meloxicam, can disturb body fluid balance via its renal adverse effect, which may

contribute to the slight elevation of blood pressure observed in the present study.

COX-2 inhibitor and vascular reactivity

Early study demonstrated that endothelial PGI₂ secretion was responsible for approximate 30% vasodilation second to endothelial nitric oxide,⁽²³⁾ emphasizing its important role in vascular function. Since COX-2 seems to be the major enzyme for PGI₂ production,⁽⁶⁾ its inhibition by selective COX-2 inhibitor in the absence of COX-1 blockade could alter the balance of vasoactive prostanoids, which may modulate vascular responses to vasoconstrictors and vasodilators as seen in hypertensive state.⁽²⁴⁾ According to the present finding, neither meloxicam nor etoricoxib had any effect on the constrictive responses of aortic rings to PE. This is in accordance with a previous report showing that celecoxib lacked effect on contractile responses to PE in aortic rings derived from both normotensive and hypertensive rats.⁽⁶⁾ Thus, vascular PGI₂ related to COX-2 may not have any role in vascular α -adrenoceptor responses, and the slight elevation of blood pressure observed in etoricoxib group of the present study is not due to its effect on α -adrenoceptor vasoconstriction. β -adrenoceptors also participate in regulating vascular tone in response to endogenous catecholamine and a decrease in vasorelaxant effect of this receptor subtype is associated with hypertension.⁽²⁴⁾ The present study assessed vascular responses to isoproterenol in rat aortas treated with meloxicam or etoricoxib. The results revealed that upon COX-2 inhibition, the β -adrenoceptor vasorelaxation was enhanced, implying that COX-2 may be involved in the reduction of this receptor response.

Correspondingly, COX-1 and COX-2 enzymes were shown to have a role in attenuated vascular β -adrenoceptor response in aging.⁽²⁵⁾ However, it remains uncertain how COX-2 reduces β -adrenoceptor relaxation. There is evidence that prostacyclin exerts its vasorelaxant effect via IP receptors linked to adenylate cyclase and cAMP which are also the major signaling pathway of β -adrenoceptors in vascular smooth muscle.^(26,27) It might be possible that when both β -adrenoceptors and IP receptors were simultaneously activated, they would compete for the same signaling pathway. Therefore, the decreased prostacyclin synthesis by COX-2 inhibitor would amplify the effect of β -adrenoceptor activation and this hypothesis needs further investigation. The clinical significance of the present finding is that the increased β -adrenoceptor vasorelaxation by COX-2 inhibition may counteract the blood pressure rising effect of some COX-2 inhibitors related to body fluid retention as observed in etoricoxib-treated rats.

It is now clear that endothelium has a major role in regulating vascular tone through production of several vasoactive mediators, such as nitric oxide, prostacyclin, endothelin-1, etc.⁽²⁸⁾ Endothelial nitric oxide was shown to cause vasodilation by about 70%, suggesting its role as a major mediator in controlling vascular tone.⁽²³⁾ A number of studies addressed the involvement of COX-2 inhibitors in endothelial function, and provided controversial results. Rofecoxib was shown to have no significant effect on endothelium-dependent vasodilation in patients with coronary artery disease,^(29,30) whereas parecoxib impaired acetylcholine-mediated vasorelaxation in patients with essential hypertension.⁽³¹⁾ Conversely, celecoxib

appears to reverse endothelial dysfunction in hypertensive patients,⁽³²⁾ and patients with coronary artery disease.⁽³³⁾ In the present study, we found no significant alteration of acetylcholine-induced vasodilation in aortic rings derived from either meloxicam-treated or etoricoxib-treated rats. This finding indicates that both COX-2 inhibitors have neutral effect on endothelial function, and the slight increase of blood pressure observed in etoricoxib group is endothelium independent. Taken together, the inconsistent results as mentioned above might be related to drug-specific differences and interferences from other concurrent drug treatments. Thus the effects of COX-2 inhibitors on endothelium are still not conclusive and need further clarification.

In conclusion our study shows that etoricoxib, but not meloxicam, causes a non-significant elevation of blood pressure. This blood pressure effect is not related to change in arterial compliance, but is associated with body fluid retention. Both COX-2 inhibitors do not alter α -adrenoceptor vasoconstriction and endothelial function, but enhance β -adrenoceptor vasodilation which may ameliorate some of their cardiovascular adverse effects.

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