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Selective COX-2 inhibition with different doses of rofecoxib does not impair endothelial function in patients with coronary artery disease.

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Abstract

In this study, we investigated the effects of both 25 and 50 mg daily doses of rofecoxib on the endothelial functions of patients with coronary artery disease (CAD). For this purpose, 34 patients with documented severe CAD and who were under aspirin treatment (300 mg/day) were randomized to receive 4 weeks of treatment with a placebo (n = 10, group I), rofecoxib 25 mg/day (n = 12, group II), and rofecoxib 50 mg/day (n = 12, group III). Brachial artery vasodilator responses were measured in order to evaluate endothelial function. The percentage of change in endothelial-dependent vasodilation in groups I, II, and III were similar at the baseline level and showed no significant change after treatment (6.2+/-3.9% vs. 5.9+/-3.1% and 5.8+/-3.3% vs. 5.6+/-3.8% and 6.1+/-4.5% vs. 5.8+/-4.1%, respectively; $P > 0.05$). Compared with the baseline, endothelium-independent vasodilatation, as assessed by nitroglycerine (NTG), remained unchanged after the treatment period (11.2+/-6.9% vs. 10.3+/-7.1% and 11.2+/-6.3% vs. 9.9+/-5.1% and 9.5+/-4.9% and 8.8+/-4.6%, respectively; $P> 0.05$). Treatment with both doses also showed no significant effects on high-sensitivity C-reactive protein (hs-CRP) levels and resting arterial diameters ($P > 0.05$). In conclusion, 4 weeks of treatment with standard and high doses of rofecoxib showed no significant effects on either endothelial-dependent or independent vasodilator response or plasma hs-CRP levels in patients with severe CAD taking concomitant aspirin.

KEYWORDS: cyclooxy genase-2inhibition, endothelial function, high-sensitivity C-reactive protein, coronary artery disease

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Original Article

Selective COX-2 Inhibition with Different Doses of Rofecoxib Does Not Impair Endothelial Function in Patients with Coronary Artery Disease

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In this study, we investigated the effects of both 25 and 50 mg daily doses of rofecoxib on the endothelial functions of patients with coronary artery disease (CAD). For this purpose, 34 patients with documented severe CAD and who were under aspirin treatment (300 mg/day) were randomized to receive 4 weeks of treatment with a placebo (n = 10, group I), rofecoxib 25 mg/day (n = 12, group II), and rofecoxib 50 mg/day (n = 12, group III). Brachial artery vasodilator responses were measured in order to evaluate endothelial function. The percentage of change in endothelial-dependent vasodilation in groups I, II, and III were similar at the baseline level and showed no significant change after treatment (6.2 ± 3.9% *vs.* 5.9 ± 3.1% and 5.8 ± 3.3% *vs.* 5.6 ± 3.8% and 6.1 ± 4.5% *vs.* 5.8 ± 4.1%, respectively; $P > 0.05$). Compared with the baseline, endothelium-independent vasodilatation, as assessed by nitroglycerine (NTG), remained unchanged after the treatment period (11.2 ± 6.9% *vs.* 10.3 ± 7.1% and 11.2 ± 6.3% *vs.* 9.9 ± 5.1% and 9.5 ± 4.9% and 8.8 ± 4.6%, respectively; $P > 0.05$). Treatment with both doses also showed no significant effects on high-sensitivity C-reactive protein (hs-CRP) levels and resting arterial diameters ($P > 0.05$). In conclusion, 4 weeks of treatment with standard and high doses of rofecoxib showed no significant effects on either endothelial-dependent or independent vasodilator response or plasma hs-CRP levels in patients with severe CAD taking concomitant aspirin.

Key words: cyclooxygenase-2 inhibition, endothelial function, high-sensitivity C-reactive protein, coronary artery disease

Since selective cyclooxygenase-2 (COX-2) inhibitors (coxibs) were introduced into clinical use in 1999, they have become the most commonly prescribed medication to treat arthritis, menstrual pain, and headache in the United States [1]. The very low risk of gastrointestinal toxicity remains the primary superiority of the selective COX-2 inhibitors over other non-steroidal anti-inflammatory drugs (NSAIDs) [2]. Because COX-2 seems to be the main enzyme responsible for the production of prostaglandin I_2 (PGI_2) in the vasculature under normal physiologic conditions [3, 4], its inhibition by selective COX-2 inhibitors, in the absence of the inhibition of thromboxane A_2 ($TX\text{-}A_2$) secretion from platelets, could theoretically cause deleterious cardiovascular events such as increase in thrombotic events and impairment in endothelial functions [5, 6]. The potential risk for

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thrombogenicity and endothelial dysfunction due to coxibs treatment in the healthy population and in patients with coronary artery disease (CAD) remains controversial due to the existence of conflicting data.

Until now, the established literature focused mostly on the thrombotic cardiovascular events and mortality in patients under COX-2 inhibitor treatment. While some studies including the Vioxx Gastrointestinal Outcomes Research trial (VIGOR) suggested that patients receiving daily 50 mg rofecoxib were predisposed to thrombotic events [7–9], a metaanalysis of Konstam *et al*. that included all studies performed with rofecoxib, failed to show any increase in cardiovascular risk in comparison to other NSAIDs [10]. These authors, as have many others, concluded that the excess risk involved with rofecoxib compared with naproxen in the VIGOR trial was caused mainly by a protective effect of naproxen rather than an increase in the event rate for patients receiving rofecoxib. Because many of the clinical trials did not include a placebo group, the question as to whether coxibs increase or decrease cardiovascular risk remains controversial.

Limited data are available concerning the effect of coxibs on endothelial function. Because endothelial PGI_2 secretion was shown to be responsible from the approximate 30% dilatation in the vascular endothelium found in one study [11], one can speculate that its inhibition by coxibs could decrease vasodilator response. In constrast to this suggested hypothetical effect, in 2 recent human studies, celecoxib was shown to improve endothelial functions in patients with CAD, while rofecoxib was found to have no significant effect on healthy volunteers [12, 13]. However, there is limited data regarding the effects of different doses of rofecoxib on vasodilator response in patients with CAD. Very recently, Title *et al*. showed that treatment with 25 mg/day rofecoxib had no significant effect on endothelial response in patients with CAD [14]. However, until now there is no data regarding the effect of a high dose of rofecoxib (50 mg/day), as given in the VIGOR trial, on endothelial functions. So, in the present study we aimed to investigate and compare the effects of both 25 and 50 mg daily doses of rofecoxib on endothelial functions determined by flow-mediated and nitroglycerine-induced vasodilation using high-sensitivity brachial ultrasonography in patients with CAD. We also evaluated the levels of plasma high-sensitivity C-reactive protein (hs-CRP) as an inflammatory marker.

Materials and Methods

Patient Population. The study was conducted between April 2003 and August 2003. The study population consisted of 34 patients (26 men, 8 women; mean 59.2 ± 10.8 years) undergoing cardiac catheterization at the University of Celal Bayar. Patients were eligible for the study if they had at least $> 70\%$ stenosis in a major vessel verified by angiography within the preceding 6 months. The exclusion criteria were: patients with unstable angina (Canadian Cardiovascular Society class 3–4), those with a history of percutaneous coronary intervention or coronary bypass surgery and myocardial infarction within 30 days, those that showed a need for bypass surgery or percutaneous coronary intervention in the subsequent 2 months, the presence of left ventricular systolic dysfunction (ejection fraction $< 40\%$), total cholesterol > 240 mg/dl, uncontrolled hypertension ($> 160/100$ mmHg), significant valvular heart disease, renal insufficiency, type I diabetes mellitus, and patients taking any kind of NSAIDs. All patients gave their written informed consent and the study protocol was approved by the Ethical Committee of University of Celal Bayar.

Study Protocol. All patients were undergoing stable cardiovascular therapy including aspirin (300 mg/day in all patients), nitrates (in all patients), angiotensin converting enzyme inhibitor (ACEI), or angiotensin receptor blocker (ARB), statin, and B-blocker. Subjects were randomly assigned to one of the 3 groups. Group I received a placebo ($n = 10$), group II received rofecoxib 25 mg/day ($n = 12$), and group III received rofecoxib 50 mg/day ($n = 12$) for 4 weeks. Concomitant medication and diet remained unchanged throughout the study course. Endothelium-dependent brachial artery flow-mediated dilatation and endothelium-independent nitroglycerin-mediated dilatation were assessed by means of high-resolution vascular ultrasound.

Assessment of Endothelial Function. Assessment of brachial artery endothelial function was performed at the baseline and after 4 weeks of treatment by a physician (PB) blinded to the patient data. Patients were studied in the morning, between 9:00–11:00, in a quite room with a temperature of 20–24 °C, after an overnight fast. Each patient avoided alcohol, caffeine, and cigarette smoking the night before, and all long-acting vasoactive medication was withheld for at least 24 h. After a fasting blood sample was withdrawn for the measurements of lipid parameters and hs-CRP, the

subject lay at rest for at least 10 min before a first resting screen was recorded. Flow-mediated dilatation (FMD) and glycerol trinitrate (GTN)-(0.4 mg sublingual, Nitrolingual sprey, Pohl-Boskamp) induced vasodilatation of the brachial artery was determined by high-resolution ultrasound with a 7.5-MHz linear array transducer (Siemens Sonoline Electra) according to a previously established and validated method [15]. Briefly, the arterial diameter was measured at a fixed distance from an anatomical marker such as a bifurcation and calculated as the mean value of 2 measurements at the end of the diastole, concurrent with the onset of the QRS complex. The average diameter of the artery then was calculated over 3 cardiac cycles. After taking the baseline measurements, increased flow was induced by inflation of a brachial cuff placed on the proximal limb and inflated to a pressure of 50 mmHg above systolic pressure for 5 min. After release, the arterial diameter was recorded every 15 sec for 3 min. Post-test arterial diameter measurements were made 60 sec after cuff deflation. Fifteen minutes was allowed for vessel recovery before GTN application, and the same procedure was repeated after GTN application. To evaluate the reproducibility of imaging and to assess intra-observer variability, additional measurements of randomly selected measurement of the images of 15 randomly selected patients were performed on 2 different days. The correlation coefficients were; $r = 0.96$ for the baseline, $r = 0.97$ for reactive hyperemia, and $r = 0.98$ for NTG induced vasodilation.

Biochemical analysis. Venous blood was withdrawn for the evaluation of plasma glucose and lipid parameters before and after 4 weeks of the treatment period, and measured by means of the colorimetric method using DDS kits (Diasys Diagnostic Systems, Vertriebs, Möhnsee, Germany). High-sensitivity CRP levels were measured by nephelometric assay (Dade Behring).

Statistical analysis. SPSS version 11.0 was used for statistical analysis. Data are expressed as mean ± standard deviation (SD). Baseline characteristics were compared using the Mann-Whitney U test or the Fischer exact test, as appropriate. Differences between the pre and post-treatment values were analyzed by 2-way repeated-measures ANOVA. Percentage changes in vasodilator response were calculated as [(post-treatment value-pre-treatment value)/pre-treatment value × 100]. P values < 0.05 were considered to be significant.

Results

All patients completed the study. The baseline demographics and clinical characteristics of the patients are summarized in Table 1. The groups were matched in terms of age, gender, body mass index, blood pressure, fasting glucose, lipid parameters, and type of medication. The number of stenotic vessels and the percentage of mean stenosis were also similar between both groups.

Effect of selective COX-2 inhibition on clinical parameters and vasodilator response. Table 2 summarizes change in clinical parameters and flow-mediated and NTG-induced vasodilator responses in both groups. Although heart rate remained unchanged, a moderate increase in blood pressure was observed in the study day perhaps because all long-acting vasoactive treatment had been withheld for 24 h before the study. No significant change in hs-CRP levels was observed in all groups. The percentage of change in endothelial-dependent vasodilation in groups I, II, and III were similar at the baseline and did not significantly change after 4 weeks of the treatment period ($6.2 \pm 3.9\%$ *vs.* $5.9 \pm 3.1\%$ and $5.8 \pm 3.3\%$ *vs.* $5.6 \pm 3.8\%$ and $6.1 \pm 4.5\%$ *vs.* $5.8 \pm 4.1\%$ respectively; $P > 0.05$). The percentage of change in endothelium-independent vasodilation as assessed by nitroglycerine (NTG-induced vasodilation) were also similar in both groups at the baseline and also showed no significant change after treatment ($11.2 \pm 6.9\%$ *vs.* $10.3 \pm 7.1\%$ and $11.2 \pm 6.3\%$ *vs.* $9.9 \pm 5.1\%$ and $9.5 \pm 4.9\%$ *vs.* $8.8 \pm 4.6\%$, respectively; $P > 0.05$). Treatment with both doses also had no significant effect on resting arterial diameters ($P > 0.05$) (Table 1).

Discussion

To our knowledge, this is the first study to demonstrate that high doses of rofecoxib (50 mg/day) has no significant effect on endothelial functions in patients with severe CAD. We also showed that both 25 and 50 mg doses of rofecoxib had neutral effects on plasma CRP levels. These findings are fully in agreement with a very recent study published by Title *et al.* [14], although they focused only on daily 25 mg rofecoxib treatment in a similar population.

The increase in thrombotic events and the decrease in vasodilatory response concerns the 2 main anxieties for patients undergoing coxib therapy [16]. This topic is of great public health importance because the patient popula-

tion most likely to use selective COX-2 inhibitors, the elderly, is also at the highest risk for atherosclerotic disease. Possible cardiovascular side effects of coxibs have been investigated in some clinical trials. VIGOR [9] and CLASS [17] are the best-known clinical trials in this field. While a 5-fold increase in cardiovascular events was observed in the VIGOR trial, CLASS failed to demonstrate a significant increase in cardiovascular risk. However, neither VIGOR nor CLASS was designed primarily to assess the risk of cardiovascular events and neither included a placebo group. Moreover, while 20% of the patients in the CLASS trial were taking concomitant aspirin, it was not allowed in the VIGOR trial. Thus, the cardiovascular results of these trials are challenging for many researchers.

The studies and randomized trials published until now

Table 1 Baseline demographics and clinical characteristics

	Placebo (n = 10)	Rofecoxib 25 mg (n = 12)	Rofecoxib 50 mg (n = 12)
Age (year)	58 ± 10.6	60.6 ± 11.9	57.9 ± 9.9
Gender (M/F)	8/2	9/3	9/3
Family history, positive (%)	30	33	25
BMI (kg/m^2)	28.4 ± 4.2	26.7 ± 3.7	27.5 ± 4.08
Active smoker (%)	40	42	50
Hypertension (%)*	40	50	50
Diabetes mellitus (%)*	20	25	17
Fasting glucose (mg/dl)	121 ± 32	119 ± 28	125 ± 36
Lipid parameters			
Total cholesterol (mg/dl)	206.4 ± 28.9	210.4 ± 32.2	216.1 ± 37.5
LDL-cholesterol (mg/dl)	135.2 ± 25.2	130.1 ± 18.3	133 ± 22.5
HDL-cholesterol (mg/dl)	41.9 ± 4.76	45.4 ± 4.69	43.4 ± 5.19
Triglyceride (mg/dl)	176.3 ± 65.1	165 ± 62.9	181 ± 68.4
Medications (%)			
Aspirin	100	100	100
Statin	70	66	75
ACEI/ARB	60	58	67
B-blockers	70	75	66
Number of stenotic vessels	1.9 ± 1.1	2.0 ± 0.9	1.8 ± 1.2
Stenosis (%)	70.8 ± 14.2	75.3 ± 11.6	71.2 ± 16.9

Data are given as mean ± standard deviation (SD). No significant differences were noted between baseline characteristics, risk factors, and medications between groups. BMI indicates body mass index; LDL, light-density lipoprotein; HDL, high-density lipoprotein; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; *under control with drug treatment.

Table 2 Results of the hemodynamic, brachial artery flow, and hs-CRP measurements

	Placebo (n = 10)		Rofecoxib 25 mg (n = 12)		Rofecoxib 50 mg (n = 12)		*P* value
	Basal	4-weeks after	Basal	4-weeks after	Basal	4-weeks after	
HR (beat/min)	68 ± 10	65 ± 8	71 ± 14	67 ± 11	66 ± 10	68 ± 12	NS
SBP (mmHg)	132.5 ± 23.2	130.5 ± 22.2	128.5 ± 20.2	137.2 ± 24.2	138 ± 24.4	145 ± 25.9	NS
DBP (mmHg)	79.4 ± 11.7	78 ± 10.2	76.2 ± 10.7	79.7 ± 12.1	84.1 ± 14.3	89 ± 16.1	NS
hs-CRP (mg/L)	2.1 ± 1.7	1.9 ± 1.3	1.9 ± 1.6	2.0 ± 1.5	2.3 ± 1.9	2.1 ± 1.8	NS
Arterial diameter (mm)	3.91 ± 0.68	4.06 ± 0.75	3.79 ± 0.77	3.62 ± 0.61	3.89 ± 0.51	3.82 ± 0.54	NS
Flow-mediated vasodilation (%)	6.2 ± 3.9	5.9 ± 3.1	5.8 ± 3.3	5.6 ± 3.8	6.1 ± 4.5	5.8 ± 4.1	NS
NTG-induced vasodilation (%)	11.2 ± 6.9	10.3 ± 7.1	11.2 ± 6.3	9.9 ± 5.1	9.5 ± 4.9	8.8 ± 4.6	NS

Data are given as mean standard deviation. HR indicates heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; hs-CRP, high-sensitivity C-reactive protein; NTG, nitroglycerine; NS, statistically not significant.

focused mostly on the effects of coxibs on cardiovascular events such as myocardial infarction or mortality. However, limited data is available regarding the effects of coxibs on endothelial functions in subjects with or without CAD. As is well known, basal vascular tone is regulated with NO, PGI_2, endothelin, and angiotensin II, in which the effect of NO is prominent [18]. It has been suggested that the inhibition of NO synthase reduces brachial artery blood flow-mediated vasodilation by about 70% and the residual vasodilation is probably dependent on PGI_2 [11]. If this is true, then one can speculate that the inhibition of PGI_2 secretion by a selective COX-2 inhibitor could diminish the vasodilator response.

This suggestion was first challenged by the observations of Verma *et al.* who were not able to demonstrate any decrease in endothelium-dependent vasodilation in healthy subjects receiving 7 days of rofecoxib treatment [13]. However, the short duration of the treatment period and the absence of a control group in their study inhibits one from reaching final conclusions regarding the effect of rofecoxib in these subjects. In the present study, we aimed to test the validity of this hypothesis in patients with CAD and, as did Verma *et al.*, we failed to show any significant decrease in the vasodilator response with daily doses of both 25 and 50 mg rofecoxib treatment. Because all of our patients were under concomitant aspirin treatment, one possible explanation for the lack of any decrease in vasodilator response is that the non-specific COX inhibition by aspirin might have reduced the baseline levels of PGI_2 and TRX-A_2, and could account for our observation that rofecoxib treatment had no further effect on systemic prostacyclin production[19]. Another possible explanation, as supposed by Wang *et al.*, is that the vascular PGI_2 synthesis could be dependent primarily on the activity of COX-1 and not COX-2 in both normal and atherosclerotic endothelium [20]. Lastly, these findings could result from the differential effects of selective COX-2 inhibitors on normal and atherosclerotic endothelium, the detrimental effect being more prominent in healthy endothelium.

Recent studies have demonstrated that COX-2 expression is induced during proinflammatory states such as atherosclerosis [21, 22]. So, it may be supposed that therapy with COX-2 inhibitors may have a suppressive effect on the development of atherosclerosis. Although the clinical consequences of this effect are currently unknown, the possible beneficial effects of selective COX-2 inhibition in patients with atherosclerosis are still under investigation. Growing evidence supports the suggestion that COX-2 inhibition may decrease endothelial inflammation, reduce monocyte infiltration, improve vascular cell function and plaque stability, and probably result in a decrease of coronary atherothrombotic events [23]. This suggestion was supported in a very recent study published by Chenevard *et al.* who showed that selective COX-2 inhibition with celecoxib (200 mg BID) improved endothelial function in patients with CAD [12]. These authors suggested that the beneficial effect resulted from a reduction in hs-CRP and oxidative stress. They concluded that the pleiotrophic effects of COX-2 inhibition decreases in CRP and oxidized LDL on the vascular wall might have beneficial effects in atherosclerotic vessel disease. Recent evidence suggests that hs-CRP, as an inflammatory marker, directly induces endothelial dysfunction by decreasing the secretion of endothelium-derived nitric oxide and may predict the risk of future cardiovascular events [24, 25]. From this point of view, drugs such as NSAIDs and coxibs which have anti-inflammatory properties could theoretically be thought to have some beneficial effects on endothelial function.

However, in the present study we could not demonstrate any significant decrease in hs-CRP levels or any improvement in endothelial vasodilator response in a population similar to that included in the study of Chenevard *et al.* This inconsistency may be explained by the differences in study duration or the pharmacological differences between both drugs. For example, although rofecoxib and celecoxib both selectively inhibit COX-2, they are chemically different compounds. While celecoxib is a sulfonamide, which is extensively disturbed into tissues and metabolized by the cytochrone P450 system, rofecoxib on the other hand is a sulfone, which is distributed less in tissues and is metabolized to a lesser degree by cytosolic reduction [23]. Thus, head-to-head comparison trials evaluating endothelial function are required to determine the differences between the 2 drugs in order to make a more precise comment for their effects on endothelial function and on inflammatory mediators such as hs-CRP. Nevertheless, the neutral effect of rofecoxib on endothelial function, as observed in the present study and based on the results of Title *et al.* [14], can also be regarded as affirmative results for the clinical safety for rofecoxib with respect to the endothelial vasodilator reserve. However, although the preliminary results were encouraging, further large scale, randomized human studies will be required to determine the net clinical

effect of coxibs on the cardiovascular system.

Study limitations. Our study has some limitations. First, we included only a relatively small sample size of patients who were otherwise well matched with regard to age, BMI, and classical cardiovascular risk factors. Thus, our results need to be confirmed by other randomized, placebo-controlled studies involving a large number of patients. Second, because we were interested only in changes in flow-mediated dilatation and hs-CRP levels, it is possible that we could have missed some of its beneficial effects at the cellular level. Third, a short treatment period (4-weeks) can be thought to prevent the existence of certain possible effects of rofecoxib on endothelial function. However, many studies performed with other pharmacological drugs have shown prominent effects on endothelial functions within 2 to 8 weeks [12, 26, 27]. Lastly, because all of our patients were under concomitant aspirin treatment and had stable angina pectoris, our results cannot be extended to the patients not taking aspirin treatment and patients with unstable angina pectoris. The effect of coxibs on the endothelial functions in this group of patients is needed to be searched.

The main result of the present study is that 25 and 50 mg daily doses of rofecoxib, which are known as standard and high doses, showed no significant effects on both endothelial-dependent and -independent vasodilator responses. Although our findings along with others are encouraging for the safe use of rofecoxib in high risk patients such as those with coronary artery disease, the effects of coxibs on thrombogenicity remain to be determined in prospective and well-designed placebo-controlled studies in order to more clearly determine their net action on the cardiovascular system.

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