Cyclooxygenase-2 Inhibition Increases Mortality, Enhances Left Ventricular Remodeling, and Impairs Systolic Function After Myocardial Infarction in the Pig

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Background—Cyclooxygenase (COX)-2 expression in the heart increases after myocardial infarction (MI). In murine models of MI, COX-2 inhibition preserves left ventricular dimensions and function. We studied the effect of selective COX-2 inhibition on left ventricular remodeling and function after MI in a pig model.

Methods and Results—Twenty-two pigs were assigned to COX-2 inhibition with a COX-2 inhibitor (COX-2i; celecoxib 400 mg twice daily; n=14) or a control group (n=8). MI was induced by left circumflex coronary artery ligation, and the animals were euthanized 6 weeks later. Cardiac dimensions and function were assessed with echocardiography and conductance catheters. Infarct size and collagen density were analyzed with triphenyltetrazolium chloride staining and picrosirius red staining, respectively. COX-2 inhibition increased mortality compared with controls (50% versus 0%, P=0.022), whereas infarct size was similar (13.1±0.7% versus 14.1±0.1%, P=0.536). The decrease in thickness of the infarcted myocardial wall was more pronounced in the COX-2i group (60.6±9.6% versus 36.2±5.7%, P=0.001). End-diastolic volume was higher in the COX-2i group (133.9±33.5 versus 91.1±24.0 mL; P=0.021), as was the end-systolic volume at 100 mm Hg (81.7±27.8 versus 56.3±21.1 mL; P=0.037), which indicates that systolic function was more severely impaired. Infarct collagen density was lower after COX-2i treatment (25.3±3.9 versus 56.1±23.8 gray value/mm²; P=0.005).

Conclusions—In pigs, COX-2 inhibition after MI is associated with increased mortality, enhanced left ventricular remodeling, and impaired systolic function, probably due to decreased infarct collagen fiber density. (Circulation. 2007; 115:326-332.)

Key Words: myocardial infarction ■ heart failure ■ remodeling ■ enzymes

Myocardial infarction (MI) is a leading cause of morbidity and mortality in Western countries. Left ventricular (LV) dilatation is commonly observed as a complication after MI and may lead to deterioration of cardiac performance over time and contribute to the progression into congestive heart failure. Many strategies (eg, use of β-blockers and angiotensin-converting enzyme inhibitors) that have been developed to attenuate expansive remodeling, or even to reverse this process, are now integrated in the treatment of patients who have experienced an MI. Despite these advances in the management of MI, the number of patients with congestive heart failure continues to grow and remains associated with a >10-fold elevated risk of death. Therefore, the search for new and effective treatments is mandatory.
COX-2, have been shown to enhance LV dilatation and infarct expansion after experimentally induced MI.\textsuperscript{5–7} Administration of these drugs to patients after MI may lead to the formation of ventricular aneurysms and ruptures. Low-dose aspirin promotes perivascular and interstitial fibrosis but does not alter infarct collagen content, cardiac dimensions, or function after MI in rats.\textsuperscript{8}

Selective inhibition of only COX-2 preserves cardiac dimensions and function in murine animal models of MI.\textsuperscript{9,10} Studies in humanlike preclinical large-animal models, however, are crucial to examine whether COX-2 inhibition may benefit patients after MI by counteracting LV remodeling.

Selective COX-2 inhibitors were originally developed to bypass the risk of gastrointestinal side effects of traditional (ie, nonselective) nonsteroidal antiinflammatory drugs. Recently, however, it became evident that COX-2 inhibitors increase the risk of major adverse cardiovascular events,\textsuperscript{11–13} which formed the basis for recent concern about the use of COX-2 inhibitors, particularly in patients at risk for cardiovascular disease. Consequently, it is of major importance to map in detail the consequences of COX-2 inhibition in patients at risk for cardiovascular problems, including a possible effect on LV remodeling. We therefore investigated the effect of selective COX-2 inhibition on post-MI LV remodeling in a porcine model of MI.

Methods

Animals

All experiments were performed in accordance with the “Guide for the Care and Use of Laboratory Animals” prepared by the Institute of Laboratory Animal Resources and with prior approval by the Animal Experimentation Committee of the Faculty of Medicine, Utrecht University, the Netherlands.

Study Design

In 26 female Dalland Landrace pigs (weight 60.3±1.4 kg; IDDL0, Leilystad, The Netherlands), an MI was induced surgically. One day after surgery, the animals were randomly assigned to COX-2 inhibitor (COX-2-i) treatment (400 mg of celecoxib [Pfizer, Inc, Capelle a/d IJssel, The Netherlands] twice daily mixed through normal feeding from the day after surgery until termination) or a control group receiving no treatment. The animals were allowed to recover from the operation and were euthanized 6 weeks later. All animals were treated with clopidogrel 75 mg/d and sotalol 320 mg/d from 4 days before surgery until termination of the study to prevent thrombosis and arrhythmias.

Anesthesia

After an overnight fast, the pigs were sedated with ketamine (10 mg/kg), midazolam (0.5 mg/kg), and atropin (0.04 mg/kg) and induced with thiopental (4 mg/kg) before they were intubated and connected to a respirator for intermittent positive pressure ventilation with a mixture of oxygen and air (1:1 vol/vol). A venous catheter was placed in an ear vein for continuous administration of saline and anesthetic drugs. (A loading dose of midazolam [0.5 mg/kg] and sufentanil citrate [6 μg/kg] was administered before ventilation.) Anesthesia was maintained by continuous infusion of midazolam (0.7 mg · kg\textsuperscript{−1} · h\textsuperscript{−1}), whereas analgesia was obtained by continuous infusion of sufentanil citrate (6 μg · kg\textsuperscript{−1} · h\textsuperscript{−1}) and muscle relaxation by infusion of pancuronium bromide (0.1 mg · kg\textsuperscript{−1} · h\textsuperscript{−1}). Before surgery, 160 mg of sotalol was infused intravenously in 30 minutes to prevent cardiac arrhythmias.

MI and Operational Procedure

During the entire operation, ECG, arterial pressure, and capnogram were monitored continuously. After a median sternotomy was performed, a pacing lead was introduced into the right atrium through a small hole in the right auricle to ensure measurements at fixed heart rates. LV pressure was measured with a pressure-tipped Millar catheter that was inserted through the apex into the LV. A transonic flow probe (Transonic Systems Inc, Ithaca, NY) was placed around the proximal aorta to measure cardiac output. Before induction of the infarct, echocardiography was performed. Sutures were then tightened to permanently occlude the proximal left circumflex coronary artery. Internal defibrillation with 50 J was used when ventricular fibrillation occurred. After stabilization of hemodynamics and heart rhythm, the thorax was closed, and the animals were allowed to recover in the stable.

Six weeks after induction of the MI, the animals were anesthetized once more, and the sternum was reopened. Echocardiography and conductance catheter–based pressure-volume recordings were obtained to assess cardiac function and geometry. After the functional measurements were obtained, the heart was excised for laboratory analysis.

Hemodynamics

The ECG, arterial pressure, cardiac output, and LV pressure were digitized at a sampling rate of 300 Hz and stored for offline analysis (Sonometrics Corp, Ontario, Canada).

Echocardiography

Short-axis epicardial ultrasound images (Prosound SSD-5000, 5-MHz probe UST-5280-5, Aloka Holding Europe AG, Zug, Switzerland) were obtained at the midpapillary level. Wall thickness (WT) of the infarct area and LV internal area (LVia) were measured at end diastole (ED) and end systole (ES). Systolic wall thickening was calculated as

\[
\text{WT}(\text{ES}) - \text{WT}(\text{ED}) \times 100 \%
\]

and fractional area shortening as

\[
\frac{\text{LVia}(\text{ED}) - \text{LVia}(\text{ES})}{\text{LVia}(\text{ED})} \times 100 \%.
\]

Conductance Catheter Protocol

The conductance catheter method provides a continuous online measurement of LV volume and LV pressure and was performed as described previously.\textsuperscript{14,15} LV pressure and volume signals derived from the conductance catheter were displayed and acquired at a 250-Hz sampling rate with a Leycom CFL-512 (CD Leycom, Zoetermeer, the Netherlands). Data were acquired during steady state and during temporal caval vein occlusion, all with the ventilator turned off at end expiration. Acquisition was performed at a fixed atrial pacing rate of 80 bpm. Analysis of the pressure-volume loops was performed with custom software as described previously.\textsuperscript{16} Systolic function was characterized by the position of the end-systolic pressure-volume relationship, quantified by calculating the end-systolic volume intercept at a fixed end-systolic pressure of 100 mm Hg (ESV\textsubscript{0}). Diastolic chamber stiffness was quantified by means of exponential regression of the end-diastolic pressure-volume relationship.\textsuperscript{17}

Infarct Size

After excision of the heart, the LV was isolated and cut into 5 slices from apex to base. The slices were incubated in 1% triphenyltetrazolium chloride (TTC, Sigma-Aldrich Chemicals, Zwijndrecht, the Netherlands) in 37°C Sørensen buffer (13.6 g/L KH\textsubscript{2}PO\textsubscript{4}+17.8 g/L Na\textsubscript{2}HPO\textsubscript{4}·2H\textsubscript{2}O; pH 7.4) for 15 minutes to discriminate infarct tissue from viable myocardium. All slices were scanned from both sides, and in each slide, the infarct area was compared with total area
by use of digital planimetry software. After correction for the weight of the slices, infarct size was calculated as a percentage of the LV.

Enzyme-Linked Immunosorbent Assay
Heparinized full blood samples and serum samples were collected from the treated animals before COX-2i treatment and before euthanasia. Full blood was stimulated for 24 hours at 37°C with 100 ng/mL lipopolysaccharide to induce COX-2. After stimulation, the plasma was collected after 5 minutes of spinning at 1000 rpm, and an ELISA was performed on prostaglandin E2, according to the manufacturer’s instructions (Assay Designs, Ann Arbor, Mich). In the serum samples, thromboxane B2 (the stable metabolite of thromboxane A2, which is downstream of COX-1) was measured with ELISA, also according to the manufacturer’s instructions (R&D Systems, Minneapolis, Minn).

Collagen Density
Samples were taken from the infarct region, border region, and remote area and fixated in 4% formalin for 24 hours before being embedded in paraffin. Quantification of collagen content was performed with picrosirus red staining and digital image microscopy with circular polarized light. The section images were converted into gray-value images that were quantified in 5 randomly picked areas within each section and averaged.

Celecoxib Tissue Content
In 5 additional pigs, of which 3 were treated with celecoxib and 3 served as control animals, an MI was induced as described above. These pigs were euthanized after 7 days to harvest tissue for analysis of collagen turnover and celecoxib tissue quantification. For the celecoxib tissue quantification, frozen tissue was ground to powder in liquid nitrogen and extracted with dichloromethane. One micro-liter of tissue extraction and 1 µL of matrix solution were mixed on the matrix-assisted laser desorption/ionization plate according to the procedure of the dried-droplet preparation. Direct quantification of celecoxib was performed by matrix-assisted laser desorption/ionization time-of-flight mass spectrometry with an ultraviolet light-absorbing ionic liquid matrix.18 Experiments were performed with a Kratos Axima CFRplus (Shimadzu Biotech, Manchester, United Kingdom) operating in positive reflectron mode.

Data Analysis
Functional data and histological data were collected blindly, and the codes were revealed afterward. Values are presented as mean±SE. Statistical comparison of mortality between treated and nontreated animals was done with Fisher exact test. MI values were compared with baseline values with a Wilcoxon signed rank test. A Mann Whitney U test was used for statistical comparison between treated and nontreated animals. Probability values <0.05 were considered significant.

The authors had full access to the data and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

COX-2i Specificity
To assess whether celecoxib specifically inhibited COX-2, without affecting COX-1, COX-2–dependent prostaglandin E2 production and COX-1–dependent thromboxane B2 production were determined from blood samples of the treated animals. After lipopolysaccharide stimulation, which induces COX-2, prostaglandin E2 production decreased after COX-2i treatment (from 241±71 to 66±25 pg/mL, P=0.028). Conversely, thromboxane B2 levels were not influenced by COX-2i treatment (from 385±96 to 361±99 pg/mL, P=0.310), which indicates that only the activity of the COX-2 isoform was inhibited.

Mortality and Infarct Size
Four animals died perioperatively owing to refractory ventricular fibrillation, before randomization, and were therefore excluded from the present study. Of the remaining 22 animals, 14 were treated with celecoxib, and 8 served as controls. Mortality was significantly higher in the celecoxib-treated animals than in control animals (50% versus 0%; P=0.022), whereas infarct size was similar in both groups (13.1±0.7% versus 14.1±1.0% of the LV; P=0.536). In the COX-2i group, death occurred 3 to 6 weeks after induction of MI as a result of LV rupture (as evidenced during obduction by cardiac tamponade and transmural myocardial leakage, n=3), cardiac decompensation (as evidenced by tachypnea, tachycardia, and the presence of pleural and abdominal fluid during obduction, n=2), and sudden death of unknown cause (n=2).

Systemic Hemodynamics: Effect of MI and COX-2i
Hemodynamic parameters are summarized in Table 1. Heart rate and cardiac output remained unchanged after MI and did not differ between the treated and nontreated animals. Mean arterial pressure decreased in the nontreated animals from 109±8.4 to 84.1±3.4 mm Hg (P=0.028) but not in the treated animals (from 97.8±13.4 to 101±7.0 mm Hg, P=1.00). The change in mean arterial pressure, however, was not significantly different between the groups (−29.3±10.2 mm Hg [controls] versus 3.7±13.1 mm Hg [COX-2i], P=0.116). After MI, end-diastolic pressure increased in both treated and nontreated animals from 6.0±0.7 to 13.4±1.6 mm Hg (P=0.018) and from 6.4±0.5 to 14.8±1.9 mm Hg (P=0.028), respectively. No differences were detected between the treated and nontreated animals.

Regional and Global LV Remodeling: Effect of MI and COX-2i
MI resulted in a decrease of the myocardial wall thickness in the infarct area and remote area (septum) and an increase in LV internal area in treated and nontreated animals. The decrease in wall thickness of the infarct area was more pronounced in the animals treated with celecoxib (60.6±3.6% versus 36.2±2.0% decrease, P<0.001; Figure 1A), as was the increase in LV internal area (100.1±21.3% versus 51.4±7.0% increase, P=0.002; Figure 1B). The absolute values are depicted in Table 1. In addition, both end-diastolic and end-systolic volumes were higher in the treated animals than in the nontreated animals (133.9±12.7 versus 90.7±8.5 mL, P=0.021 and 85.8±9.5 versus 56.5±8.3 mL, P=0.029, respectively; Figure 1C).

Regional and Global Function: Effect of MI and COX-2i
Both regional and global function decreased after MI. After MI, the left circumflex coronary artery perfusion territory was completely akinetic, and fractional area shortening decreased in both treated and nontreated animals (Table 1). The ESVL as a measure of systolic function, was higher in the treated animals than in the nontreated animals (81.7±10.5 versus
56.3±7.5 mL, *P=0.040; Figure 1D). No differences were observed in diastolic and other systolic parameters (Table 1).

Collagen Density
Collagen density in the infarct area was lower after celecoxib treatment (25.3±3.9 versus 56.1±23.8 gray value/mm²; *P=0.004). No differences were found in the border area (14.2±1.0 versus 14.0±0.8 gray value/mm²; *P=1.000) or remote area (14.8±2.0 versus 12.1±1.1 gray value/mm²; *P=0.259; Figures 2 and 3).

Celecoxib Tissue Concentration
Celecoxib tissue concentration (Table 2) was determined before and after infarction in the infarct, border, and remote areas. No differences were found between infarct area (290±165 µg/g tissue) and border or remote area (295±143 and 288±230 µg/g tissue, respectively). No celecoxib was found before infarction or in control animals.

### Discussion
In the present study, we investigated the effect of the selective COX-2i celecoxib on post-MI LV remodeling in a porcine model of MI. Left circumflex coronary artery ligation in these pigs resulted in necrosis of the posterior LV wall followed by scar formation, thinning of the infarcted myocardial wall, LV dilatation, and functional impairment. Selective COX-2 inhibition promoted myocardial infarct thinning and LV dilatation. Whereas diastolic and most systolic functional parameters were similar between treated and nontreated animals, $E_{SV_{100}}$ was higher in the treated animals, which indicates that systolic function was also more severely impaired after COX-2 inhibition. Myocardial collagen density was found to be lower in the infarct area in the treated animals than in nontreated control animals. These findings correlate with higher mortality rates in the treated animals caused by LV ruptures and congestive heart failure.

Somewhat unexpected was that the $dP/dt_{max}$ did not decrease as a consequence of MI. We would speculate that this finding is...
due to the load-dependence of $\frac{dP}{dt_{\text{max}}}$ and a compensatory increase in end-diastolic volume, as reflected by the increased LV dimensions obtained by epicardial ultrasound. Ejection fractions of 40.2% and 36.6% in the nontreated and treated animals, respectively, do not point to end-stage heart failure. Nonetheless, COX-2 inhibition negatively influenced mortality, remodeling, and function in this model, which indicates that the inhibitor exerts a strong effect on these end points.

The occurrence and extent of LV remodeling after MI depend on multiple parameters, such as size and location of the infarct,19 mechanical forces, and matrix turnover.20 Location of the infarct in the present study was standardized, and infarct size was similar between treated and nontreated animals, which indicates that COX-2i–induced remodeling was independent of infarct size. COX-2 is known to be involved in cardiomyocyte protection in models of ischemia-reperfusion injury, and COX-2 inhibition increases infarct size in these models.21–23 In the present model of permanent coronary artery ligation, however, the probability of cardiomyocytes surviving the duration of the ischemia is minimal in the poorly collateralized porcine heart. Furthermore, COX-2i treatment was started the day after the induction of MI. An effect of COX-2 inhibition on infarct size in the present study was therefore not expected.

A decreased collagen density in the infarct zone induced by COX-2 inhibition was probably responsible for the promotion of expansive LV remodeling in the present study. Although the left

Figure 1. LV dimensions and systolic function. Myocardial wall thickness in the infarct area and the LV internal area were determined with epicardial ultrasound. The decrease in wall thickness (A) and the increase in LV internal area (B) as a percentage of the baseline value were more pronounced in treated animals than in control animals. In addition, end-diastolic and end-systolic volume 6 weeks after MI (C), as measured with a conductance catheter, were higher in treated animals than in controls, which indicates that COX-2i treatment promotes LV dilatation. $\text{ESV}_{100}$ was higher in treated animals (D), which indicates that systolic function was more severely impaired. Control: $n=8$; COX-2i: $n=7$. *$P<0.05$ compared with baseline value; †$P<0.05$ compared with control animals; ‡$P<0.01$ compared with control animals.

Figure 2. Representative myocardial infarct sections of control animals (A, C) and COX-2i–treated animals (B, D) 6 weeks after MI, stained with picrosirius red. With polarized light, sections of the COX-2i–treated animals were shown to contain a lower collagen density than sections from controls.
COX-2 inhibition in small-animal models preserved cardiac isoforms. In contrast to the results of the present study, selective remodeling is to be attributed to COX-1, COX-2, or both. It is unknown whether the effect of remodeling is to be attributed to COX-1, COX-2, or both. In the present study, we found no differences in collagen in the border and remote myocardium. Farcted myocardium in mice, whereas collagen in the infarct area increased interstitial collagen fraction was found in the noninfarcted myocardium. Differences in collagen in the border and remote myocardium. In the infarct area, however, collagen density was lower in the COX-2i-treated animals. Control: n=8; COX-2i: n=7. *P≤0.05 compared with control animals.

circumflex coronary artery was permanently ligated, the COX-2 inhibitor was also found within the infarct zone, 1 week after the start of the treatment, and could therefore have affected collagen turnover. We found no evidence, however, for COX-2i–induced differences in gelatinase and collagenase protein expression or in procollagen I and transforming growth factor-β mRNA expression. After coronary occlusion, cardiomyocytes residing in the perfusion territory of the infarct-related artery perish and are replaced by fibrous scar tissue. A decreased collagen density might have had a negative impact on the firmness of the myocardial scar, which facilitates remodeling driven by increasing wall stresses after MI. Enhanced infarct thinning and impaired function after MI has also been described for nonselective inhibition of cyclooxygenases.5–7 These inhibitors act on both COX-1 and COX-2, and it is unknown whether the effect on remodeling is to be attributed to COX-1, COX-2, or both isoforms. In contrast to the results of the present study, selective COX-2 inhibition in small-animal models preserved cardiac dimensions and improved function after MI,9,10 as well as after doxorubicin-induced heart failure.24 In those studies, however, other selective COX-2 inhibitors were used. Although it is unlikely that different COX-2 inhibitors produce fundamentally different outcomes, it cannot be completely excluded. A decreased interstitial collagen fraction was found in the noninfarcted myocardium in mice, whereas collagen in the infarct area had not been analyzed. In the present study, we found no differences in collagen in the border and remote myocardium.

### TABLE 2. Celecoxib Concentration in Pig Heart Tissue

<table>
<thead>
<tr>
<th>Pig No. and Group</th>
<th>Before Infarct</th>
<th>Remote Area</th>
<th>Border Area</th>
<th>Infarct Area</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 COX-2i</td>
<td>0</td>
<td>534</td>
<td>362</td>
<td>469</td>
</tr>
<tr>
<td>2 COX-2i</td>
<td>0</td>
<td>254</td>
<td>393</td>
<td>256</td>
</tr>
<tr>
<td>3 COX-2i</td>
<td>0</td>
<td>77</td>
<td>130</td>
<td>144</td>
</tr>
<tr>
<td>4 Control</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>5 Control</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

These discordant findings indicate that results in small animals cannot be extrapolated to larger animals with no reservations. The differences in mechanical forces may have influenced LV remodeling and underline the significance of using appropriate animal models before clinical application of new treatment modalities.

COX-2 inhibitors initially conquered the market because of a lower incidence of the gastrointestinal side effects associated with traditional nonsteroidal antiinflammatory drugs and aspirin. In addition, COX-2 inhibitors are capable of reducing the incidence of colonic polyps. A number of large, randomized, clinical trials have been undertaken in the last several years for this reason, and these have revealed that the use of these COX-2 inhibitors increases the risk of serious adverse cardiovascular side effects, such as MI and stroke, probably by inducing a prothrombotic state.11–13,25 This has even led to the voluntary withdrawal of the most frequently prescribed COX-2i, rofecoxib, from the market. Although other studies failed to show this effect,26–28 this has evoked vigorous discussion as to whether COX-2 inhibitors should continue to be used in patients at risk for cardiovascular events. Therefore, it is of major importance to carefully weigh the beneficial and adverse effects of COX-2 inhibitors. As mentioned above, COX-2 inhibition abolishes the cytoprotective function of COX-2 in the acute phase after MI. On the other hand, advantageous effects of COX-2 inhibitors are described with respect to endothelial function and atherogenesis,29–32 which formed the rationale for a potential use of selective COX-2 inhibitors in patients with coronary heart disease.33 The present study for the first time describes harmful effects of selective COX-2 inhibition on mortality, LV remodeling, and systolic function after acute MI. We must keep in mind, however, that COX-2 inhibition in the present study was initiated shortly after MI. Whether COX-2 inhibitors have similar effects when administered in a chronic phase of MI or before MI remain a subject for further investigation. We are also aware that celecoxib was administered to the animals in a relatively high dose; however, lower doses did not sufficiently inhibit COX-2 activity in pigs (data not shown). Furthermore, the dose was identical to 1 of the doses studied in 2 of the large clinical trials that provided data on the prothrombotic effect of celecoxib.11,26 Nonetheless, the information provided in the present report should be taken into consideration when one weighs the advantageous and disadvantageous properties of COX-2 inhibitors, particularly for patients at risk for cardiovascular disease.

In conclusion, in contrast to murine models of MI, in the pig, selective COX-2 inhibition increased mortality, enhanced LV remodeling, and impaired systolic function after MI. These adverse effects are attributed to diminished collagen fiber deposition in the healing infarct zone. Therefore, the present study provides additional motivation to be cautious when prescribing COX-2 inhibitors to patients who have had an MI.

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Disclosures

None.

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