Preferential Venoconstriction by Cyclooxygenase Inhibition In Vivo Without Attenuation of Nitroglycerin Venodilation

Thomas Münzel, MD, Duncan J. Stewart, MD, Jürgen Holtz, MD, and Eberhard Bassenge, MD

Because prostacyclin is a rather potent venodilator in vivo, we analyzed the effect of cyclooxygenase inhibition on venous tone in 14 anesthetized dogs during ganglionic and β-adrenergic blockade and atraumatic conditions. Effective vascular stiffness (a reciprocal of effective vascular compliance) as a variable of integrated venous tone was 0.30±0.01 mm Hg·kg/ml (n=35) and was augmented up to twofold by diclofenac (1, 3, and 10 mg/kg i.v.), ibuprofen (6 and 60 mg/kg), or indomethacin (5 mg/kg) parallel to augmentations in central venous pressure, while the rise in arterial pressure was less than half of the increase induced by equivenoconstrictor dosages of norepinephrine. After preconstriction by indomethacin or diclofenac, nitroglycerin (1.5 μg/kg/min) lowered effective vascular stiffness (by 24±2% or 23±5%, respectively), similarly as during preconstriction by norepinephrine (by 24±4%). Long-term cyclooxygenase inhibition (diclofenac 2×1 mg/kg/day for 4 days) did not modify arterial pressure, heart rate, or hematocrit levels in conscious dogs at rest, but it lowered plasma volume to 52.5±1.9 ml/kg (sham treatment: 59.1±1.6 ml/kg, p<0.05, n=4). In conclusion, venoconstriction by clinical dosages of cyclooxygenase inhibitors does not interfere with the venodilator action of nitroglycerin and is compensated chronically by adjustments of plasma volume. (Circulation 1988;78:407–415)

Inhibitors of the cyclooxygenase pathway are in common clinical usage for a wide variety of symptoms. Although their principle pharmacological action is to inhibit the formation of prostaglandin-mediated inflammation, it is known that they exhibit a variety of cardiovascular effects. Increases in arterial pressure and coronary constrictions in vivo and in vitro have been described; such increases may be relevant to the use of these inhibitors in patients with concomitant cardiovascular disease. However, the full spectrum of hemodynamic effects of the cyclooxygenase inhibitors (COI) is incompletely understood. Despite the recent demonstration of the important venodilator action of prostaglandins, little attention has been paid to the effects of COI on venous tone. Because changes in preload are instrumental in the modulation of symptoms both in congestive heart failure and angina pectoris, any tendency toward venoconstriction by COI might have important and potentially detrimental clinical implications. Furthermore, it has been suggested that the vasodilator effects of nitrates, which are paramount to their antianginal actions, might be mediated by nitrate-induced vascular prostacyclin synthesis, although this remains controversial. Therefore, the aim of the present investigation was twofold: to determine whether COI with different anti-inflammatory agents results in alterations in venous compliance in vivo, and to test the hypothesis whether nitroglycerin-induced venodilation is mediated by prostaglandin synthesis.

Materials and Methods

Animals and Experimental Preparation

In all, 14 dogs of either sex, weighing 17–40 kg (mean, 27±4 kg) were used repeatedly (two or three times) in different acute protocols as listed in Table 1, and they were used in an additional protocol with long-term pretreatment (see below) without repeating the same protocol in any dog. Intervals of at least 2 weeks were allowed between two consecutive protocols in the same dog. The protocols 5–7 required acute laparotomy in anesthesia for place-
ment of occlusive snares around arteries of the splanchnic bed or the hindquarter bed (Table 1). At the end of one of these protocols, the dogs were killed by an overdose of pentobarbital. Throughout the experimental period, the dogs were maintained on a standard diet containing 2–4 meq/kg Na⁺ daily with free access to tap water. They remained in a vigorous condition and were checked repeatedly for maintenance of body weight, rectal temperature, and hematocrit level. The care of the animals and the performance of experimental protocols were under the supervision of an independent veterinarian in strict accordance with the animal welfare regulations of the University of Freiburg and the recommendations of the American Physiological Society.

For each experimental protocol, the dogs were anesthetized with sodium pentobarbital (25 mg/kg and 2.5 mg/kg/hr i.v.) and were allowed to breathe spontaneously through an endotracheal tube. Repeated measurements of arterial blood gases and pH were performed, and values were kept within 35–43 mm Hg PCO₂, 75–90 mm Hg PO₂, and 7.37–7.44 pH by adjusting the infusion rate of anesthesia or by intravenous infusion of 8.4% sodium bicarbonate. Two peripheral intravenous lines were inserted for separate infusion sites. The femoral artery was punctured percutaneously for recording blood pressure and for changing blood volume. A second catheter was placed in the right atrium under fluoroscopic control for recording of central venous pressure.

Reflexes were minimized by ganglionic blockade (10 mg/kg and 10 mg/kg/hr hexamethonium, and 0.5 mg/kg methylatropine) and β-blockade (2 mg/kg nadolol). Heparin was administered intravenously (500 units/kg initial and 250 units/kg/hr maintenance). Saline and dextran were infused continuously, both at a rate of 2.5 ml/kg/hr after an initial infusion of 10 ml/kg during an equilibration period of 45 minutes. A 4-ml/kg volume of dextran (Macrodex) was exchanged for the same volume of blood, which was stored in a water bath at 37°C.

**Measurements**

Arterial and venous pressure were measured with Statham P23ID pressure transducers (Gould, Cleveland, Ohio) and recorded continuously on a Watanabe (Herrsching, FRG) linear recorder. Effective vascular compliance was measured as modified from Echt et al.; the stored blood (4 ml/kg) was injected into the abdominal aorta through the femoral artery catheter at a rate of 2 ml/kg/min. After 1 minute, the same volume was withdrawn. After another minute, the withdrawal procedure was repeated and followed by reinfusion in an identical manner. Thus, the total cycle time was 11 minutes (Figure 1). From the central venous pressure tracings recorded during these cycles, 12 readings at 1-minute intervals were obtained (integrating central venous pressure over several respiratory cycles for each measurement). For each cycle of volume change, a linear regression was calculated, relating the observed central venous pressure to the induced

**Table 1. Experimental Protocols With Ganglionic and β-Adrenergic Blockade, Diclofenac, Ibuprofen, and Norepinephrine**

<table>
<thead>
<tr>
<th>1 (n=5)</th>
<th>2 (n=5)</th>
<th>3 (n=6)</th>
<th>4 (n=5)</th>
<th>5 (n=4)</th>
<th>6 (n=6)</th>
<th>7 (n=4)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ganglionic + β-blockade</strong></td>
<td><strong>Ganglionic + β-blockade</strong></td>
<td><strong>Part A</strong></td>
<td><strong>Part A</strong></td>
<td><strong>Ganglionic + β-blockade</strong></td>
<td><strong>Ganglionic + β-blockade</strong></td>
<td><strong>Ganglionic + β-blockade</strong></td>
</tr>
<tr>
<td>Diclofenac 1 mg/kg</td>
<td>Ibuprofen 6 mg/kg</td>
<td>Norepinephrine 0.15 μg/kg/min</td>
<td>Norepinephrine 0.08 μg/kg/min</td>
<td>Diclofenac 10 mg/kg</td>
<td>Norepinephrine 0.15 μg/kg/min</td>
<td>Temporary splanchnic arterial occlusion and reperfusion</td>
</tr>
<tr>
<td>Diclofenac 3 mg/kg</td>
<td>Ibuprofen 60 mg/kg</td>
<td>Norepinephrine + nitroglycerin 1.5 μg/kg/min</td>
<td>Norepinephrine 0.15 μg/kg/min</td>
<td>Diclofenac 10 mg/kg</td>
<td>Norepinephrine + nitroglycerin 1.5 μg/kg/min</td>
<td>Temporary splanchnic arterial occlusion and reperfusion</td>
</tr>
<tr>
<td><strong>Part B</strong></td>
<td><strong>Ganglionic + β-blockade</strong></td>
<td><strong>Part B</strong></td>
<td><strong>Ganglionic + β-blockade</strong></td>
<td><strong>Ganglionic + β-blockade</strong></td>
<td><strong>Ganglionic + β-blockade</strong></td>
<td><strong>Ganglionic + β-blockade</strong></td>
</tr>
<tr>
<td>Diclofenac 10 mg/kg</td>
<td>Nitroglycerin 1.5 μg/kg/min</td>
<td>Indomethacin 5 mg/kg/min</td>
<td>Nitroglycerin 1.5 μg/kg/min</td>
<td>Indomethacin 5 mg/kg/min</td>
<td>Nitroglycerin 1.5 μg/kg/min</td>
<td>Indomethacin 5 mg/kg/min</td>
</tr>
</tbody>
</table>

*n, number of dogs used in each protocol.*
changes in blood volume. The effective vascular compliance of the total vascular bed was calculated as the inverse of the slope of this regression line (units: ml/mm Hg/kg).

Experimental Protocols

At each step of the acute protocols listed in Table 1, one cycle of volume change was performed to obtain a value of effective vascular compliance of the total vascular system (see Figure 1). COI were infused during 15 minutes, and 10 minutes were allowed for equilibration before the compliance measurement was performed. In protocols 3 and 4, we tested whether the nitroglycerin-induced reduction in venous tone is attenuated by COI. To this end, the COI administration was preceded by nor-epinephrine infusions. The higher infusion rate (0.15 μg/kg/min) was adjusted according to pilot experiments to yield an increase in slope of the pressure-volume relation (Figure 1) similar to that induced by the higher dosages of COI. Compliance measurements started 5 minutes after the onset of norepinephrine or nitroglycerin infusions. Eventual contributions of redistribution of cardiac output to the observed changes in effective vascular stiffness (EVS) were investigated in protocols 5–7. In protocols 5 and 6, the dogs had occlusive snares around the truncus coeliacus and the superior and inferior mesenteric arteries, implanted by acute laparotomy. In protocol 7, an additional occlusive snare was placed around the distal aorta proximal to the bifurcation. Before the start of the protocol, the abdomen was closed by sutures. The arteries were occluded by the snares, and compliance measurement was started 3 minutes later. After 15 minutes, the snares were released, and the beds were reperfused, and 20 minutes later, the compliance was measured again. After the end of the protocols 1–4, drug infusions were discontinued, protamine sulfate was given, the catheters were removed, and the animals were allowed to recover. After completing protocols 5–7, the dogs were killed by an overdose of anesthetic.

Before their use in the terminal protocols 5–7, four of the dogs were studied in an additional protocol that included long-term treatment by diclofenac, 1 mg/kg i.m., twice daily for 4 days. These dogs were trained to lie quietly on the experimental table. One carotid artery was translocated into a cutaneous loop in each dog. This artery could be punctured transcutaneously in the conscious dogs for recording of arterial pressure and for blood withdrawal. These dogs were studied in the conscious resting state at a control day, at days 3 and 4 of sham treatment (saline i.m., twice daily for 4 days) and at days 3 and 4 of diclofenac treatment. Four hours after the last intramuscular injection, the dogs rested for 30 minutes on the table; afterward, mean arterial pressure, heart rate, arterial hematocrit level, and plasma volume were measured. The latter was determined by 10 mg Evan’s blue i.v. (Sigma Chemical, Munich, FRG) and by semilogarithmic extrapolation of arterial plasma concentration at injection time from several plasma samples, analyzed photometrically at 578 nm, obtained 10–40 minutes after the injection. At 12–18 hours after the final diclofenac injection, these dogs were anesthetized and prepared for measurement of compliance under ganglionic and β-adrenergic blockade as described for protocols 1–7.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Protocol 1 (n=5)</th>
<th>Protocol 2 (n=5)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>1</td>
</tr>
<tr>
<td>Effective vascular stiffness (mm Hg · kg/ml)</td>
<td>0.32 ± 0.01</td>
<td>0.48 ± 0.01*</td>
</tr>
<tr>
<td>Central venous pressure (mm Hg)</td>
<td>1.1 ± 0.1</td>
<td>1.8 ± 0.2†</td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>96 ± 4</td>
<td>104 ± 6†</td>
</tr>
</tbody>
</table>

*p<0.01 vs. control, †p<0.05 vs. control.
FIGURE 2. Plot of changes in effective vascular stiffness (EVS) in relation to changes in mean arterial pressure (MAP) induced by cyclooxygenase inhibition (COI) or by norepinephrine (NE). ●, diclofenac 1 and 3 mg/kg (protocol 1, n=5), 10 mg/kg (protocols 3, 5, and 7, n=14); ■, ibuprofen 6 and 60 mg/kg (protocol 2, n=5); ▲, indomethacin 5 mg/kg (protocol 4, n=5); ○, norepinephrine (0.08 μg/kg/min, protocol 4, n=5), 0.15 μg/kg/min, protocols 3, 4, and 6, n=17). Regression line (r=0.76, n=20) is calculated from the data from protocols 1 and 2, in which COI was applied without any prior manipulation. COI data after laparotomy for snare application (protocols 5 and 7) or after infusions of norepinephrine and nitroglycerin (protocols 3 and 4) are marked by circles and do not deviate from this relation, indicating that the preferential vasoconstriction by COI (relative to NE) is probably no artifact induced by these manipulations.

Calculations and Drugs

Values of mean ± SEM are presented. For comparisons within a protocol, an analysis of variance for multiple comparisons within the same group followed by t test with Bonferroni's correction for the number of comparisons was applied. The following drugs and intravenous solutions were used: pentobarbital sodium (Ceva, Bad Segeberg, FRG), hexamethonium bromide and methylatropine (Merck, Darmstadt, FRG), nadolol (Von Heyden, Regensburg, FRG), heparin sodium (Hoffmann-La Roche, Grazenz-Wyhlen, FRG), l-norepinephrine HCl (Hoechst, Frankfurt, FRG), nitroglycerin (Pohl-Boskamp, Hohenlockstedt, FRG), diclofenac (CIBAGEigy, Basel, Switzerland), indomethacin (Sigma Chemical, Munich, FRG), ibuprofen (Klinge, Munich, FRG), protamine HCl (Hoffmann-La Roche, Grazenz-Wyhlen, FRG), sodium bicarbonate.

Table 3. Effects of Nitroglycerin During Norepinephrine or Cyclooxygenase Inhibition (Protocol 4, n=5)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control</th>
<th>Norepinephrine (0.08 μg/kg/min)</th>
<th>Norepinephrine (0.15 μg/kg/min)</th>
<th>Nitroglycerin (1.5 μg/kg/min)</th>
<th>Control</th>
<th>Indomethacin (5 mg/kg)</th>
<th>Nitroglycerin (1.5 μg/kg/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effective vascular stiffness</td>
<td>Control 0.31 ± 0.05</td>
<td>0.38 ± 0.06+</td>
<td>0.30 ± 0.03</td>
<td>0.58 ± 0.03†</td>
<td>0.43 ± 0.03†</td>
<td>0.34 ± 0.02</td>
<td>0.57 ± 0.04†</td>
</tr>
<tr>
<td>Central venous pressure</td>
<td>1.4 ± 0.4</td>
<td>2.9 ± 0.07†</td>
<td>1.2 ± 0.2</td>
<td>4.2 ± 0.6†</td>
<td>1.6 ± 0.3§</td>
<td>1.3 ± 0.1</td>
<td>3.0 ± 0.3†</td>
</tr>
<tr>
<td>Mean arterial pressure</td>
<td>88 ± 4</td>
<td>127 ± 4†</td>
<td>83 ± 7</td>
<td>152 ± 4†</td>
<td>131 ± 5§</td>
<td>99 ± 4</td>
<td>122 ± 4†</td>
</tr>
</tbody>
</table>

*p<0.05 vs. before control; †p<0.01 vs. control; ‡p<0.05 vs. constriction; §p<0.01 vs. constriction.

Results

Initial basal hemodynamic values under ganglionic and β-adrenergic blockade in anesthetized dogs through protocols 1–7 were total effective vascular compliance, 3.50 ± 0.15 ml/kg/mm Hg (n = 35); central venous pressure, 1.2 ± 0.1 mm Hg; mean arterial pressure, 91 ± 2 mm Hg; and heart rate, 126 ± 2 beats/min. Heart rate did not change consistently throughout any of the protocols.

Cyclooxygenase Inhibition

An example of the action of COI on the pressure-volume relation in the anesthetized dogs during pharmacological attenuation of autonomic cardiovascular control is given in Figure 1. COI augmented central venous pressure and the slope of the relation. Thus, COI reduced the total effective vascular compliance. To illustrate the vasoconstrictor effect of COI, the data on this relation are presented as the slope, that is, as effective vascular stiffness (EVS). COI by diclofenac (1 and 3 mg/kg) or by ibuprofen (6 and 60 mg/kg) dose dependently elevated EVS (Table 2) above the value found in untreated conscious dogs at rest (0.36 mm Hg · kg/ml).

Compared with the effects of norepinephrine infusion in the same model, the COI in protocols 1 and 2 caused preferential vasoconstriction. At dosages causing comparable elevations of EVS, the augmentation of mean arterial pressure induced by COI was less than half that of the elevation induced by norepinephrine (Figure 2). In other protocols with longer duration or with more traumatic manipulations, COI by indomethacin (5 mg/kg) or by diclofenac (10 mg/kg) caused comparably preferential vasoconstrictions (Figure 2). The rise in EVS induced by the highest dose of diclofenac (10 mg/kg, protocols 3, 5, and 7, n=14) was 87 ± 7%, which is similar to the respective rise induced by 60 mg/kg ibuprofen (98 ± 11%, protocol 2, n=5) and by 0.15 μg/kg/min norepinephrine (95 ± 13%, protocols 3, 4, and 6, n=17). However, the increase in mean arterial pressure was 8.4% (Delta Pharma, Pfulling, FRG), and dextran 60 (Makrodex, Schiw, Glandorf, FRG).
pressure induced by these dosages of the two inhibitors (34 ± 2% by ibuprofen and 34 ± 5% by diclofenac) was significantly (p < 0.01) less than the rise induced by high dosages of norepinephrine (73 ± 7%). The absolute data during norepinephrine-induced constrictions in the various protocols are shown in Table 3, Part A, and in Figures 3 and 4. In all protocols, the norepinephrine-induced augmentations were significant.

Nitroglycerin-Induced Venodilation

In dogs with ganglionic and β-adrenergic blockade during preconstriction by 0.15 μg/kg/min norepinephrine, the infusion of 1.5 μg/kg/min nitroglycerin caused significant (p < 0.01) declines in EVS (from 0.55 ± 0.03 to 0.41 ± 0.02 mm Hg·kg/ml, n = 11, Part A of protocols 3 and 4), in central venous pressure (from 4.4 ± 0.4 to 2.1 ± 0.3 mm Hg), and in mean arterial pressure (from 148 ± 5 to 128 ± 6 mm Hg). With the same dosage of nitroglycerin after preconstriction by diclofenac, EVS was lowered to a similar degree from 0.49 ± 0.05 to 0.37 ± 0.03 mm Hg·kg/ml (Figure 3B). In the dogs of protocol 3, the relative decline in EVS with nitroglycerin was 23 ± 5% after preconstriction by diclofenac and 24 ± 5% under preconstriction by norepinephrine. In the parallel protocol with indomethacin (Table 3), the nitroglycerin effect on EVS was not attenuated by COI either: a 24 ± 2% decline after indomethacin and a 24 ± 6% decline with norepinephrine. Because arterial pressure with preconstriction by norepinephrine was higher than after preconstriction by COI (Figures 2, 3, and 4), the nitroglycerin-induced declines in arterial pressures cannot be compared directly.

Redistribution of Cardiac Output

The effective vascular stiffness, as well as any other variable of overall venous tone in situ, can be modified substantially by changes in the distribution of cardiac output between organs with different venous compliances. In particular, any redistribution of perfusion between the splanchnic bed (a vascular bed with large volume and compliance and, hence, a large time constant for venous return) and the extravascular beds (with smaller volumes, compliances, and time constants for venous return) can affect the functional characteristics of the entire venous system without any real change in venous tone.16,17 Therefore, we compared the consequences of redistribution of cardiac output completely away from the splanchnic bed with the actions of COI or of norepinephrine in our anesthetized model under autonomic blockade (Figure 4). Under ganglionic and β-adrenergic blockade, the temporal occlusion of the arteries to the splanchnic organs reversibly augmented EVS by 23 ± 7% (protocols 5 and 6, n = 10, p < 0.05) concomitantly with elevations in mean arterial and central venous pressures (Figure 4). After a transient hypotension of several minutes with the onset of splanchnic reperfusion, normal basal values were obtained 15–20 minutes later (Figure 4). Later during protocols 5 and 6, constrictive venous and arterial responses to COI or to norepinephrine did not differ from the responses obtained in protocols without previous splanchnic occlusion (compare Figures 3 and 4), confirming previous observations in this model.18 However, the elevation in EVS during splanchnic
5. Elevations induced by or splanchnic occlusion (Figure 4). In EVS and compartment, as was prediction of EVS, see Figure 5), while the prevention of flow to the splanchnic bed lowered EVS (Figure 6).

**Long-term Cyclooxygenase Inhibition**

Treatment by diclofenac (1 mg/kg i.m., twice daily) for 4 days did not modify heart rate, mean arterial pressure, or hematocrit level in the resting conscious dogs (n = 4). Control heart rate was 94 ± 11 beats/min, and it amounted to 107 ± 6 and 100 ± 5 beats/min on the last 2 days of sham treatment and of diclofenac treatment, respectively. The corresponding values for mean arterial pressure and hematocrit level were 91 ± 4, 86 ± 4, and 82 ± 2 mm Hg and 40 ± 2%, 38 ± 2%, and 40 ± 3%, respectively. However, plasma volume on the last 2 days of diclofenac treatment was 52.5 ± 1.9 ml/kg, which was significantly (p<0.05) less than on sham treatment (59.1 ± 1.6 ml/kg). Control plasma volume was 55.8 ± 1.8 ml/kg. From 12 to 18 hours after the last diclofenac injection, these four dogs were studied during anesthesia, ganglionic and β-adrenergic blockade, and volume infusion as described in protocols 1–7. Heart rate was 122 ± 2 beats/min; mean arterial pressure was 62 ± 1 mm Hg, which was significantly (p<0.01) lower than mean arterial pressure in these four dogs in protocols without diclofenac pretreatment; CVP was 1.0 ± 0.1 mm Hg, and EVS was 0.49 ± 0.01 mm Hg · kg/min, which was significantly (p<0.01) higher than in protocols without pretreatment.

**Discussion**

In the anesthetized dogs under autonomic blockade, COI lowered the effective vascular compliance, or in other words, it increased EVS. However, it did not attenuate the action of nitroglycerin on this variable (Figure 3 and Table 3).

**Effective Vascular Compliance and Venous Tone**

Though the total effective vascular compliance in an intact organism mainly reflects the compliance of the venous system, measured changes in this variable do not necessarily reflect only changes in venous tone. Our recent analyses of the model used in the present study demonstrate that changes in mean arterial pressure, intravascular volume, and cardiac output do not affect significantly the measured changes in effective vascular compliance. Furthermore, the present protocols with splanchnic occlusion under ganglionic and β-adrenergic blockade (Figure 4) demonstrate that redistribution of cardiac output away from the splanchnic bed can at most account for only a small fraction of the increase in EVS observed during COI. Thus, other mechanisms must be largely responsible.
One such mechanism could be a progressive accumulation of interstitial fluid under the influence of COI. Elevation of interstitial fluid pressure has been shown to lower the compliance of peripheral veins. After the induction of heart failure with interstitial fluid accumulation in our canine model, the elevated EVS is not lowered by nitroglycerin (at a dosage similar to that used in the present study) or by a prostacyclin analogue. Similar observations have been made in patients with severe congestive heart failure unless diuretics are applied to get rid of the edema. However, in the present study, nitroglycerin rapidly and substantially lowered the EVS augmented by COI. Thus, elevated interstitial fluid pressure as a cause for the augmented stiffness after COI is excluded.

The experiments with temporal occlusion of the arterial supply to various beds (Figures 4 and 6) helped to localize the vascular bed in which most of the augmentation in venous tone must have occurred (Figure 5). These simple occlusion experiments under autonomic blockade qualitatively demonstrate that the observed changes in the overall compliance of the entire venous system are mainly determined by the changes in the venous compliance of the splanchnic bed. This is exactly in agreement with more sophisticated approaches for evaluating the venous system (for review, see Hainsworth). Furthermore, these occlusion experiments prove that the observed actions of nitroglycerin on EVS must reflect reductions in venous tone: the parallel reduction of CVP and EVS cannot be the consequence of redistribution of perfusion away from the splanchnic bed (for this would lower stiffness and augment venous pressure, see Figure 6) or from redistributing perfusion more toward the splanchnic bed (for this would augment stiffness without changing venous pressure, see Figure 6).

Based on this analysis, the following conclusions appear sound: 1) The data on EVS in the anesthetized dog demonstrate substantial venous constriction induced by COI, and this constriction occurs mainly in the veins of the splanchnic bed. The documentation of this venoconstriction under autonomic blockade argues for a direct vascular action of COI on the veins. Its documentation in an atraumatic model indicates that excessive prostaglandin activation due to extensive surgical manipulation and extracorporeal circuits is not a prerequisite for the induction of venoconstriction by COI. 2) The actions of nitroglycerin on EVS demonstrate real venodilation under preconstriction induced by COI or by norepinephrine. This allows testing the interactions of COI and nitroglycerin at the venous level (see below).

Cyclooxygenase Inhibition and Nitroglycerin

The interest in a potential involvement of prostacyclin in the antianginal actions of nitrates has been triggered by two types of observations: nitrate-induced prostacyclin formation in vitro by blood vessels and by cultured endothelial cells, and nitrate-induced augmentations in bleeding time and inhibitions in platelet function in vivo. Both observations are somewhat controversial and have not been confirmed in general, but any inhibitory action of COI on therapeutic actions of nitroglycerin would be of considerable importance.

By comparing the nitroglycerin-induced venodilation after COI with the control reaction to nitroglycerin starting from a similar, norepinephrine-induced venoconstriction (Figure 2 and Table 3), we could not identify any attenuation of nitrate venodilation by COI. The dosages of the inhibitors applied in our studyabolished the coronary resistance vessel dilation induced by intracoronary arachidonic acid, suppressed systemic cyclooxygenase activity and were sufficient to identify the role of prostaglandins in the renal vasodilation in response to hydralazine. Thus, it must be concluded that cyclooxygenase products are not involved in the venodilation induced by therapeutic dosages of nitroglycerin.

This conclusion is in agreement with recent observations in humans and animals, which could not identify any attenuation of vascular nitroglycerin actions by COI (a partial attenuation of coronary resistance vessel dilation in response to high nitroglycerin has only been observed in extensively manipulated, open-chest dogs).

Cyclooxygenase Inhibition and Angina

The reports by Miwa and coworkers have shown that antirheumatic dosages of COI can aggravate exertional angina in patients characterized as suffering from variant angina. Apart from constriction of large epicardial coronary arteries, COI...
augments coronary vascular resistance,3–7 though not consistently with all inhibitors,45 and raises the mean arterial pressure,2–7 all of which can contribute to an imbalance between myocardial oxygen demand and supply. With the COI-induced venoconstriction documented in this study, we identified another mechanism of COI, which could have contributed to the reported aggravation of angina.43,44

This venoconstriction is not drug specific (Figure 2) as was shown for the indomethacin-induced coronary constriction in humans,45 suggesting that the venoconstriction was indeed related to the inhibition of vascular cyclooxygenase. The venoconstriction might have resulted from the suppression of continuous formation of prostacyclin or of another dilatory prostanoid in the venous wall and from the shift of arachidonic acid metabolism toward lipooxygenase pathways.46 This venoconstriction by COI occurs in a rather atraumatic model with dosages well within the clinically applied range, but it remains unclear whether COI-induced venoconstriction and augmented ventricular filling occur in humans. Acute systemic venoconstriction, induced by increasing dosages of ergonovine, causes myocardial ischemia and angina in patients with stable angina.47 However, a large survey of clinical trials with indomethacin did not identify provocation of myocardial ischemia as a major problem in patients with angina.48

Several more recent studies in patients with stable angina could not demonstrate a lowered anginal threshold after COI with treadmill exercise or pacing as provocative tests.7,12,49 While these observations do not support the assumption of a COI-induced venoconstriction in humans, they cannot exclude this possibility. Normally, cyclooxygenase inhibitors in patients are not applied intravenously, which might be expected to trigger acute venoconstriction and angina. Under long-term COI, however, the state of the vascular low-pressure system may be comparable to its state in hypertension: in untreated essential hypertension, venous tone is higher than in normal probands, but this is largely balanced by a reduced intravascular volume in such a way that mean central venous pressure is close to normal.50 If a similar combination (i.e., augmented effective stiffness and reduced plasma volume) really existed under long-term COI in patients, this would explain why preload-triggered angina is seldom observed under this medication. However, it would also mean that a physiological volume stimulus (i.e., postprandial resorption) causes more preload elevation than normal. Preload elevation by blood volume expansion can trigger angina.51 Thus, even without chronically elevating preload, long-term COI would predispose to episodic preload-induced anginal attacks or worsening of heart failure. Our observations of reduced plasma volume and enhanced basal EVS in the dogs on diclofenac treatment for 4 days are in agreement with this hypothesis.

By and large, COI-induced venoconstriction may be only of marginal importance for provocation of ischemia, even assuming that it occurs in humans as in our model. However, the widespread use of these drugs requires careful testing to determine whether even marginally unfavorable actions, as identified in our model, might occur with their routine application in patients.

In conclusion, our study demonstrates that short-term COI by various drugs in antirheumatic dosages causes direct venoconstriction in an atraumatic in vivo model. This COI does not interfere with nitroglycerin-induced venodilation, arguing against a role of cyclooxygenase products in this therapeutically important action of nitroglycerin. Although a persistent venoconstriction under long-term COI may have only borderline importance for the myocardial demand-supply relation in coronary heart disease, it can contribute to masking and counteracting other potentially beneficial actions of COI.

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References


Key Words • cardiac preload • volume regulation • angina pectoris
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