Available online at www.sciencedirect.com
SCIENCE DIRECT
European Journal of Pharmacology 536 (2006) 296–300
www.elsevier.com/locate/ejphar

Prostaglandin I_2 release following mesenteric traction during abdominal surgery is mediated by cyclooxygenase-1

Michael Bucher [a,*], Frieder K. Kees [b], Barbara Meβmann [a], Dirk Lunz [a], Stephan Rath [a], Marek Zelenka [a], Hans J. Schlitt [c], Jonny Hobbhahn [a]

[a] Department of Anesthesiology, Regensburg University, 93042 Regensburg, Germany
[b] Department of Pharmacology, Regensburg University, 93042 Regensburg, Germany
[c] Department of Surgery, Regensburg University, 93042 Regensburg, Germany

Received 11 January 2006; received in revised form 20 February 2006; accepted 6 March 2006
Available online 13 March 2006

Abstract

Our study aimed to determine the role of cyclooxygenase-2 in the release of prostaglandin-(PG)-I_2 following mesenteric traction during abdominal surgery. In a prospective double-blind, randomized, placebo-controlled study, 40 patients electively scheduled for non-laparoscopic abdominal surgery, were pretreated with the cyclooxygenase-2 inhibitor parecoxib ($n=20$) or placebo ($n=20$). Heart rate, arterial blood pressure, oxygenation ratio and plasma concentrations of the stable PGI_2-metabolite 6-keto-$PGF_{1\alpha}$ were compared between groups before injection of parecoxib (−40 min), immediately before mesenteric traction (0 min), and 5, 10, and 30 min thereafter. In addition, plasma concentrations of valdecoxib, the active metabolite of the prodrug parecoxib, were determined. Plasma concentrations of 6-keto-$PGF_{1\alpha}$ and heart rate increased in both groups after mesenteric traction. There were no significant differences between groups at individual times in heart rate, arterial blood pressure and plasma concentrations of 6-keto-$PGF_{1\alpha}$. Oxygenation ratio decreased after 10 and 30 min following mesenteric traction in the parecoxib group with a significant difference between treatment groups at 10 and 30 min. Plasma concentrations of valdecoxib revealed therapeutic values. Our data indicate that PGI_2 release following mesenteric traction is mediated by cyclooxygenase-1.

Keywords: Mesenteric traction; Cyclooxygenase-inhibitor; Prostaglandin; Hemodynamics; Oxygenation

1. Introduction

Traction on the mesentery and eventeration of the bowel for exploration of the abdominal cavity during non-laparoscopic surgery is temporally related to arterial hypotension, tachycardia, decreased arterial pO_2 and facial flushing (Brinkmann et al., 1994; Gottlieb et al., 1989; Hudson et al., 1990, 1988; Seeling et al., 1986; Seltzer et al., 1988, 1985). These symptoms describe the mesenteric traction syndrome. The vasodilatory prostanoid prostaglandin-(PG)-I_2 has been identified as the cause for the changes in hemodynamics and oxygenation.

Accordingly, pretreatment of patients with the non-selective cyclooxygenase (COX) inhibitor ibuprofen has been shown to prevent the increase of plasma concentrations of 6-keto-$PGF_{1\alpha}$, the stable metabolite of PGI_2, as well as the changes in oxygenation and hemodynamics after mesenteric traction (Brinkmann et al., 1994; Hudson et al., 1990). Two isoforms of COX have been identified so far. COX-1 is ubiquitously and constitutively expressed in mammalian tissues and cells, whereas COX-2 is highly inducible and is generally present in mammalian tissues at very low levels, unless increased by one of various stimuli such as cytokines or growth factors (Chandrasekharan and Simmons, 2004; Simmons et al., 2004). Immunhistochemical studies, however, demonstrated noteworthy basal COX-2 expression in the stomach as well as in the adventitial and endothelial layers of mesenteric arteries (Iseki, 1995; Tabernero et al., 2003). Therefore, the question arises whether PGI_2 release in response to mesenteric traction is possibly COX-2-dependent. Accordingly, we performed a study to determine if pretreatment with parecoxib, the prodrug of the

* Corresponding author. Tel.: +49 941 944 7801; fax: +49 941 944 7802.
E-mail address: michael.bucher@klinik.uni-regensburg.de (M. Bucher).

0014-2999/$ - see front matter © 2006 Elsevier B.V. All rights reserved.
doi:10.1016/j.ejphar.2006.03.009

Table 1
Patient characteristics

	Placebo (n=20)	Parecoxib (n=20)	
Age (years)	60±3	58±3	ns
Gender (F/M)	8/12	8/12	ns
BMI (kg/m^2)	26±0.8	27±0.9	ns
ASA I/II/III	4/11/5	0/18/2	ns
EDA	8	5	ns

Data are given as mean±S.E.M., body mass index (BMI), ASA physical status (ASA), epidural anaesthesia (EDA), not significant (ns).

COX-2 inhibitor valdecoxib, would prevent the PGI_2 release associated with mesenteric traction.

2. Methods

2.1. Patients and study design

With the approval of the authors' institutional human investigation committee and written informed consent, 40 adult patients scheduled for elective abdominal non-laparoscopic surgery were studied according to a prospective, randomized, double-blind, placebo controlled protocol. No patient was taking any steroidal or non-steroidal anti-inflammatory drug including aspirin that could influence the expression or activity of cyclooxygenases. Premedication with clorazepam (Tranxilium®, 20–30 mg) was given orally in the evening prior to surgery. 13 patients (8 placebo group, 5 parecoxib group) received supplementary continuous, thoracic epidural anaesthesia with ropivacaine 0.75% and sufentanil gaining a sensory blockade from about T4 to L2. Anaesthesia was induced with propofol 2–3 mg/kg i.v. and fentanyl 3–5 μg/kg i.v. without nitrous oxide. Tracheal intubation was facilitated after injection of rocuronium 0.6 mg/kg i.v. Anaesthesia was maintained with sevoflurane or desflurane and supplemented with fentanyl i.v. or ropivacaine epidural according to the patients' individual needs. Approximately 40 min prior to mesenteric traction, patients received parecoxib 0.6 mg/kg i.v. (Dynastat®, n=20) or placebo (saline, n=20). Heart rate and invasive radial arterial blood pressure were recorded by a Sirecust 9000 monitor (Siemens). Arterial pO_2 was measured in heparinized whole blood using the blood gas analyzer Rapidpoint™ 405 (Bayer) and fraction of inspired oxygen (FiO_2) was determined. Oxygenation ratio was calculated as quotient of arterial pO_2 and FiO_2. Hemodynamic measurements were performed and arterial blood samples were obtained 40 min prior to drug administration (−40 min), immediately prior to mesenteric traction (0), and 5, 10 and 30 min thereafter. Blood samples for prostaglandin and drug measurement were drawn in Lithium–Heparin monovettes (Sarstedt) containing indomethacin (0.2 mg/4 ml whole blood) in order to inhibit an ex vivo prostanoid synthesis (Brinkmann et al., 1994). Urine was collected at the time intervals −40 to 0 and 0 to 30 min. Blood specimens were centrifuged immediately, and plasma and urine were stored at −70 °C until assay.

2.2. Determination of 6-keto-$PGF_{1\alpha}$ in plasma and urine

6-keto-$PGF_{1\alpha}$ in plasma and urine was determined using a commercially available kit (Cayman Chemical). All samples (appropriate diluted plasma and urine samples, and standard curve samples) were assayed in duplicate. The precision was better than 20%, the detection limit was 11 pg/ml.

2.3. Determination of creatinine in urine

Urine concentration of creatinine was determined using the Jaffé method (Schneiderka et al., 1993).

2.4. Determination of parecoxib and valdecoxib

Parecoxib and the active metabolite valdecoxib were determined by high performance liquid chromatography (HPLC) with photometric detection at 210 nm adapting a published method (Ramakrishna et al., 2004). Briefly, 200 μl plasma was mixed with 20 μl rofecoxib 50 μg/ml (internal standard) and 400 μl acetonitrile. The precipitated protein was spun down, and 10 μl of the supernatant were injected into the HPLC system (Type LC-10A, Shimadzu). Separation was performed using a Synergi Polar-RP column (Phenomenex) with 20 mM sodium phosphate buffer/acetonitrile 60:40 (v/v) pH 6.3 as mobile phase. Parecoxib eluted after 5.6 min, rofecoxib after 8.4 min and valdecoxib after 10.3 min (flow rate 1.0 ml/min, column temperature 30 °C). Indomethacin added as preservative (Brinkmann et al., 1994) eluted after 6.3 min. Quality assessment gave the following specifications: Spiked dilution series demonstrated linearity of the assay with r>0.9995 (parecoxib) and r>0.9996 (valdecoxib), respectively, down to 0.1 mg/l parecoxib and 0.2 mg/l valdecoxib which were taken as limits of quantification. The lower limit of detection was 200 pg (parecoxib) or 250 pg (valdecoxib) injected onto the column. The precision determined processing spiked plasma samples with each assay (n=5) was better than 10% (level 3 and 0.3 μg/ml parecoxib and 6 and 0.6 μg/ml valdecoxib, respectively). The accuracy was better than 5%.

2.5. Statistics

Primary endpoint of the study was the plasma concentration of 6-keto-$PGF_{1\alpha}$ at a fixed time point of 10 min after eventeration. A

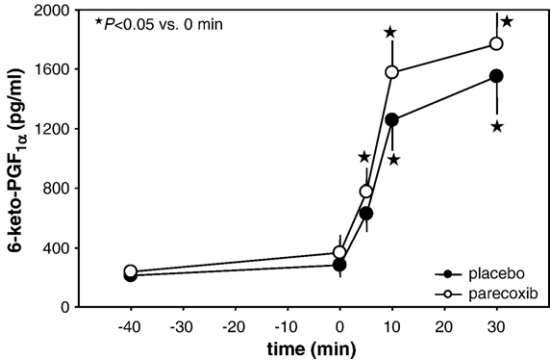

Fig. 1. Plasma concentrations of 6-keto-$PGF_{1\alpha}$ before and after mesenteric traction in the placebo group and the parecoxib group. Time zero is immediately before mesenteric traction. Means±S.E.M. of 20 patients per group; ★P<0.05 vs. 0 min.

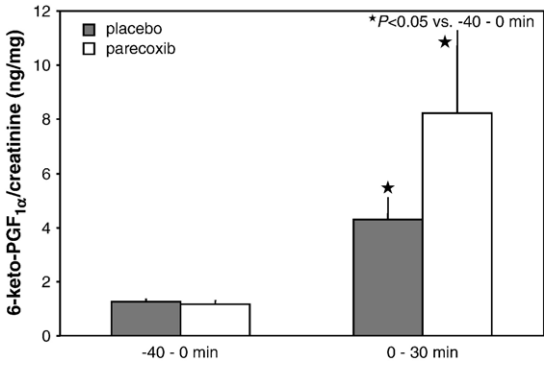

Fig. 2. Urinary excretion of 6-keto-$PGF_{1\alpha}$ before and after mesenteric traction in the placebo group and the parecoxib group. Time zero is immediately before mesenteric traction. Concentration of 6-keto-$PGF_{1\alpha}$ is referred to the concentration of creatinine in the same urine fractions. Means±S.E.M. of 20 patients per group; $^{\star}P<0.05$ vs. −40–0 min.

power calculation ($\alpha=0.05$, power 80%) based on published data (Brinkmann et al., 1994; Hudson et al., 1990) estimated the need for 17 patients in each group to detect a clinically meaningful difference in the plasma concentrations of 6-keto-$PGF_{1\alpha}$ of 400 vs. 100 pg/ml between placebo and parecoxib with estimated group standard deviation of 400 and 100 pg/ml, respectively, using a two-sided two sample *t*-test (Hintze J (2001) NCSS and PASS. Number Cruncher Statistical Systems. Kaysville, Utah).

Statistical analysis was performed with SPSS 12.0. Data are expressed as mean±S.E.M. Demographic data and treatment effects were analyzed by unpaired *t*-test. Variation of data over time was analyzed by analysis of variance (ANOVA) for repeated measurements. $P<0.05$ was considered significant.

3. Results

The patient characteristics are shown in Table 1. There were no differences between treatment groups in age, gender, body mass index (BMI), The American Society of Anesthesiologists' (ASA) physical status, or concomitant drug medication concerning β-adrenergic-receptor antagonists, angiotensin converting enzyme inhibitors, AT_1-receptor antagonists, calcium antagonists, diuretics or β-adrenergic-receptor agonists.

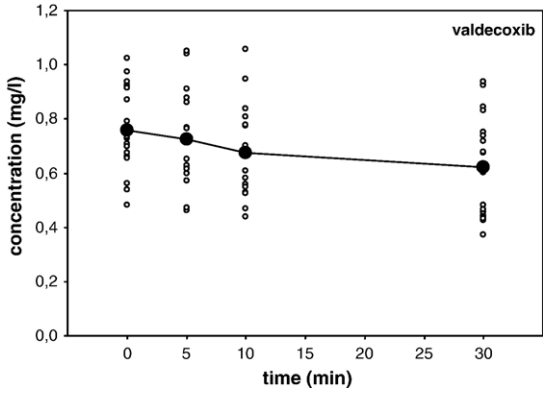

Fig. 3. Individual (open circles) and mean (closed circles) plasma concentrations of valdecoxib in the parecoxib group ($n=20$). Time zero is immediately before mesenteric traction.

Table 2
Heart rate, arterial blood pressure and oxygenation ratio before and after mesenteric traction in the placebo group and the parecoxib group

	Group	−40 min	0 min	5 min	10 min	30 min
HR (min^{-1})	Placebo	63±2	61±3	67±3	74±4[a]	76±3[a]
	Parecoxib	61±4	58±3	68±3[a]	76±3[a]	75±3[a]
BP_{mean} (mm Hg)	Placebo	71±4	76±3	85±3	81±3	82±3
	Parecoxib	71±2	73±4	80±3	78±4	77±2
PaO_2/FiO_2 (mm Hg)	Placebo	456±21	452±29	439±26	425±25	415±25
	Parecoxib	398±29	384±26	364±26	333±29[a,b]	316±31[a,b]

Values are mean±S.E.M., $n=20$ per group, heart rate (HR), mean arterial blood pressure (BP_{mean}), time zero is immediately before mesenteric traction, [a]$P<0.05$ vs. 0 min, [b]$P<0.05$ vs. placebo.

3.1. 6-keto-$PGF_{1\alpha}$ in plasma and urine

Plasma concentrations of 6-keto-$PGF_{1\alpha}$ were increased 5, 10, and 30 min following mesenteric traction (Fig. 1). Also urine excretion of 6-keto-$PGF_{1\alpha}$ was increased 0–30 min post-dose compared to −40–0 min pre-dose (Fig. 2). There were no significant differences between groups at individual times in 6-keto-$PGF_{1\alpha}$.

3.2. Parecoxib and valdecoxib in plasma

Plasma concentrations of valdecoxib are shown in Fig. 3. The mean plasma concentrations of parecoxib were 0.19 and 0.12 mg/l at times 0 and 5 min after mesenteric traction and were below the limit of quantification thereafter.

3.3. Hemodynamic measurements and oxygenation ratio

Heart rate was increased 5, 10, and 30 min following mesenteric traction in both groups without a significant change in arterial blood pressure. There were no significant differences between groups at individual times in heart rate and blood pressure (Table 2).

Oxygenation ratio was decreased 10 and 30 min after mesenteric traction in the parecoxib group accompanied by a difference in oxygenation ratios between both groups. However, oxygenation ratios tended to be lower in the parecoxib group before study medication (−40 min, $P=0.11$) indicating

Table 3
Heart rate and arterial blood pressure before and after mesenteric traction in patients without (∅ EDA, $n=27$) or with supplementary thoracic epidural anaesthesia (EDA, $n=13$)

	Group	−40 min	0 min	5 min	10 min	30 min
HR (min^{-1})	∅ EDA	64±3	60±2	69±3[a]	78±3[a,b]	80±3[a,b]
	EDA	58±4	59±3	64±3	67±3	67±3
BP_{mean} (mm Hg)	∅ EDA	71±3	74±3	85±3[a]	83±3[a]	83±2[a,b]
	EDA	72±5	77±6	78±4	73±4	73±3

Values are mean±S.E.M., heart rate (HR), mean arterial blood pressure (BP_{mean}), time zero is immediately before mesenteric traction, [a]$P<0.05$ vs. 0 min, [b]$P<0.05$ vs. EDA.

a possible preexisting difference between treatment groups (Table 2).

There was a significant increase in heart rate in patients without epidural anaesthesia in contrast to patients with supplementary thoracic epidural anaesthesia. Also mean arterial blood pressure increased significantly in patients without epidural anaesthesia, whereas the blood pressure remained stable in patients with supplementary epidural anaesthesia (Table 3).

4. Discussion

Several studies demonstrated an increase in mean plasma concentrations of 6-keto-$PGF_{1\alpha}$ up to 950 pg/ml (Krausz et al., 1983), 1169 pg/ml (Seeling et al., 1986), 1689 pg/ml (Hudson et al., 1988), 1950 pg/ml, 2955 pg/ml (Brinkmann et al., 1994), 3168 pg/ml (Seltzer et al., 1988) or 3179 pg/ml (Hudson et al., 1990) after traction to the bowel. These values for untreated patients are comparable to the plasma values for 6-keto-$PGF_{1\alpha}$ we found after mesenteric traction. PGI_2 is generated and released from the gastrointestinal mucosa and different layers of the arterial wall (Moncada et al., 1977, 1978). Pretreatment of patients with non-selective COX inhibitors such as ibuprofen or aspirin prevented the PGI_2 release associated with mesenteric traction (Brinkmann et al., 1994; Hudson et al., 1990; Krausz et al., 1983; Seltzer et al., 1988). However, routine premedication with ibuprofen or aspirin of patients scheduled for transperitoneal abdominal surgery is not recommended due to a possible impairment of coagulation. Selective COX-2 inhibitors would be a reasonable alternative medication. Certainly a constitutively COX must be responsible for PGI_2 formation, since its release is instantaneous. Reports of a substantial basal COX-2 expression in the adventitial and endothelial layer of small mesenteric arteries (Tabernero et al., 2003) as well as in the stomach (Iseki, 1995) focused our interest on the impact of this isozyme on PGI_2 formation after mesenteric traction. To address this issue we performed the present double-blind, placebo-controlled trial with 40 patients who received parecoxib or placebo about 40 min prior to surgery according to a randomized protocol. Parecoxib is a water-soluble prodrug and releases the active metabolite valdecoxib within 15 min. Peak plasma concentrations of 0.45 mg/l valdecoxib were observed 0.5 h after intravenous injection of 20 mg parecoxib (Cheer and Goa, 2001). In agree with these published data we measured mean plasma concentrations of valdecoxib of 0.76 mg/l (=2.42 μmol/l) right before mesenteric traction i.e., 40 min following parecoxib 40 mg. Thus, the concentrations of valdecoxib in the present study were in the expected therapeutic range and should have been sufficiently high to inhibit COX-2 (Cheer and Goa, 2001).

Our results demonstrate that COX-2 inhibition does not affect PGI_2 release in response to traction to the bowel. This indicates no relevant role of COX-2 and a predominant role of COX-1 for the PGI_2 formation after mesenteric traction, as nonselective COX inhibitors prevented PGI_2 release (Brinkmann et al., 1994; Hudson et al., 1990; Seeling et al., 1986).

In addition, non-selective COX inhibitors blunted the hemodynamic changes (Brinkmann et al., 1994; Hudson et al., 1990) associated with mesenteric traction such as reduced systemic vascular resistance (Gottlieb et al., 1989; Hudson et al., 1990, 1988; Seltzer et al., 1988, 1985), reduced arterial blood pressure (Brinkmann et al., 1994; Gottlieb et al., 1989; Seltzer et al., 1988, 1985; Woehlck et al., 2004), increased heart rate (Brinkmann et al., 1994; Gottlieb et al., 1989; Hudson et al., 1990, 1988; Seeling et al., 1986; Seltzer et al., 1985), and increased cardiac index (Gottlieb et al., 1989; Hudson et al., 1990, 1988; Seltzer et al., 1988, 1985), revealing PGI_2 as the possible mediator of the cardiovascular changes in response to mesenteric traction. In the present study, mesenteric traction resulted in a significant PGI_2 release which was accompanied by an increase of heart rate but without arterial hypotension. These data as well as findings that arterial hypotension is reversed within 30 min after mesenteric traction, even though plasma levels of PGI_2 are still markedly elevated, question the role of PGI_2 in mediating arterial hypotension (Brinkmann et al., 1994, 1998; Hudson et al., 1990). There are some studies that do not report a significant decrease in arterial blood pressure after traction to the bowel (Brinkmann et al., 1998; Hudson et al., 1990; Seeling et al., 1986). One could assume that a possibly decreased systemic vascular resistance due to elevated levels of the vasodilatory prostanoid PGI_2 may have been counterbalanced by the increased heart rate with consecutively increased cardiac index. In addition, there are many other factors that could influence arterial blood pressure during surgery such as depth of anaesthesia, intravasal volume status or activity of endogenous vasopressor agents. Increased plasma concentrations of epinephrine, vasopressin and renin have been reported after mesenteric traction (Brinkmann et al., 1998) which could compensate for the arterial hypotension. The hypothesis that the hemodynamic changes in our study are caused by sympathetic stimulation possibly due to inadequate analgesia rather than by increased PGI_2 release is strengthened by the finding that increase of arterial blood pressure and heart rate predominantly occurred in patients without thoracic epidural anaesthesia.

In addition, with respect to the rarity of severe hemodynamic changes there might be a very small subpopulation of patients, which develops severe hypotension following mesenteric traction and which has not been encountered in our study. This subgroup of patients may respond differently to COX inhibitors which represents a limitation of a study population of this size.

Oxygenation is reportedly impaired after mesenteric traction. The decrease of arterial oxygen tension has been shown to be inversely correlated with plasma levels of 6-keto-$PGF_{1\alpha}$ (Seeling et al., 1986), and was prevented by pretreatment of patients with non-selective COX inhibitors (Brinkmann et al., 1994). In the present study oxygenation ratio decreased significantly in the parecoxib group. This is in accordance with data in the literature since in our study plasma levels of 6-keto-$PGF_{1\alpha}$ tended to be higher in the parecoxib group compared to the placebo group. In addition, oxygenation ratio was significantly lower 10 and 30 min after mesenteric traction in the parecoxib group.

This is the first clinical study investigating the role of COX-2 for the PGI_2 formation following mesenteric traction. Our data

show a strong increase of PGI_2 release after traction to the bowel which was not influenced by pretreatment of patients with a selective COX-2 inhibitor. We conclude that mesenteric traction-induced PGI_2 formation during abdominal surgery is mediated by COX-1.

Acknowledgements

The expert technical assistance provided by Gertraud Wilberg is gratefully acknowledged.

References

Brinkmann, A., Seeling, W., Wolf, C.F., Kneitinger, E., Junger, S., Rockemann, M., Oettinger, W., Georgieff, M., 1994. The effect of thoracic epidural anesthesia on the pathophysiology of the eventration syndrome. Anaesthesist 43, 235–244.

Brinkmann, A., Seeling, W., Wolf, C.F., Kneitinger, E., Schonberger, C., Vogt, N., Orend, K.H., Buchler, M., Radermacher, P., Georgieff, M., 1998. Vasopressor hormone response following mesenteric traction during major abdominal surgery. Acta Anaesthesiol. Scand. 42, 948–956.

Chandrasekharan, N.V., Simmons, D.L., 2004. The cyclooxygenases. Genome Biol. 5, 241.

Cheer, S.M., Goa, K.L., 2001. Parecoxib (parecoxib sodium). Drugs 61, 1133–1141 (discussion 1142–1133).

Gottlieb, A., Skrinska, V.A., O'Hara, P., Boutros, A.R., Melia, M., Beck, G.J., 1989. The role of prostacyclin in the mesenteric traction syndrome during anesthesia for abdominal aortic reconstructive surgery. Ann. Surg. 209, 363–367.

Hudson, J.C., Wurm, W.H., O'Donnell Jr., T.F., Shoenfeld, N.A., Mackey, W.C., Callow, A.D., Su, Y.F., Watkins, W.D., 1988. Hemodynamics and prostacyclin release in the early phases of aortic surgery: comparison of transabdominal and retroperitoneal approaches. J. Vasc. Surg. 7, 190–198.

Hudson, J.C., Wurm, W.H., O'Donnel Jr., T.F., Kane, F.R., Mackey, W.C., Su, Y.F., Watkins, W.D., 1990. Ibuprofen pretreatment inhibits prostacyclin release during abdominal exploration in aortic surgery. Anesthesiology 72, 443–449.

Iseki, S., 1995. Immunocytochemical localization of cyclooxygenase-1 and cyclooxygenase-2 in the rat stomach. Histochem. J. 27, 323–328.

Krausz, M.M., Utsunomiya, T., McIrvine, A.J., Allen, P.D., Levine, L., Mannick, J.A., Shepro, D., Hechtman, H.B., 1983. Modulation of cardiovascular function and platelet survival by endogenous prostacyclin released during surgery. Surgery 93, 554–559.

Moncada, S., Herman, A.G., Higgs, E.A., Vane, J.R., 1977. Differential formation of prostacyclin (PGX or PGI2) by layers of the arterial wall. An explanation for the anti-thrombotic properties of vascular endothelium. Thromb. Res. 11, 323–344.

Moncada, S., Salmon, J.A., Vane, J.R., Whittle, B.J., 1978. Formation of prostacyclin and its product 6-oxo-PGF1alpha by the gastric mucosa of several species [proceedings]. J. Physiol. 275, 4P–5P.

Ramakrishna, N.V., Vishwottam, K.N., Wishu, S., Koteshwara, M., 2004. Quantitation of Valdecoxib in human plasma by high-performance liquid chromatography with ultraviolet absorbance detection using liquid–liquid extraction. J. Chromatogr. B Anal. Technol. Biomed. Life. Sci. 802, 271–275.

Schneiderka, P., Pacakova, V., Stulik, K., Kloudova, M., Jelinkova, K., 1993. High performance liquid chromatographic determination of creatinine in serum, and a correlation of the results with those of the Jaffe and enzymic methods. J. Chromatogr. 614, 221–226.

Seeling, W., Heinrich, H., Oettinger, W., 1986. The eventration syndrome: prostacyclin liberation and acute hypoxemia due to eventration of the small intestine. Anaesthesist 35, 738–743.

Seltzer, J.L., Ritter, D.E., Starsnic, M.A., Marr, A.T., 1985. The hemodynamic response to traction on the abdominal mesentery. Anesthesiology 63, 96–99.

Seltzer, J.L., Goldberg, M.E., Larijani, G.E., Ritter, D.E., Starsnic, M.A., Stahl, G.L., Lefer, A.M., 1988. Prostacyclin mediation of vasodilation following mesenteric traction. Anesthesiology 68, 514–518.

Simmons, D.L., Botting, R.M., Hla, T., 2004. Cyclooxygenase isozymes: the biology of prostaglandin synthesis and inhibition. Pharmacol. Rev. 56, 387–437.

Tabernero, A., Reimund, J.M., Chasserot, S., Muller, C.D., Andriantsitohaina, R., 2003. Cyclooxygenase-2 expression and role of vasoconstrictor prostanoids in small mesenteric arteries from patients with Crohn's disease. Circulation 107, 1407–1410.

Woehlck, H., Antapli, M., Mann, A., 2004. Treatment of refractory mesenteric traction syndrome without cyclooxygenase inhibitors. J. Clin. Anesth. 16, 542–544.