Inhibition of nitric oxide synthase reverses changes in peritoneal permeability in a rat model of acute peritonitis

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Background. Acute peritonitis is the most frequent complication of peritoneal dialysis (PD), and nitric oxide (NO) is thought to play a role in the structural and permeability changes observed in this condition. We have used a combination of expression, enzymatic and pharmacological studies to substantiate the potential role(s) played by NO during peritonitis.

Methods. The peritoneal equilibration test was performed in control rats and rats with acute peritonitis (originating from skin flora), using standard dialysate supplemented or not with the NO synthase (NOS) inhibitor N^G^-nitro-L-arginine methyl ester (L-NAME). In parallel, peritoneal NOS enzymatic activities were measured and expression studies for NOS isoforms and S-nitrosocysteine reactivity performed in the peritoneum.

Results. In comparison with controls, rats with acute peritonitis were characterized by inflammatory changes, increased S-nitrosocysteine immunoreactivity, and increased NOS activities in the peritoneum, due to the up-regulation of endothelial and inducible NOS. In parallel, rats with acute peritonitis showed increased permeability for small solutes; decreased sodium sieving; loss of ultrafiltration (UF); and increased protein loss in the dialysate. Addition of L-NAME to the dialysate did not induce permeability changes in control rats, but significantly improved UF and reversed permeability modifications in rats with peritonitis. The effect of L-NAME was reflected by a mild but consistent increase in blood pressure during PD exchange.

Conclusions. Our results demonstrate that local generation of NO, secondary to up-regulation of NOS isoforms, plays an important role in the regulation of peritoneal permeability during acute peritonitis in rats. By itself, NOS inhibition improves UF and reverses permeability changes, which might offer new therapeutic perspectives in acute peritonitis.

Acute peritonitis remains the most frequent and serious complication of peritoneal dialysis (PD) [1]. The functional modifications observed during acute peritonitis include a major increase in permeability for small solutes and glucose, leading to a faster than normal dissipation of the osmotic gradient, a decrease of free-water permeability, and a loss of ultrafiltration (UF) [2]. Fundamentally, the transport of solutes across the peritoneum during PD depends on the intrinsic permeability of the membrane to each solute and the effective peritoneal surface area (EPSA), characterized by the number of perfused capillaries within the peritoneum [3]. In view of its role in the regulation of vascular tone and permeability [4] and its interference with growth factors to promote angiogenesis [5, 6], nitric oxide (NO) is increasingly considered as a key mediator of peritoneal permeability [7–9]. This hypothesis has been supported by experiments showing an increase in peritoneal permeability with the NO donor nitroprusside in animal models [10] and stable PD patients [11].

Nitric oxide is produced from L-arginine by a family of NO synthase (NOS) isoforms that are expressed in a large variety of tissues and cells [4, 6]. The neuronal and endothelial NOS (nNOS and eNOS, respectively) are constitutive isoforms and their activity depends on the intracellular concentration of Ca^{2+}. Inducible NOS (iNOS) is regulated at a transcriptional level and its activity is independent of Ca^{2+} [4]. Previous studies have shown that the three NOS isoforms are expressed in the peritoneum, and a significant NOS activity can be detected in peritoneum extracts [7, 9, 12]. The putative role played by NO during PD across the normal, non-infected peritoneum remains controversial. Functional studies in rats have shown that addition of the NOS inhibitor N^G^-nitro-L-arginine methyl ester (L-NAME) to the dialysate does not affect the permeability to small solutes [13]. Addition of another NOS inhibitor (N^G^-monomethyl-L-arginine, L-NMMA) to the dialysate did not affect peritoneal permeability in a chronic PD model in rabbits [14]. In contrast, it has been suggested that permeability modifications during acute peritonitis might be the consequence...
of increased NO production [7, 8]. This hypothesis was recently supported by studies demonstrating increased NOS activity and up-regulation of eNOS and iNOS during peritonitis [9].

The aim of this study was to perform a series of functional, biochemical and expression studies to test the effects of a specific inhibitor of NOS in a well-characterized rat model, in order to substantiate the role of NO in the regulation of peritoneal permeability.

METHODS

Rat model, PD protocol, tissue sampling

Adult (8-week-old) male Sprague-Dawley rats (Iffa Credo, Brussels, Belgium) weighing 279 ± 2 g were randomly assigned to control and peritonitis groups. As previously described [9], peritonitis was induced by non-sterile implantation of a peritoneal catheter under anesthesia with SC Nembutal® (Sanofi, Brussels; day 1) followed for six days by a daily two-hour exchange with 15 mL of 1.36% glucose dialysate (Dianeal®; Baxter, Nivelles, Belgium). Both catheter insertion and PD exchanges were performed without aseptic precautions, in order to reflect manipulation errors and touch contamination from the skin flora in PD patients [15]. Control rats matched for age and weight were left untouched for six days. All rats had access to standard chow and tap water ad libitum. On day 7, control and peritonitis rats were anesthetized to perform a two-hour exchange PD with 15 mL of a 7% glucose dialysate (Dianeal) as described previously [9]. The NOS inhibitor L-NAME (Sigma, St. Louis, MO, USA) was added to the dialysate at concentrations ranging from 2.5 to 10 mmol/L, immediately before instillation. Preliminary experiments have verified that variations of pH and osmolality corresponding to the different L-NAME concentrations in the dialysate [13] do not influence peritoneal parameters in rats. Blood pressure was measured by means of a transducer (Pressure Set Uniflow type 43-600F; Bentley Laboratories Europe, Uden, The Netherlands) implanted in the carotid artery and connected to a Linearcorder polygraph (Ankersmit, Groot-Bijgaarden, Belgium). Blood and dialysate samples were obtained before (T0), at 30 minutes (T30), 60 minutes (T60), and 120 minutes (T120) of dwell time. Creatinine, hematocrit, glucose, sodium, potassium, total protein, osmolality, and enzymatic levels were assayed by standard methods; white blood cells (WBC) in the dialysate (elts/µL) were counted in a Bürker chamber; and dialysate cultures were obtained [9]. Rats with positive culture and WBC count in the dialysate >1500 elts/µL were considered to have peritonitis [12]. They represented 75% of the rats that had been infected according to the protocol. At the end of the dwell, animals were sacrificed by exsanguination, and similar samples from the parietal and visceral peritoneum were processed for fixation in 4% paraformaldehyde and protein extraction as previously detailed [9, 12]. All experiments were conducted in accord with local prescriptions and the NIH Guide for the Care and Use of Laboratory Animals.

Immunohistochemistry

Immunostaining was performed on 6-µm peritoneal sections embedded in paraffin [9, 16]. After blocking in 0.3% H2O2 and incubation with 10% normal serum, sections were incubated successively for 45 minutes each with well-characterized monoclonal antibodies against eNOS and iNOS (Transduction Laboratories, Lexington, KY, USA) [12] or polyclonal antibodies against S-nitrosocysteine (Alexis, Lausen, Switzerland) [17, 18], biotinylated IgG (Vector Laboratories, Burlingame, CA, USA), and avidin-biotin peroxidase (Vector). Immunolabeling was visualized using aminoethylcarbazole (Vector). The specificity of the immunolabeling was confirmed by incubation without primary antibody; with non-immune mouse or rabbit IgG [9, 16]; or after incubation with 0.2% HgCl2 as indicated by the manufacturer (Alexis). Peritoneal sections stained with hemalun eosine or trichrome blue were used for systematic pathological examinations.

Western blot analyses

Sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) and immunoblotting were performed as described [9, 12, 16]. Efficiency of transfer to nitrocellulose was routinely tested by Ponceau red (Sigma) staining and β-actin immunoreactivity (Sigma). The membranes were blocked for 30 minutes at room temperature, followed by incubation with monoclonal antibodies raised against eNOS and iNOS at 4°C for 16 to 18 hours. After washing, the membranes were incubated for one hour at room temperature with peroxidase-labeled secondary antibodies (Dako), before visualization with enhanced chemiluminescence (Amersham, Little Chalfont, UK). Negative controls included incubation with non-immune mouse IgG (Dako).

NOS activity assay

Nitric oxide synthase enzymatic activities were measured using the L-citrulline assay as described [12]. Briefly, 25 µL of tissue extract (350 µg of total protein) containing 20 mmol/L 3-[(3-cholamidopropyl) dimethylammonio] 1-propane sulfonate (CHAPS) were added to 200 µL of Tris buffer (50 mmol/L, pH 7.4) containing 10 mmol/L dithiothreitol (DTT), 10 µg/mL calmodulin, 1 mmol/L nicotinamide adenine dinucleotide phosphate (NADEPH), 4 µmol/L flavin adenine dinucleotide (FAD), 4 µmol/L flavin adenine mononucleotide (FMN), 2 µmol/L L-arginine, and 10⁻³ mCi/mL L-[³H]-arginine.
Table 1. Body weight, hematocrit (Hct), plasma creatinine (P\textsubscript{Cr}) and blood pressure during the dwell in control and peritonitis rats

<table>
<thead>
<tr>
<th>Rat group</th>
<th>N</th>
<th>Body weight</th>
<th>Hct</th>
<th>P\textsubscript{Cr}</th>
<th>T\textsubscript{0}</th>
<th>T\textsubscript{120}</th>
<th>T\textsubscript{120} - T\textsubscript{0}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (C)</td>
<td>6</td>
<td>277 ± 3</td>
<td>47 ± 1</td>
<td>0.19 ± 0.01</td>
<td>124 ± 5</td>
<td>82 ± 7</td>
<td>−33 ± 8</td>
</tr>
<tr>
<td>Control + 5 mmol/L L-NAME (C-LA5)</td>
<td>6</td>
<td>284 ± 4</td>
<td>49 ± 1</td>
<td>0.15 ± 0.02</td>
<td>112 ± 6</td>
<td>113 ± 15*</td>
<td>3 ± 16*</td>
</tr>
<tr>
<td>Peritonitis (P)</td>
<td>6</td>
<td>274 ± 2</td>
<td>45 ± 1</td>
<td>0.18 ± 0.03</td>
<td>143 ± 8</td>
<td>122 ± 17*</td>
<td>−14 ± 11</td>
</tr>
<tr>
<td>Peritonitis + 2.5 mmol/L L-NAME (P-LA2.5)</td>
<td>4</td>
<td>270 ± 6</td>
<td>46 ± 1</td>
<td>0.16 ± 0.01</td>
<td>105 ± 4*</td>
<td>143 ± 7</td>
<td>36 ± 6*</td>
</tr>
<tr>
<td>Peritonitis + 5 mmol/L L-NAME (P-LA5)</td>
<td>6</td>
<td>277 ± 6</td>
<td>47 ± 1</td>
<td>0.18 ± 0.02</td>
<td>125 ± 9</td>
<td>156 ± 5*</td>
<td>27 ± 7*</td>
</tr>
<tr>
<td>Peritonitis + 10 mmol/L L-NAME (P-LA10)</td>
<td>3</td>
<td>271 ± 5</td>
<td>50 ± 1*</td>
<td>0.16 ± 0.01</td>
<td>128 ± 6</td>
<td>140 ± 20</td>
<td>9 ± 13</td>
</tr>
</tbody>
</table>

\*\% T = \frac{(T_{120} - T_{0})}{T_{0}}

\* P < 0.05 vs. C

\* P < 0.05 vs. P

Data are mean ± SEM. ∆ (%) = (T\textsubscript{120} - T\textsubscript{0})/T\textsubscript{0}.

Data are presented as mean ± SEM. Statistical significance was analyzed using the Student t test or one-way ANOVA, as appropriate.

RESULTS

Clinical and biological parameters

In comparison with controls, rats with acute peritonitis were characterized by (a) decreased UF (1 ± 1 vs. 7.6 ± 0.5 mL, P < 0.001), (b) increased protein loss in the dialysate (4.7 ± 0.9 vs. 0.8 ± 0.1 g/L, P < 0.001), (c) cloudy dialysate with an increased WBC count (9844 ± 3335 vs. 313 ± 35 elts/µL, P = 0.03), and (d) positive dialysate cultures. Analysis of the pathogens responsible for peritonitis showed a single organism in about 2/3 of cases, and multiple germs in others. Gram-positive organisms were identified in 85% of cases, the remaining being gram-negative. The most frequent causative organism was *Staphylococcus aureus*, which accounted for 2/3 of the cases, followed by coagulase-negative *Staphylococci*, *Streptococcus G*, and *E. coli*. In contrast, none of the cultures obtained from control rats was positive. There was a significant, inverse correlation between the magnitude of UF and the severity of peritonitis as reflected by WBC count in the dialysate (P = 0.03; r² = 0.31). Body weight, hematocrit, plasma creatinine, and blood pressure at T\textsubscript{0} were similar in control and peritonitis rats (Table 1). Other biological parameters including pancreatic and liver enzymes, as well as lactate dehydrogenase levels, were similar in all groups (data not shown). The addition of L-NAME to the dialysate in control and peritonitis rats was reflected by an increase in blood pressure during the exchange, in contrast with the decrease observed when PD was performed with the 7% glucose dialysate (Table 1).

Peritoneum structure and reactivity for S-nitrosothiocyansine

Morphological examination of the visceral peritoneum (Fig. 1) showed that acute peritonitis in rats was reflected by a massive sub-mesothelial infiltrate of mononuclear cells, together with edema and vasodilation of the peritoneal capillaries (Fig. 1A, B). Acute peritonitis was associated with capillary proliferation, as shown by the increased immunoreactivity for eNOS located in capillary endothelium (Fig. 1C, D). As previously reported [9], a faint staining for iNOS was detected in mononuclear endothelium (Fig. 1C, D). In contrast, none of the cultures obtained from control rats was positive. The addition of L-NAME to the dialysate in control and peritonitis rats was reflected by an increase in blood pressure during the exchange, in contrast with the decrease observed when PD was performed with the 7% glucose dialysate (Table 1).
S-nitrosocysteine in the peritoneum (Fig. 1 G, H), which was particularly concentrated in mesothelial and endothelial cells (Fig. 1H, inset). Incubation with L-NAME during the dwell did not affect the immunostaining for S-nitrosocysteine (Fig. 1I).

**NOS expression and enzymatic activities in the peritoneum**

Immunoblot analyses confirmed that acute peritonitis induced a significant up-regulation of both the endothelial (140 kD) and inducible (130 kD) NOS isoforms in the peritoneum (Fig. 2A). As previously described [9], induction of iNOS was variable in intensity, ranging from weak to very strong (Fig. 2A, lower band of the gel). As expected, the up-regulation of NOS isoforms in the peritoneum was reflected by a significant increase in total NOS activity (0.39 ± 0.04 vs. 0.12 ± 0.06 pmol citruline/mg protein/min, P < 0.01), due to both Ca²⁺-dependent and Ca²⁺-independent NOS isoforms (Fig. 2B). The presence of NOS inhibitor L-NAME in the peritoneum extracts during the l-citrulline assay prevented reliable measurements of NOS activities in control and peritonitis rats treated with L-NAME.

**Peritoneal permeability**

Acute peritonitis induced a major increase in peritoneal permeability for small solutes such as urea (Fig. 3A), a faster glucose absorption from the dialysate (Fig. 3B), and a reduced free-water permeability (as attested by the loss of sodium sieving, Fig. 3C). These changes
were reflected by a fall in UF and an increased protein loss in the dialysate (cf. above, Fig. 4 A, B), as well as an increased cumulative urea transport during the two hour dwell (Fig. 4C).

Addition of 5 mmol/L L-NAME to the dialysate in control rats did not change peritoneal permeability parameters (Fig. 3), and was not reflected by significant changes in UF (− vs. + L-NAME: 7.6 ± 0.5 vs. 8.8 ± 0.5 mL) and protein loss in the dialysate (− vs. + L-NAME: 0.8 ± 0.1 vs. 1 ± 0.1 g/L). In contrast, addition of 5 mmol/L L-NAME to the dialysate in rats with acute peritonitis significantly reduced the hyperpermeability to urea and glucose (Fig. 3 A, B), and significantly improved the dialysate-over-plasma ratio for sodium (Fig. 3C). Also, treatment with L-NAME in rats with acute peritonitis induced a significant increase in the dialysate-over-plasma ratio for osmolality at T₃₀, from 2.29 ± 0.02 (P) to 2.34 ± 0.02 (P-LA5) and further to 2.42 ± 0.03 (P-LA10).

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Fig. 2. Effects of acute peritonitis on NOS expression and activity in the peritoneum. (A) Immunoblot analysis for endothelial (eNOS) and inducible (iNOS) nitric oxide synthase in peritoneum extracts prepared from control rats and rats with acute peritonitis (40 μg protein/lane, 6 samples in each group). Extracts from bovine aortic endothelial cells (eNOS) and mouse macrophages (iNOS) were used as positive controls (lane C). A consistent up-regulation of eNOS (140 kD) is detected in samples from rats with acute peritonitis. The signal for iNOS (130 kD, lower band of the blot), never detected in control samples, is up-regulated with variable intensity in rats with acute peritonitis. Note that the monoclonal antibody against iNOS cross-reacts with eNOS (middle band at 140 kD) and nNOS (upper band at 155 kD), as previously reported [12]. (B) NOS enzymatic activities in the peritoneum of control rats (C) and rats with acute peritonitis (P). Total NOS activity (pmol citrulline/mg protein/min) was assayed by the conversion of L-[3H]-arginine to L-[3H]-citrulline in the visceral peritoneum. Assays were performed with or without Ca²⁺, to distinguish between Ca²⁺-dependent (*) and Ca²⁺-independent (●) NOS activities. Total NOS activity is increased (~3-fold) in rats with peritonitis. The increased NOS activity results from both Ca²⁺-dependent and Ca²⁺-independent NOS. *P < 0.05 between peritonitis and control rats.

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Fig. 3. Effect of L-NAME on functional parameters of peritoneal dialysis in control and peritonitis rats. The dialysate-to-plasma (D/P) ratio of urea (A) and sodium (C), and the progressive removal of glucose from the dialysate (D/D₀, B) were determined in control rats ( ), and rats with peritonitis ( ), during a two-hour exchange with 15 mL of 7% glucose supplemented ( ) or not ( ) with 5 mmol/L L-NAME. All parameters were obtained for 6 rats in each group. Acute peritonitis induces a significant increase in permeability for urea and glucose, and a loss of sodium sieving (*P < 0.05 vs. C). These modifications are significantly reduced when L-NAME is added to the dialysate (#P < 0.05 vs. P).
The effect of L-NAME on UF was maximal at 2.5 mmol/L (Fig. 4A), whereas the effect on protein loss and permeability for urea was dose-dependent and maximal at 10 mmol/L (Fig. 4B, C).

**DISCUSSION**

This study used a well-characterized model of acute peritonitis in rats to demonstrate that local generation of NO, secondary to the up-regulation of NOS isoforms, induces major, detrimental changes in peritoneal permeability. These functional changes are partially reversed by acute NOS inhibition, whereas structural modifications associated with the release of NO (formation of S-nitrosocysteine) are not affected. In contrast, the lack of functional consequences of NOS inhibition in control rats suggests that NO does not influence significantly peritoneal permeability in stable, uninfected PD.

Analogues of L-arginine can inhibit the production of NO by NOS isoforms. L-NAME has proven to be one of the most useful NOS inhibitors due to its low cost, commercial availability, chemical stability, solubility in water, and effectiveness in the millimolar range both for tissue studies and in vivo investigations [13, 19, 20]. Because previous studies have shown that local, intra-peritoneal production of NO might be critical for regulating PD parameters [7–9, 13], we postulated that administration of L-NAME in the dialysate was probably more relevant than systemic infusion, which induces acute and severe hypertension [21]. Nevertheless, hemodynamic monitoring revealed that rats treated with L-NAME in the dialysate had a mild but consistent increase in systolic blood pressure during the exchange, which contrasts with the drop observed in absence of L-NAME (Table 1). Addition of L-NAME to the dialysate did not induce other clinical or biological side effects, and did not alter the morphology of the peritoneum. In particular, morphological examination confirmed the absence of congestion, infarction, or infiltrate in control rats treated with L-NAME.

A modified peritoneal equilibration test [9] was used to investigate the effects of L-NAME on peritoneal permeability (Fig. 2A). Addition of 5 mmol/L L-NAME to the dialysate in control rats did not affect UF and protein loss in the dialysate significantly, and was not associated with permeability changes (Fig. 3). The lack of effect of NOS inhibition on the permeability for small solutes is consistent with the results obtained in a chronic PD model in rabbits [14] and control Wistar rats [13]. Taken together, these results suggest that the very low levels of bioactive NO generated by the peritoneum during stable uninfected PD [9, 12] do not critically affect peritoneal permeability.

The situation is strikingly different in acute peritonitis. In comparison with controls, rats with peritonitis were
characterized by structural modifications in the peritoneum (Fig. 1); up-regulation of eNOS and iNOS, paralleled by increased NO activities in the peritoneum (Fig. 2); increased permeability for urea and glucose, and loss of free-water permeability (Fig. 3); and the combination of decreased UF and increased protein loss in the dialysate (Fig. 4). These changes, which confirm our previous observations in this model [9], are characteristic of acute peritonitis [2]. Furthermore, bacteriological findings in rats with peritonitis are similar to the situation encountered in PD-related peritonitis, particularly in case of touch contamination from skin flora [15].

Recent studies have suggested that increased EPSON and functional modifications observed in acute peritonitis might be the consequence of increased NO production mediated by the up-regulation of NO isoforms in the peritoneum [7–9]. This hypothesis was supported by the effect of L-NAME on peritoneal permeability for small solutes and proteins in rats treated with lipopolysaccharides from E. coli [13]. Our expression and enzymatic studies (Figs. 1 and 2) confirm that peritonitis induces a major increase in NO activity and up-regulates both eNOS and iNOS in the peritoneum. As described earlier [12], the induction of iNOS is variable in intensity and related to the severity of the peritonitis (as reflected by the WBC count in the dialysate). Furthermore, our results provide direct evidence supporting the key role of NO in that the addition of L-NAME to the dialysate was sufficient to restore UF and decrease protein loss during acute peritonitis (Fig. 4). This clinical benefit reflected a significant effect of L-NAME on the permeability for small solutes and glucose (Fig. 3) as well as hemodynamic changes, as attested by an increase in blood pressure during the course of the dwell (Table 1). It is interesting to note that the effect of L-NAME on UF is maximal at 2.5 mmol/L, whereas its effect on permeability for urea and proteins is dose-dependent and maximal at 10 mmol/L (Fig. 4). This observation suggests that NO might have a differential effect on the permeability for ultrasmall molecules such as water (free-water permeability is an important component of UF) and that of solutes such as urea and proteins.

Although it has significant functional consequences, the addition of L-NAME in the dialysate does not totally reverse the permeability changes induced by acute peritonitis. Vasoactive substances and pro-inflammatory cytokines liberated during the course of infection/inflammation might interfere [22, 23]. Alternatively, it is tempting to suggest that the incomplete reversibility might be due to stable structural modifications induced by NO within the peritoneum. Our demonstration of increased S-nitrosylation in the peritoneum of rats with peritonitis, and the lack of effect of L-NAME on this modification, support the latter hypothesis. In addition to its actions mediated by cyclic GMP, NO targets specific cysteine residues and, via S-nitrosylation, regulate proteins such as receptors, enzymes, ion channels, and transcription factors [24]. The concentration of S-nitrosocysteine reactivity in endothelial cells (Fig. 1) might be relevant when considering the potential interaction of NO with the critical cysteine 189 within aquaporin-1 (AQP1), the molecular counterpart of the ultrasmall pore in the endothelium [25]. Indeed, recent structural data on AQP1 [26] confirm that this cysteine 189 is flanked by consensus motifs (acidic and/or basic residues) for S-nitrosylation [27]. Arguably, the persistence of S-nitrosocysteine reactivity implies that biochemical and/or structural conditions involved in NO-induced modifications were not modified by acute incubation with L-NAME. Finally, L-NAME may inhibit constitutive NO isoforms preferentially over iNOS [28], which might explain its partial effect in a situation characterized by the up-regulation of both eNOS and iNOS (Fig. 2). Studies in mouse models lacking specific NO isoforms will be necessary to delineate the precise involvement of each NO isoform in the pathophysiological changes observed.

Thus, our results demonstrate that inhibition of NO in the peritoneum during acute peritonitis significantly improves UF and reduces protein loss in the dialysate. In view of the current effort to develop more specific NOS inhibitors [20], our observations suggest that this type of drug may offer new therapeutic perspectives for functional alterations encountered during acute peritonitis.

ACKNOWLEDGMENTS

These studies were supported in part by the Fonds National de la Recherche Scientifique (crédit 9.4540.96), the Fonds de la Recherche Scientifique Médicale (convention 3.4566.97), an Action de Recherche Concertée (ARC 00/05-260), and grants from Baxter Healthcare (Round Lake, IL, USA). We thank Drs. J.-L. Balligand and E. Goffin for providing invaluable suggestions and critiques. The expert technical assistance of Mr. T. Dheuvaert, Ms. C. Verkaeren, and Mr. L. Wenderickx is highly appreciated.

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