Viscosity of Contrast Media Perturbs Renal Hemodynamics

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ABSTRACT
Contrast-induced nephropathy is a common cause of acute renal failure, and the mechanisms underlying this injury are not completely understood. We sought to determine how physicochemical properties of contrast media may contribute to kidney damage in rats. We administered contrast media of equivalent iodine concentrations but differing physicochemical properties: the high-osmolality iopromide was compared to the high-viscosity iodixanol. In addition, the non-iodinated substances mannitol (equivalent osmolality to iopromide) and dextran (equivalent viscosity to iodixanol) were also studied. Both types of contrast media transiently increased renal and hindquarter blood flow. The high-osmolality agents iopromide and mannitol markedly increased urine production whereas iodixanol, which caused less diuresis, significantly enhanced urine viscosity. Only the high-viscosity agents iodixanol and dextran decreased renal medullary blood flux, erythrocyte concentration, and pO₂. Moreover, iodixanol prolonged the tubuloglomerular feedback response and increased plasma creatinine levels to a greater extent than iopromide or dextran. Therefore, the viscosity of contrast media may play a significant role in contrast-induced nephropathy.


Contrast media (CM) are usually tolerated well; however, increasing numbers of investigations requiring CM make CM-induced damage a leading cause of renal failure.1 In 1999, 58% of all CM-related deaths in the United States were associated with renal failure and contrast medium–induced nephropathy (CIN).2 Volume depletion greatly enhances the risk for CIN, and volume expansion is the only generally accepted preventive measure to reduce the risk for CIN, besides limiting the CM dosage to the minimum required.3,4

Mechanisms may act in concert in causing CIN, such as hypoxia, apoptosis, and oxidative stress.5,6 Also, direct toxic effects of CM on renal cells7,8 and the kidney-specific tubuloglomerular feedback (TGF) may play a role.3 The specific kidney damage caused by CM indicates that perturbed renal medullary hemodynamics is critically involved.9–14 The renal medulla is vulnerable to changes in vascular resistance, because the vasa recta are very narrow and extremely long.15 In resemblance to changes reported in human CIN, it is the inner stripe of the rat outer renal medulla that is harmed.9 Injury may result in necrosis of medullary thick ascending limbs distant from vasa recta in zones remote from oxygen supply. Tubular collapse and casts of the inner region of the outer medulla are also observed.9

This study investigated the role of two major
physicochemical properties of commonly used CM on renal hemodynamics: Osmolality and viscosity (Table 1). Two CM were tested: A nonionic dimer, iodixanol that is isoosmolar to plasma but has a much higher fluid viscosity than whole blood, and a nonionic monomer, iopromide, which has a greater osmolality than plasma but a much lower viscosity than iodixanol. Effects of dextran (same viscous properties as iodixanol) and mannitol (same osmolality as iopromide) were also studied. The TGF response was assessed, and renal hemodynamics and regional PO₂ levels were studied at controlled levels of perfusion pressure. The effects were compared with the hindquarter circulation. Taking the impact of volume depletion into account, renal hemodynamics was assessed in 12-h water-deprived rats.

RESULTS

Urine Flow and Urine Viscosity
Solutions of higher osmolalities exhibited the strongest increase in urine flow (details in Figure 1). As described for dimeric nonionic CM, iodixanol markedly increased urine viscosity. Dextran (molecular weight [MW] 500,000) is not filtered by the kidney and did not enhance urine viscosity.

As shown in Table 2, human urine sampled during percutaneous cardiac interventions with CM also became more viscous. The increase in viscosity was significantly higher in patients who were given iodixanol. Because all patients were well hydrated, the effect of CM on viscosity is not dramatic.

Hemodynamic Response and Renal Medullary PO₂
As measured in protocol 2 (Figure 2), renal blood flow (RBF), renal medullary blood flux (RMBF), hindquarter flow (HQF), and mean arterial BP (MAP) increased within seconds after injection of 1.5 ml of CM as a bolus (data not shown). Total renal, renal medullary, and hindquarter conductance increased markedly (Figure 3). Hindquarter conductance took on values up to seven-fold higher than control. The CM exhibited greater effects than dextran or mannitol, indicating that there may be a specific action of CM on resistance vessels in the muscle. Total renal conductance increased by a lesser degree; moreover, the initial vasodilation was followed by mild vasoconstriction 16 min (iodixanol) and 35 min (iopromide) after CM. Intriguing, large differences among the groups were observed in renal medullary conductance and PO₂. The groups receiving the substances of higher viscosity (iodixanol and dextran) exhibited early and long-lasting reductions in medullary conductance and had lower medullary PO₂.

TGF Response
Iodixanol significantly delayed the TGF response (Figure 4), indicating prolonged tubular passage time. Dextran (MW 500,000) is not filtered by the kidney and increases plasma

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Table 1. Iodine concentration, osmolality, and viscosity of the test solutions

<table>
<thead>
<tr>
<th>Solution</th>
<th>Iodine Concentration (mg/ml)</th>
<th>Osmolality (mOsm/kg H₂O)</th>
<th>Viscosity (37°C; mm²/s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iopromide</td>
<td>320⁺</td>
<td>710⁺</td>
<td>4.64</td>
</tr>
<tr>
<td>Mannitol</td>
<td>–</td>
<td>730</td>
<td>0.91</td>
</tr>
<tr>
<td>Iodixanol</td>
<td>320⁺</td>
<td>290⁺</td>
<td>8.53</td>
</tr>
<tr>
<td>Dextran</td>
<td>–</td>
<td>293</td>
<td>8.56</td>
</tr>
</tbody>
</table>

⁻Manufacturer’s specification. For comparison, the viscosity of rat whole blood at hematocrit 0.43 is 3.05 mm²/s.
Urine osmolality pre (mOsmol/kg H2O) 539
Urine volume (ml) 162
Urine viscosity pre (mm2/s) 0.791
Urine sampling time (min) 58
Urine osmolality post (mOsmol/kg H2O) 515
Urine viscosity post (mm2/s) 0.902
Δurine viscosity (%) 14.1

The concentration of plasma creatinine was significantly increased in renal medullary PO2. Iodixanol showed a slight decrease in renal medullary RBF and RMBF (data not shown). Mannitol tended to increase CM volume given (ml) 134

Age (y) 68.8
N (male, female) 12 (10, 2) 12 (8, 4)

CM volume given (ml) 134 ± 24
Urine volume (ml) 162 ± 38
Urine osmolality pre (mOsmol/kg H2O) 539 ± 61
Urine osmolality post (mOsmol/kg H2O) 515 ± 45
Urine viscosity pre (mm2/s) 0.791 ± 0.007
Urine viscosity post (mm2/s) 0.902 ± 0.026
Δurine viscosity (mm2/s) 0.112 ± 0.025
Δurine viscosity (%) 14.1 ± 3.2

Patients underwent percutaneous coronary angiography/interventions. CM used was either iodixanol (Visipaque 320) or iopromide (Ultravist 300). Patients voided immediately before the start of the intervention (urine sample pre), then, for the second time, immediately after the intervention (urine sample post); sampling time and urine volume apply to the latter.

Significant difference, iodixanol versus iopromide (Kruskal-Wallis test).

Table 2. Patient data following percutaneous coronary angiographya

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Iodixanol</th>
<th>Iopromide</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (male, female)</td>
<td>12 (10, 2)</td>
<td>12 (8, 4)</td>
</tr>
<tr>
<td>Age (y)</td>
<td>68.8 ± 1.6</td>
<td>66.8 ± 3.3</td>
</tr>
<tr>
<td>CM volume given (ml)</td>
<td>134 ± 24</td>
<td>180 ± 29</td>
</tr>
<tr>
<td>Urine sampling time (min)</td>
<td>58 ± 12</td>
<td>65 ± 9</td>
</tr>
<tr>
<td>Urine volume (ml)</td>
<td>162 ± 38</td>
<td>226 ± 40</td>
</tr>
<tr>
<td>Urine osmolality pre (mOsmol/kg H2O)</td>
<td>539 ± 61</td>
<td>562 ± 62</td>
</tr>
<tr>
<td>Urine osmolality post (mOsmol/kg H2O)</td>
<td>515 ± 45</td>
<td>504 ± 45</td>
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<td>Urine viscosity pre (mm2/s)</td>
<td>0.791 ± 0.007</td>
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<td>Δurine viscosity (mm2/s)</td>
<td>0.112 ± 0.025</td>
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</tr>
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<td>Δurine viscosity (%)</td>
<td>14.1 ± 3.2</td>
<td>6.8 ± 2.5</td>
</tr>
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</table>

**BASIC RESEARCH**

Figure 2. Scheme depicting the time course of experiments in protocol 2 (numbers indicate minutes). Experiments started with a stabilization period (stabilis.) and baseline recordings. The TGF was assessed by the step response method (steps; 30- or 60-s reductions of RPP, followed by recovery periods and intermittent data recordings of 100 s without RPP manipulations), and RPP was decreased in a staircase manner to assess the RPP-dependent response (staircase). Thereafter, a test solution was administered and the immediate response (im.resp.) was recorded. Then, the TGF was assessed and intermittent recordings without manipulations of RPP were done as before. Finally, RPP was staircase-wise decreased again.

Renal Perfusion Pressure–Dependent Responses

For the substances with high osmolalities, minor changes were noted (Figure 5). Animals receiving high-viscous substances showed marked decreases in RMBF and renal medullary erythrocyte concentration (RMEC; Figure 6). In the iodixanol-treated animals, there were also marked reductions in RBF, especially in the renal perfusion pressure (RPP) range between 80 and 40 mmHg, and in HQF.

Renal medullary PO2 measurements behaved similar to RBF and RMBF (data not shown). Mannitol tended to increase PO2. Iopromide showed a slight decrease in renal medullary PO2 at 80 to 40 mmHg. Iodixanol lowered renal medullary PO2 in the same RPP range. Dextran caused only a minor reduction in renal medullary PO2.

Plasma Creatinine

The concentration of plasma creatinine was significantly elevated 90 min after giving iodixanol, iopromide, or dextran. Conversely, mannitol lowered plasma creatinine concentration (Figure 7). Iodixanol increased plasma creatinine more than iopromide. It was confirmed that CM did not interact with the creatinine measurement.

**DISCUSSION**

CM vary in terms of osmolality and viscosity. First-generation CM had seven-fold greater osmolalities than plasma and caused considerably more adverse effects than presently used compounds. The subsequent CM generation (mainly nonionic monomers) was designed to reduce osmolality and is well tolerated. In the quest to reduce osmolality further, a new class of CM was designed, which achieved isoosmolality by creating a nonionic dimeric structure but at the price of a considerably increased viscosity (Table 1). To our knowledge, CM are unique compounds in that they are highly viscous yet small enough to be freely filtered by the kidney. These properties may rely on molecular interactions of CM, such as stacking. This study underscores that fluid viscosity of CM is of particular importance for CIN. Increased viscosity compromises blood flow and oxygen supply to the critical region of the kidney (Figures 3, 5, and 6), delays the TGF probably as a result of increased tubular fluid viscosity (Figure 4, Table 2), and impairs glomerular filtration (Figure 7).

Renal Circulation and Oxygenation

As reported previously, the vascular response to CM is biphasic (Figure 3). Following peak values after seconds to minutes, vasodilation tapers off. In the renal medullary vasculature, initial vasodilation is followed by vasoconstriction in rats given iodixanol or dextran (substances of high viscosity). In line with medullary vascular conductance, medullary PO2 was lower in the rats receiving the high-viscous compounds.

Our data only partly agree with previous studies. Heyman et al. reported impaired RBF in rats after iothalamate. In com-

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**Table 2. Patient data following percutaneous coronary angiography**

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bination with nitric oxide blockade, iothalamate increases plasma creatinine (after 24 h),\(^20\) and when iothalamate is combined with indomethacin, medullary hypoxia occurs in the salt-depleted uninephrectomized rat.\(^21\) Liss et al.\(^22\) measured medullary blood flow with two different techniques and confirmed that iothalamate significantly impairs renal medullary blood flow. Iothalamate is a first-generation, ionic, highly osmolar CM with low viscosity; its ionicity and osmolarity distinguish it from the low-viscous CM iopromide used in this study. Iopromide was previously shown actually to increase RMBF in control rats, although it reduces RMBF in diabetic rats\(^23\); however, a reduction in PO\(_2\) by iopromide has also been reported.\(^24\) Taken together, the experimental setting seems to be crucial for determining the ultimate effect of CM on RMBF and PO\(_2\). In this study, iopromide did not reduce PO\(_2\) or RMBF, which may in part rely on our particular dehydration protocol: Our rats were not given water for 12 h before the experiment. Because iopromide has a higher osmolality than plasma (Table 1), iopromide causes greater extracellular volume expansion than isoosmolar CM. Although not unequivocally found,\(^25\) volume expansion may enhance RMBF,\(^26,27\) thus potentially explaining this effect; however, beyond doubt, CM of lower viscosity can also cause CIN. Because many factors may contribute to CIN, high viscosity may merely augment CM-specific effects not related to physicochemical properties.

The RPP-dependent effects are depicted in Figures 5 and 6. Again, only the substances of higher viscosity markedly decrease RMBF. The reduction of RMBF at higher RPP\(^14\) is more pronounced for iodixanol than for dextran (Figure 6), which may be explained by filtration of CM: In addition to a direct vascular effect, filtration of high-viscous CM causes higher tubular pressures,\(^28\) which may add to impaired RMBF. At lower RPP, where filtration of CM ceases (<60 mmHg), RMBF eventually approaches the control measurements.

RMEC mirror the effects on RMBF (Figure 6). The erythrocyte concentration is important for oxygen supply of the medullary region and depends on the amount of blood flowing through the medulla and plasma skimming. Also, other features may be important, such as altered rheologic properties and erythrocyte stacking.\(^29\)

### Plasma Creatinine

Both CM as well as dextran markedly increased plasma creatinine concentrations, but the increase was significantly higher after iodixanol than iopromide (Figure 7). Because creatinine was determined 90 min after administration of the solutions, the results must be interpreted with caution. First, it cannot be ruled out that, in addition to reduced GFR, CM-induced flushing of muscle tissues contributed to increased plasma creatinine. Creatinine concentrations are several-fold higher in muscle tissue than in plasma,\(^30\) and CM dramatically increased blood flow to the hindquarter (Figure 3), a vascular bed mainly comprising muscle.

Second, the creatinine accumulated as a result of GFR reduction may still, to a great deal, be confined to the intravas-
According to creatinine kinetics, it takes 5 h for creatinine to distribute evenly throughout all compartments\(^{31,32}\) (plasma, remaining extracellular space, and intracellular space). Thus, 90-min values can be considerably higher than after 24 h. In other words, abrupt decrease in creatinine clearance may markedly raise plasma creatinine; however, this acute increase will level off and decrease with ongoing equilibration. Accordingly, clamping the human kidney for 60 min acutely doubles plasma creatinine.\(^{33}\)

In a single-compartment model for plasma (modified model from Moran and Myers\(^{34}\)) and provided that creatinine production and secretion are not influenced by CM, a two-fold increase in plasma creatinine within 90 min (as seen for iodoxan-ol) corresponds to a 35% decline in GFR. A decrease in GFR by 85% would be required to cause the same plasma creatinine increase should creatinine immediately distribute and equilibrate throughout the entire extracellular space. In the healthy rat, decreases in GFR caused by CM are only transient; therefore, we expect plasma creatinine to normalize during the subsequent hours.

Dextran also increased plasma creatinine. GFR lowering by dextran may rely on higher plasma oncotic pressure and a reduced filtration coefficient.\(^{35}\) Mannitol has a very low viscosity and high osmolality, giving this compound decreased plasma creatinine, most likely as a result of the effective volume expansion by mannitol.

### Hindquarter Circulation

We compared RBF with HQF, a vascular bed consisting mainly of muscle, to assess whether the effects are specific for the kidney vasculature. The administration of the CM iopromide and iodixanol resulted in an immediate several-fold increase of hindquarter conductance, which gradually tapered off (Figure 3). This may be best described as a massive vasodilation as a result of an immediate CM effect. Although less pronounced, mannitol and dextran also exhibited an effect.

A biphasic RBF response with initial vasodilation has been described during selective renal artery catheterization and renal angiography\(^{18}\); however, to our knowledge, more generalized vasodilation is a novel observation. The very pronounced vasodilation in the hindquarter may rely on CM-induced release of potassium.\(^{36}\) When considering that MAP tended to increase during this immediate response, it becomes clear that the heart is subjected to a larger hemodynamic challenge during the first minutes after oscillation reflecting the TGF response (C), and, finally, a very slow oscillation possibly accounting for the metabolic component (B). As has been previously demonstrated,\(^{44}\) eigenoscillations with oscillation periods ranging from 20 to 60 s represent the TGF response. (D) Oscillation periods of the TGF. Oscillation periods obtained before administration of the test solutions did not differ among the groups and were thus pooled (Control). *Significant difference to control; +significant difference to iopromide (Kruskal-Wallis test). The amplitudes of eigenoscillations that characterizes the relative power of the respective mechanism did not change significantly.

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**Figure 4.** Method to quantify the temporal characteristics of the RBF autoregulation including the TGF by the step response technique. The so-called step response stimulates the mechanisms of RBF autoregulation including the TGF feedback loop. Zero RBF is held for 30 s by means of the aortic occluder, then the occlusion is rapidly released, and the time course of restoration of renal vascular conductance (RBF/RPP) is analyzed. The conductance restoration roughly follows an exponential function with superimposed dampened oscillations. The parameters of this function are calculated by an iterative least square fitting procedure that, after three iterations, reaches coefficients of determination \(r^2\) of approximately 0.98.\(^{44}\) (A through C) Typical example of the three subsequent fitting procedures. As a result, three separate eigenoscillations are detected (inserts), each of which is characterized by certain values of angular frequency, amplitude, dampening, and phase angle. By use of the parameter angular frequency (or oscillation period), the oscillations are ascribed to one of the mechanisms of RBF autoregulation: A rapid oscillation referring to the myogenic response of vascular smooth muscles (A), a slower oscillation possibly accounting for the metabolic component (B). As has been previously demonstrated,\(^{44}\) eigenoscillations with oscillation periods ranging from 20 to 60 s represent the TGF response. (D) Oscillation periods of the TGF. Oscillation periods obtained before administration of the test solutions did not differ among the groups and were thus pooled (Control). *Significant difference to control; +significant difference to iopromide (Kruskal-Wallis test). The amplitudes of eigenoscillations that characterizes the relative power of the respective mechanism did not change significantly.
giving CM. Cardiac output increases of such magnitude can be hazardous for patients with heart failure.

Iodixanol and iopromide both seem to exert CM-specific RPP-dependent effects on HQF and RBF (Figures 5 and 6). At RPP between 40 and 80 mmHg, iodixanol significantly lowered HQF and RBF. Iopromide had a similar, although less pronounced, effect, whereas mannitol and dextran did not. We therefore conclude that, at lowered RPP, these CM elicit a specific vasoconstrictor effect on the vasculature of the renal and hindquarter vascular bed.

**Clinical Implications**

A clinical head-to-head study in 129 patients suggested that dimeric iso-osmolar CM have better renal tolerability compared with a monomeric, less viscous CM.37 A recent study with a related design in 153 patients found no benefit of the dimeric iso-osmolar CM versus another monomeric, less viscous CM.38 These two studies refer to a definition of CIN, based on increases in serum creatinine as a surrogate marker of renal function. Conversely, a retrospective registry study in 57,925 patients using patient outcome–related end points indicated that iso-osmolar, high-viscous iodixanol causes significantly more often renal failure than less viscous CM.39

This experimental study shows that the high-viscous CM given at dosages corresponding to approximately 200 ml in the human compromise RMBF, RMEC, and renal medullary PO2. Moreover, the TGF response is delayed by the CM of higher viscosity (Figure 4), which fits to the finding that the viscous CM iotrolan decreases single-nephron filtration.40 These findings suggest that increased plasma viscosity directly impairs blood flow to the renal medulla by vascular and tubular mechanisms.

The renal medulla is supplied by very long-reaching vasa recta that depend on a reduction of blood viscosity to maintain low vascular resistance (Fåhraeus-Lindqvist effect). CM seem to diminish directly renal medullary blood flow by increasing plasma viscosity. A similar finding was made for nailfold circulation.41 Moreover, because CM are freely filtered but cannot be reabsorbed by the kidney, tubular fluid becomes viscous...
(Figure 1, Table 2) and may cease to flow. Impairing tubular flow will increase renal tubular pressure and thereby further compromise renal medullary hemodynamics. As a result, GFR and renal medullary blood flow decrease. Taken together, in addition to other effects, viscosity of CM may play a significant role in CIN.

CONCISE METHODS

Experiments conformed with the National Institutes of Health Guidelines for the Care and Use of Laboratory Animals. A total of 122 male, 3- to 4-mo-old, Wistar rats (body weight 300 to 400 g; BFR, Berlin, Germany) were used.

Surgical Procedures and Measurements

Urethane intraperitoneally (2% in water; 6 ml/kg body wt; Sigma, Taufkirchen, Germany) caused anesthesia. Rats were maintained at 39°C and breathed through a tracheal cannula. Catheters were advanced into a jugular vein, the left common carotid artery (tip toward aorta) for substance administration, and the femoral artery for pressure recording (RPP; Gould, Valley View, OH). The abdominal cavity was opened and flushed (saline, 37°C). For protocol 1, the urinary bladder was cannulated. For protocol 2, an inflatable aortic cuff was placed above the renal arteries for servo-controlled reduction of RPP.42 One ultrasound transit time flow probe (Transonic Systems, Ithaca, NY) was positioned around the left renal artery to measure RBF; another was positioned on the aorta (below renal arteries) for HQF quantification. An optical probe (outer diameter 230 μm) was inserted into the kidney at 4-mm depth (outer medullary region) by micromanipulators to measure local medullary oxygen tension (PO2) by fluorescence quenching (OxyLite, Oxford Optronics, Oxford, UK). Another 500-μm optical fiber was inserted into the same region to assess RMEC and RMBF by laser-Doppler fleximetry (Moore Instruments, Axminster, UK). By operating within a specific wavelength, the laser assesses erythrocyte concentration (RMEC). Moreover, by recording the wavelength shift (Doppler), the average velocity of erythrocyte movements is determined, and, from this and REMC, an estimate of blood flow is calculated. This estimate is general.

Figure 6. RPP-dependent effects of RBF, HQF, RMBF, and RMEC before (control) and 35 min after administration of dextran (left) or iodixanol (right). Dextran and iodixanol solutions had the same viscosities; however, dextran (MW 500,000) is not filtered by the kidney. *Significant difference to control (Friedman test for paired data).
Figure 7. Creatinine plasma concentration 90 min after bolus injection of 1.5 ml of the test solutions or isotonic NaCl (Control) as measured in a separate series of experiments in a protocol similar to protocol 2 in mildly dehydrated rats (12 h without drinking water; n = 7 to 12 rats per group). Note: Acute changes in plasma creatinine cannot be extrapolated to long-term values because equilibrium throughout total body water requires 5 h.

*Significant difference to control; + significant difference to iopromide (Kruskal-Wallis test).

Studies in Dehydrated Animals.

Hemodynamic studies (see time course, Figure 2) were conducted after 12 h without water. Values were stored at 50 Hz. In a separate series of experiments with a similar protocol, creatinine plasma concentration 90 min after bolus injection of 1.5 ml of the test solutions or isotonic NaCl was measured (Creatinine Analyser II; Beckman, Galway, Ireland).

TGF Analysis

The TGF is a pivotal feedback mechanism to control renal hemodynamics. The macula densa senses NaCl concentration in the distal tubule and adjusts afferent arteriolar resistance accordingly. As for all feedback loops, the TGF has specific frequency characteristics, which are used to assess TGF activity44,45 (for details, see Figure 4).

Statistical Analysis

Statistical comparisons were made by Kruskal-Wallis test for unpaired and the Friedman test for paired data. P < 0.05 indicates significance. All data are means ± SE.

ACKNOWLEDGMENTS

Parts of this study were supported by the German Research Foundation (M.L.), Bayer-Schering Pharma AG (M.G.), and the Studienstiftung des Berliner Abgeordnetenhauses (K.A.).

We thank M.S. Gerhardt for expert technical assistance.

DISCLOSURES

P.B.P. consults for Bayer-Schering-Pharma AG and is member of the speaker bureau of Bayer-Schering-Pharma, Bracco, and Guerbet.

REFERENCES