Fenoterol but not dobutamine increases erythropoietin production in humans

Objective: This study assessed the role of adrenergic signal transmission in the control of renal erythropoietin (EPO) production in humans.

Methods: Forty-six healthy male volunteers underwent a hemorrhage of 750 ml. After phlebotomy, they received (intravenously for 6 hours in a parallel, randomized, placebo-controlled and single-blind design) either placebo (0.9% sodium chloride), or the β_2-adrenergic receptor agonist fenoterol (1.5 μg/min), or the β_1-adrenergic receptor agonist dobutamine (5 μg/kg/min), or the nonselective β-adrenergic receptor antagonist propranolol (loading dose of 0.14 mg/kg over 20 minutes, followed by 0.63 μg/kg/min).

Results: The $AUC_{EPO(0\text{-}48hr)fenoterol}$ was 37% higher ($p < 0.03$) than $AUC_{EPO(0\text{-}48hr)placebo}$, whereas $AUC_{EPO(0\text{-}48hr)dobutamine}$ and $AUC_{EPO(0\text{-}48hr)propranolol}$ were comparable with placebo. Creatinine clearance was significantly increased during dobutamine treatment. Urinary cyclic adenosine monophosphate excretion was increased only by fenoterol treatment, whereas serum potassium levels were decreased. Plasma renin activity was significantly increased during dobutamine and fenoterol infusion.

Conclusions: This study shows in a model of controlled, physiologic stimulation of renal erythropoietin production that the β_2-adrenergic receptor agonist fenoterol but not the β_1-adrenergic receptor agonist dobutamine is able to increase erythropoietin levels in humans. The result can be interpreted as a hint that signals for the control of erythropoietin production may be mediated by β_2-adrenergic receptors rather than by β_1-adrenergic receptors. It appears to be unlikely that an increase of renin concentrations or glomerular filtration rate is causally linked to the control of erythropoietin production in this experimental setting. (Clin Pharmacol Ther 1997;61:669-76.)

Christoph H. Gleiter, MD, Tilmann Becker, PhD, Katharina H. Schreeb, MD, Stefan Freudenthaler, MD, and Ursula Gundert-Remy, MD *Göttingen, Germany*

Erythropoietin, a glycoprotein hormone, is an essential growth factor that regulates erythropoiesis and is, in humans, predominantly synthesized in the kidneys.[1] Little is known about the cellular mechanism by which the kidney senses a decreased oxygen delivery to the kidney and the signal transduction that controls erythropoietin gene activity. Several possibilities have been proposed to understand this mechanism that eventually leads to increased renal erythropoietin production.

A number of findings may support the hypothesis that adrenergic transmitters may play a role in the control of erythropoietin production. Fink et al.[2] demonstrated in rabbits that the nonselective β-adrenergic receptor blocker propranolol was able to block an hypoxia-induced increase of erythropoietin concentration, which was indirectly measured by the polycythemic mouse assay. The same authors were not able to reproduce the latter finding; however, they showed that bilateral renal denervation reduces the effect of hypoxia on erythropoietin production in rabbits.[3] Later, experiments by that laboratory showed that the β_2-adrenergic receptor agonist albuterol (INN, salbutamol) stimulated erythropoiesis in rabbit bone marrow culture, and in vivo administration of albuterol to rabbits showed an increase of erythropoietin production.[4] Again, these experiments used the indirect measure of erythropoietin concentrations, the polycythemic mouse assay.[4] Ibrahim et al.[5] showed that application of the β_2-adrenergic receptor agonist ritodrine to dams was able to decrease erythropoietin concentrations in the dams and fetuses.

From the Abteilung Klinische Pharmakologie, Georg-August-Universität Göttingen.

Received for publication Aug. 22, 1996; accepted Jan. 5, 1997.

Reprint requests: Christoph H. Gleiter, MD, Abteilung Klinische Pharmakologie, Universität Göttingen, Robert-Koch-Strasse 40, D-37075 Göttingen, Germany. E-mail: Gleiter@med.uni-goettingen.de

0009-9236/97/$5.00 + 0 **13/1/80342**

Taken together, it appears from animal experimentation as though adrenergic mediators could affect erythropoietin production in the kidney. This may be one explanation for the capability of angiotensin converting enzyme (ACE) inhibitors to suppress posttransplant erythrocytosis from native remnant kidneys.[6] Among other mechanisms of action, ACE inhibitors block renal sympathetic activity and decrease noradrenergic neurotransmission in the kidney.[7]

The hypothesis that renal erythropoietin production is pharmacologically modulated by adrenergic mediators has never been tested in humans. Therefore we systematically investigated in healthy subjects whether a β_2- or a β_1-adrenergic agonist—namely, fenoterol and dobutamine—can influence erythropoietin concentrations after hemorrhage as a human model for a controlled physiologic stimulus of erythropoietin production.

METHODS

Subjects. Forty-six healthy male nonsmoking volunteers (mean age, 25.4 years; age range, 21 to 30 years; mean body weight, 79.5 kg; weight range, 63.2 to 98 kg) participated in the trial. Age was limited up to 30 years because our own animal experiments showed an age-dependent decrease in stimulated erythropoietin production. Body weight was defined within ±15% of the normal weight as calculated by the formula of Broca. Before inclusion they underwent a medical examination comprising physical status, blood chemistry (including iron and ferritin), urinalysis, and electrocardiography. No drugs were allowed for 2 weeks before or during the trial. In addition, the volunteers were not allowed a stay in an altitude of 1000 m or more (including air travel) for 4 weeks before or during the trial. Food or beverages that contained xanthine derivatives were not allowed from 1 day before the study and during the study days. Subjects who had donated blood during the previous 3-month period were excluded. The study was approved by the Ethics Committee of the Medical Faculty of the University of Göttingen. Written informed consent was obtained from each participant.

Protocol. The trial design was parallel, randomized, single-blind, and placebo-controlled. The volunteers were subjected to a phlebotomy of 750 ml (about 15% of their blood volume) for 20 minutes (with use of a Biomixer 314, Labstatus AB, Stockholm, Sweden). Immediately at the end of the phlebotomy (0 hour), 1000 ml physiologic electrolyte solution (Sterofundin) was infused as volume replacement for 40 minutes. In parallel, intravenous drug medication was started and administered for 6 hours by an infusion pump (Perfusor, Braun Melsungen AG, Germany). The subjects received either placebo (0.9 gm/dl sodium chloride; n = 12; mean age, 25.7 years; mean body weight, 80.4 kg), or fenoterol (1.5 μg/min; Partusisten; n = 12; mean age, 25.9 years; mean body weight, 79.9 kg), dobutamine (5 μg/kg/min; Dobutrex; n = 12; mean age, 24.7 years; mean body weight, 76.8 kg), or propranolol (loading dose, 0.14 mg/kg for 20 minutes followed by 0.63 μg/kg/min for the remaining 340 minutes; Dociton; n = 10; mean age, 25.4 years, mean body weight, 81 kg). For the latter treatment two volunteers had to be excluded because of illness. The subjects remained in the supine position from 1 hour before phlebotomy and during the following 6-hour intravenous treatment. Parallel to the intravenous treatment, they received 150 ml 0.9% sodium chloride per hour intravenously. Drinking was not allowed during these 6 hours. Hemoglobin and hematocrit were measured before phlebotomy and 4, 24, and 48 hours thereafter. Blood pressure (manual sphygmomanometer) and heart rate were recorded before and at 1, 2, 4, 6, 8, and 12 hours after termination of phlebotomy. Blood samples for erythropoietin concentrations were taken before and at 1, 2, 4, 6, 8, 12, 24, and 48 hours after termination of phlebotomy. Serum potassium levels were measured before and at 1 and 4 hours after the start of the infusion. Plasma renin activity (PRA) was measured before phlebotomy and at 1, 2, 4, 8, and 12 hours after the termination of phlebotomy. Blood samples for the control of propranolol concentrations were collected before and 4 hours after the start of the infusion. Urine collection (creatinine concentration, cyclic adenosine monophosphate [cAMP], or both) comprised the following intervals after the start of the drug infusion: 0 to 6, 6 to 12, 12 to 24, and 24 to 48 hours. The volunteers remained in the hospital for a total of 14 hours after arrival on the ward.

Analytics. Hemoglobin, hematocrit, potassium, and creatinine (serum and urine) were measured in the Department of Clinical Chemistry, University of Göttingen. The following assays were carried out with use of commercial kits: Serum erythropoietin was analyzed with a monoclonal enzyme-linked immunosorbent assay (catalog number 500, Medac GmbH, Hamburg, Germany); PRA was analyzed with an angiotensin I [^{125}I] radioimmunoassay (RENK P2510, Sorin Biomedica, Saluggia, Italy); urinary cAMP was measured by means of a cAMP [^{3}H] assay system

Table I. Effect of a hemorrhage of 750 ml on hemoglobin and hematocrit in the respective treatment groups

	Hemoglobin (gm%)		*Hematocrit (%)*	
	Before phlebotomy	*4 hr after phlebotomy*	*Before phlebotomy*	*4 hr after phlebotomy*
Placebo	14.8 ± 0.1	13.1 ± 0.1**	43.2 ± 0.5	38.2 ± 0.4**
Fenoterol	14.9 ± 0.2	12.9 ± 0.2**	43.9 ± 0.7	38.1 ± 0.8**
Dobutamine	15.1 ± 0.1	13.1 ± 0.2**	43.9 ± 0.4	38.8 ± 0.6**
Propranolol	15.1 ± 0.3	13.4 ± 0.2**	44.2 ± 0.7	39.2 ± 0.7**

Data are mean values ± SEM.
** $p < 0.01$.

Table II. Effects of study drugs on serum potassium levels before (0 hour) and 4 hours, creatinine clearance (CL_{CR}) up to 6 hours, and area under the plasma renin activity-time curve up to12 hours ($AUC_{PRA(0\text{-}12hr)}$) after the start of intravenous treatment

	Placebo	*Fenoterol*	*Dobutamine*	*Propranolol*
Potassium [mmol/L]				
0 Hour	4.0 ± 0.1	3.7 ± 0.1	3.9 ± 0.1	3.8 ± 0.1
4 Hours	3.8 ± 0.1	2.9 ± 0.01**	3.7 ± 0.1	4.0 ± 0.1
$AUC_{PRA(0\text{-}12hr)}$ [(ng/ml/hr) · hr)]	21.1 ± 1.7	44.3 ± 4.3**	39.2 ± 4.0**	13.5 ± 0.7
CL_{CR} (0-6hr) [ml/min/1.73 m^2]	119 ± 7	115 ± 14	141 ± 8*	120 ± 9

Data are mean values ± SEM.
* $p < 0.05$; ** $p < 0.01$.

(TRK 432, Amersham International, Amersham, England), with a purified binding protein from bovine muscle and a charcoal separation step according to the method by Brown et al.[8] Propranolol concentrations were measured by means of HPLC with fluorometric detection according to Panton et al.[9]

Calculations. Creatinine clearance (CL_{CR}; during the interval from 0 to 6 hours after the start of the drug administration) was calculated as follows:

$$CL_{CR} = U_{CR} \cdot V_{urine}/S_{CR}$$

in which U_{CR} is the creatinine concentration in urine, V_{urine} is the volume of urine, and S_{CR} is the serum concentration of creatinine taken in the middle of the collection period. Individual CL_{CR} values were adjusted to a body surface of 1.73 m^2. The area under the erythropoietin serum concentration–time curve ($AUC_{EPO(0\text{-}48hr)}$), using data adjusted to percent of baseline) and the area under the PRA–time curve ($AUC_{PRA(0\text{-}12hr)}$) were calculated by the linear trapezoidal rule.

Statistics. Values are expressed as mean ± SEM and were analyzed by ANOVA followed by post hoc *t* tests with the Bonferroni-Holm correction, and $p < 0.05$ was considered to be statistically significant. When meaningful, 95% confidence intervals (CI) were calculated for differences of sample means.

RESULTS

Before phlebotomy, hemoglobin and hematocrit were in the normal range (Table I). After phlebotomy, hemoglobin and hematocrit decreased in all treatment groups to the same extent as shown by the comparison of the 0-hour and 4-hour values (Table I).

At baseline, blood pressure (RR) and heart rate were comparable in all treatment groups (Fig. 1; other data not shown). During placebo treatment, mean systolic RR was unchanged. Fenoterol increased it by up to 15 mm Hg, dobutamine by up to 40 mm Hg (Fig. 1). Propranolol significantly decreased systolic RR (Fig. 1). Diastolic RR showed a slight decrease under placebo which was more pronounced during dobutamine infusion, however, not significantly different (data not shown). Fenoterol and propranolol produced a statistically significant decrease of diastolic RR by up to 20 mm Hg (data not shown). Heart rate remained unaltered during placebo administration and was significantly increased during fenoterol infusion (by approximately 40 per minute) and during dobutamine (by approx-

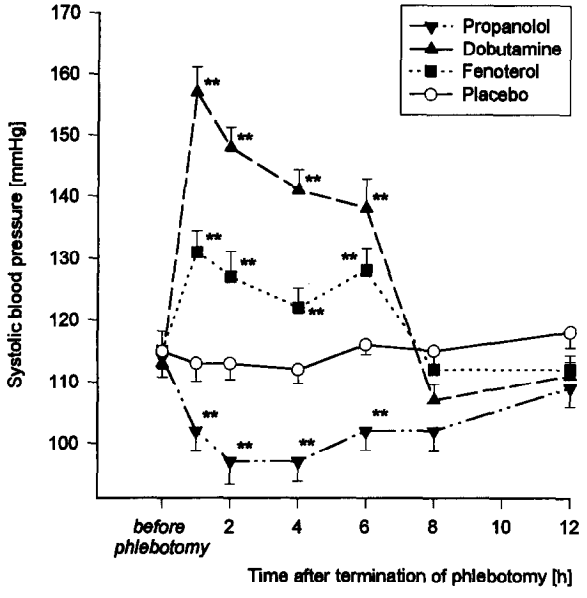

Fig. 1. Time course of systolic blood pressure during (up to 6 hours after termination of the phlebotomy) and up to 6 hours after the end of intravenous drug administration (12 hours after termination of the phlebotomy; mean ± SEM; $^{**}p < 0.01$).

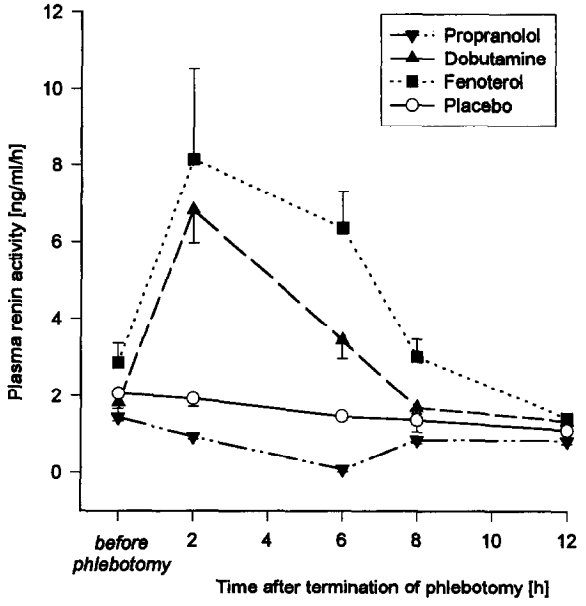

Fig. 2. Time course of plasma renin activity (PRA) during (up to 6 hours after termination of the phlebotomy) and up to 6 hours after the end of intravenous drug administration (12 hours after termination of the phlebotomy; mean ± SEM). The $AUC_{PRA,fenoterol(0\text{-}12hr)}$ and the $AUC_{PRA,dobutamine(0\text{-}12hr)}$ were significantly larger than $AUC_{PRA,placebo(0\text{-}12hr)}$ ($p < 0.001$ and $p < 0.01$, respectively).

imately 25 per minute), whereas it decreased significantly by 10 beats/min during propranolol treatment (data not shown).

The serum potassium levels were unaltered in the 4-hour sample during placebo, dobutamine, and propranolol infusion, whereas fenoterol led to a decrease after 4 hours of intravenous application (Table II; difference of means, 0.8 mmol/L; 95% CI, 0.97 to 0.63 mmol/L; $p < 0.001$).

Fig. 2 shows the PRA profiles up to 12 hours after the start of intravenous treatment. Propranolol infusion had a slightly decreasing effect on PRA compared with placebo. PRA increased statistically significant during fenoterol and dobutamine infusion (compared with placebo). $AUC_{PRA,fenoterol(0\text{-}12hr)}$ was statistically significantly larger than $AUC_{PRA,placebo(0\text{-}12hr)}$ [Table II; difference of means, 23.2 (ng/ml/hr) · hr; 95% CI, 27.5 to 18.8 (ng/ml/hr) · hr; $p < 0.001$]. $AUC_{PRA,dobutamine(0\text{-}12hr)}$ was larger than $AUC_{PRA,placebo(0\text{-}12hr)}$ [Table II; difference of means, 18.1 (ng/ml/hr) · hr; 95% CI, 27.0 to 9.2 (ng/ml/hr) · hr; $p < 0.01$). Four hours after the start of the intravenous drug infusion the mean plasma concentration of propranolol was 75 ± 7.9 ng/ml.

Creatinine clearance measured during the drug treatment period (0 to 6 hours) was in the normal age-related range (Table II). The clearance of the dobutamine-treated group was statistically significantly different from the placebo group (difference of means, 21.6 ml/min; 95% CI, 2.8 to 40.4 ml/min; $p < 0.05$). There was no difference in any of the treatment groups during the other periods (data not shown).

Urinary cAMP excretion was statistically significantly increased during fenoterol infusion and the first collection period thereafter (Fig. 3). It then declined to normal levels. There was no significant change of cAMP excretion in any other treatment group during all collection periods up to 48 hours after the start of treatment.

Baseline erythropoietin concentrations were similar in all treatment groups (propranolol, 6.2 ± 1.3 mU/ml; dobutamine, 8.2 ± 2.2 mU/ml; fenoterol, 5.3 ± 0.9 mU/ml; placebo, 5.3 ± 0.9 mU/ml). Maximal erythropoietin concentrations (C_{max}) had a statistically significant increase up to 300% of baseline

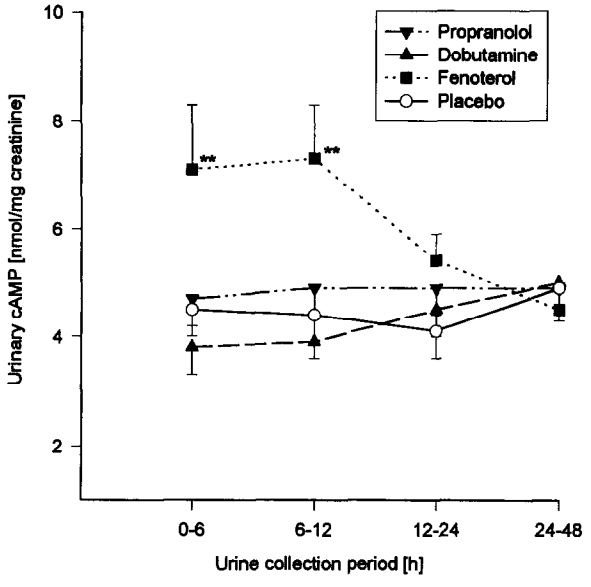

Fig. 3. Urinary excretion of cyclic adenosine monophosphate (cAMP) during the entire trial period. The collection period from 0 to 6 hours covers intravenous medication (mean ± SEM; $^{**}p < 0.01$).

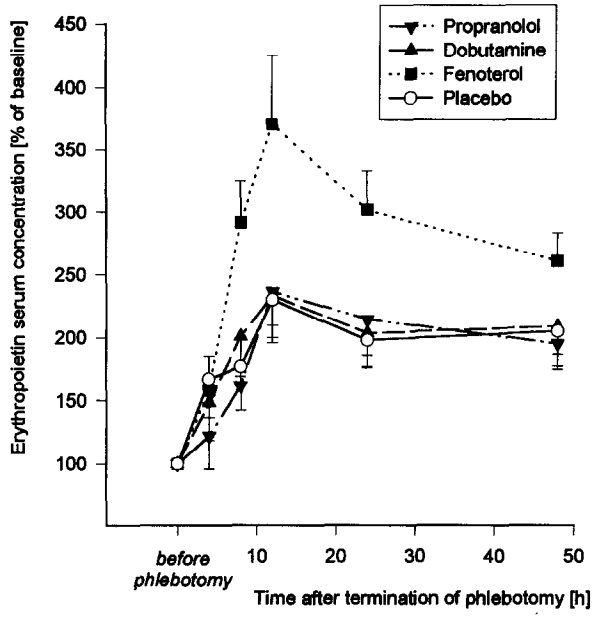

Fig. 4. Time course of erythropoietin serum concentrations expressed as a percentage of baseline values (mean ± SEM). For improved clarity the 1-, 2-, and 6-hour values were omitted.

during fenoterol infusion (Fig. 4). $AUC_{EPO(0\text{-}48hr)}$ values are depicted in Fig. 5. The mean $AUC_{EPO(0\text{-}48hr)}$ of fenoterol-treated subjects was 37% larger than the placebo value (difference of means, 4310; 95% CI, 1076 to 7545 [hour × percent of baseline erythropoietin concentrations]). The erythropoietin serum concentrations declined toward the baseline during the second half of the observation period (Fig. 4).

DISCUSSION

Current state of knowledge. There is circumstantial evidence that adrenergic activity can modulate erythropoietin production. However, the earlier investigations were done in bone marrow cultures or they used assays that measured erythropoietin concentrations only indirectly. The experiments by Ibrahim et al.[5] gave hints that β_2-adrenergic receptor agonists decrease erythropoietin production in animals. On the basis of earlier results,[10] we suggested that adrenergic activity may also lead to an increase of erythropoietin concentrations in humans: After phlebotomy, the nonspecific adenosine receptor antagonist theophylline increased erythropoietin concentrations and plasma renin activity in healthy subjects.[10] We hypothesized that these parallel effects were caused by an increased sympathetic tone caused by a block of presynaptic inhibitory adenosine receptors by theophylline. However, there was no evidence at that time that adrenergic mechanisms would influence erythropoietin production in humans.

This investigation used phlebotomy as a model of controlled physiologic stimulation of erythropoietin production, which was then modulated by adrenergic receptor stimulating and blocking agents. Fenoterol was chosen as a predominantly selective β_2-adrenergic receptor agonist[11] because of the vast experience with intravenous administration of this compound in obstetrics. Dobutamine was considered to be the most specific β_1-adrenergic receptor agonist available for human use with a strong, predominantly direct β_1-adrenergic activity and no effect on dopamine receptors.[11,12] The infusion rate for fenoterol was identical with the regular rate used for tocolytic treatment in the Department of Obstetrics at the University of Göttingen. The infusion rate for dobutamine was the clinically recommended rate that is supposed to exert predominantly β_1-adrenergic receptor agonist activity.[11] Because the doses for the latter treatments have a clinically undisputed effect, plasma concentrations were not measured and only pharmacodynamic measures, such as blood pressure and heart rate, were taken as

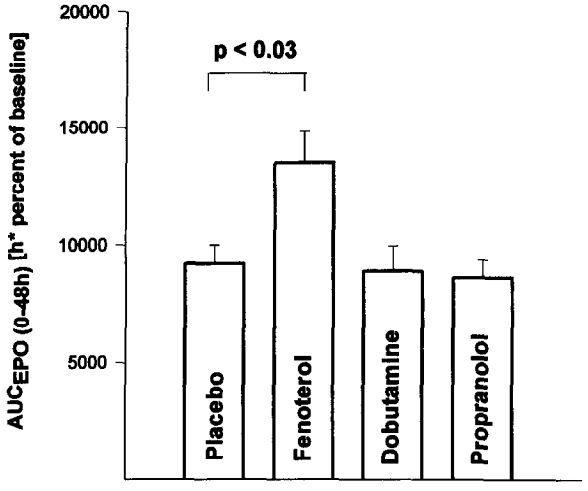

Fig. 5. Area under the erythropoietin serum–concentration time curve (AUC) for the respective treatments (mean ± SEM). Fenoterol raised AUC by 37% compared with placebo.

a control for effective treatment (e.g., Fig. 1). The nonselective β-adrenergic receptor blocker propranolol was added to investigate whether β-adrenergic receptor blockade would influence the erythropoietin response after hemorrhage. The plasma concentrations aimed for are associated with an almost complete blockade of β-adrenergic receptors.[13] Because the infusion scheme for propranolol was estimated from a computer simulation (Topfit 2.0), the plasma concentrations for propranolol were controlled in addition to the control of pharmacodynamic measures.

Control of tools. Basal concentrations of erythropoietin in our study were similar in all treatment groups and were in the normal range for healthy subjects with the erythropoietin ELISA used (2.5 to 25 mIU/L).[14] The tool for stimulation of erythropoietin production—hemorrhage—resulted in a similar decrease of hemoglobin and of hematocrit in all treatment groups. Within 2 hours after the end of phlebotomy, erythropoietin concentrations increased up to a maximum of about twofold of baseline values during placebo treatment. This increase was on the order of magnitude that could be expected after a hemorrhage of this volume.[10]

The specific effects of the drugs through β-adrenergic receptors can be confirmed by their effect on blood pressure and heart rate. As expected, dobutamine had a positive inotropic effect, causing the highest increase of systolic RR in all groups together with a moderate increase of heart rate. The β_2-adrenergic receptor–mediated, inodilatory effects of fenoterol were clearly visible by the moderate increase of systolic RR and the drop of diastolic RR, together with the highest increase in heart rate in all groups. Propranolol caused the expected decrease of systolic and diastolic RR and heart rate. Propranolol serum concentrations were in a range that has been associated with an almost complete blockade of β-adrenergic receptors.[13] Furthermore, fenoterol lowered serum potassium and increased urinary cAMP excretion, typical effects of this class of drugs.[11] The cAMP values in the placebo, dobutamine, and propranolol groups were within the range that was expected for normal subjects.[15] The PRA baseline values in all groups were in the expected range for supine position (0.2 to 2.7 ng/ml/hr).[16] The effect of the study drugs on PRA confirmed the respective β-adrenergic receptor stimulation or blockade: Increased renin production has been shown to be attributable to β_1-and β_2-adrenergic stimulation and to decreased renin secretion under β-adrenergic receptor blockade by propranolol.[17] Taken together, our control parameters suggest that the drugs used exerted the desired pharmacodynamic response through the respective adrenergic receptors.

Effect of treatment on erythropoietin concentrations. In this model of controlled erythropoietin stimulation, fenoterol did significantly increase erythropoietin concentrations, in contrast to dobutamine. Our finding is in agreement with the earlier in vitro and in vivo animal experiments[4,18,19] and suggests that β_2-adrenergic stimulation can also increase erythropoietin production in humans. The nonspecific β-adrenergic receptor antagonist propranolol did not influence the physiologic course of erythropoietin concentrations after phlebotomy. As shown above by pharmacodynamic and pharmacokinetic measures, the dose of propranolol can be considered to be appropriate to block β-adrenergic receptors. This finding may be interpreted that other endogenous regulators of erythropoietin production may overrule the presumed block by propranolol. However, the reason is not yet clear, and this finding is currently under further investigation.

A number of underlying mechanisms may be discussed for the presumably β_2-adrenergic receptor–mediated effect of fenoterol on erythropoietin concentrations. First, a positive correlation of renin levels and plasma erythropoietin concentrations has been shown in hypoxic rats, leading to the sugges-

tion that renin may influence erythropoietin production.[20] In our experimental setting PRA increased during fenoterol and dobutamine administration by a similar order of magnitude. However, a clear effect on erythropoietin concentrations was measured exclusively in the fenoterol group. Therefore one would not conclude that renin does play a major role in our model.

Second, changes of glomerular filtration rate (GFR) have been discussed as a signal for erythropoietin production.[21,22] Increased GFR would increase the solute load of the proximal tubules and in turn increase the activity of tubular sodium-potassium-ATPase activity because of increased reabsorption of sodium. As a result of this reabsorptive process, oxygen consumption increases and would thus elicit a signal for erythropoietin production. In our model, GFR—as measured by creatinine clearance—was significantly higher only during dobutamine infusion, most likely because of increased cardiac output and its weak dilatory effect on afferent arterioles in the kidney.[17] However, this increase in GFR occurred without an effect on erythropoietin concentrations. Therefore altered GFR can be excluded as a cause of erythropoietin concentration changes in our experiment.

Third, the administration of fenoterol causes two typical effects for this class of drugs: namely, a decrease of serum potassium levels (and the following hyperpolarization of cells) and an increase of cAMP concentrations. Either mechanism may be considered relevant for erythropoietin production. However, it is difficult to decide whether hypokalemia or cAMP increase or both together are linked to the increase of erythropoietin concentrations in our experiment. β-Adrenergic agents exert their influence on potassium metabolism through a β_2-adrenergic receptor mechanism. In humans, hypokalemia induced by epinephrine infusions can be prevented by concomitant infusion of a selective β_2-adrenergic antagonist.[23] The cellular mechanism of this β_2-adrenergic effect appears to be caused by stimulation of sodium-potassium-ATPase after activation of membrane-bound adenylate cyclase.[24]

Alternatively, the effect of fenoterol on erythropoietin concentrations may be mediated by a β_2-adrenergic receptor–mediated mechanism that is cAMP driven. The increased urinary cAMP excretion during fenoterol infusion would allow this interpretation. Data from liver cell cultures and rat renal mesangial cells point toward this mechanism of action because activation of adenylate cyclase by forskolin or isoproterenol (INN, isoprenaline) greatly enhanced erythropoietin production by these cells.[25,26]

The proposed link between β-adrenergic receptor effects and erythropoietin production would allow to explain the action of ACE inhibitors on serum erythropoietin levels in humans. In a number of clinical settings (e.g., patients receiving hemodialysis or healthy volunteers; for a review see Gleiter[27]) ACE inhibitors are able to reduce hematocrit and erythropoietin levels. This may be a result of their blocking activity on angiotensin II–mediated increase of central sympathetic outflow and facilitation of peripheral sympathetic (i.e., adrenergic) transmission in the kidney.[28] Experiments in hypoxic animals have shown the influence of the autonomic nerve system in the control of erythropoietin production.[29] Finally, this line of evidence can be extended by our earlier findings[10] that theophylline increases erythropoietin concentrations after hemorrhage, possibly by inhibition of the blocking effect of adenosine receptors on sympathetic nerves.

We thank the following manufacturers for gifts of Partusisten, Dobutrex, and Dociton: Boehringer Ingelheim KG, Ingelheim am Rhein, Germany, Lilly Deutschland GmbH, Giessen, Germany, and Zeneca/Rhein Pharma, Schlettstadt, Germany.

References

1. Jelkmann W. Erythropoietin: structure, control of production, and function. Physiol Rev 1992;72:449-9.
2. Fink GD, Paulo LG, Fisher JW. Effects of beta adrenergic blocking agents on erythropoietin production in rabbits exposed to hypoxia. J Pharmacol Exp Ther 1975;193:176-81.
3. Fink GD, Fisher JW. Erythropoietin production after renal denervation or beta-adrenergic blockade. Am J Physiol 1976;230:508-13.
4. Fink GD, Fisher JW. Stimulation of erythropoiesis by beta adrenergic agonists; II: mechanism of action. J Pharmacol Exp Ther 1977;202:199-208.
5. Ibrahim H, Kahn E, Harper RG, Wapnir RA. Erythropoietin levels in fetal rats after ritodrine and terbutaline administration. Biochem Med Metabol Biol 1994;52:128-31.
6. Perazella MA, Bia MJ. Posttransplant erythrocytosis: case report and review of newer treatment modalities. J Am Soc Nephrol 1992;3:1653-9.
7. Jackson EK, Garrison JC. Renin and angiotensin. In: Hardman JG, Limbird LE, Molinoff PB, Ruddon RW, Gilman AG, editors. Goodman and Gilman's the pharmacological basis of therapeutics. New York: McGraw-Hill, 1996:659-82.

8. Brown BL, Albano JDM, Ekins RP, Sgherzi AM. A simple and sensitive saturation assay method for the measurement of adenosine 3′,5′-cyclic monophosphate. Biochem J 1971;121:561-2.
9. Panton LB, Guillen GJ, Williams L, Graves JE, Vivas C, Cediel M, et al. The lack of effect of aerobic exercise training on propranolol pharmacokinetics in young and elderly adults. J Clin Pharmacol 1995;35: 885-94.
10. Gleiter CH, Freudenthaler S, Delabar U, Eckardt KU, Mühlbauer B, Gundert-Remy U, et al. Erythropoietin production in healthy volunteers subjected to controlled haemorrhage: evidence against a major role for adenosine. Br J Clin Pharmacol 1996;46:729-35.
11. Hofman BB, Lefkowitz RJ. Catecholamines, sympathomimetic drugs, and adrenergic receptor antagonists. In: Hardman JG, Limbird LE, Molinoff PB, Ruddon RW, Gilman AG, editors. Godman and Gilman's the pharmacological basis of therapeutics. New York: McGraw-Hill, 1996:199-248.
12. Vapaatalo H, Säynävälammi P. Effects on the general hemodynamics and peripheral circulation. In: Szekeeres L, editor. Adrenergic activators and inhibitors; part I: handbook of experimental pharmacology; vol 54/I. Berlin: Springer, 1980:853-947.
13. Coltart DJ, Shand DG. Plasma propranolol levels in the quantitative assessment of beta adrenergic blockade in man. Br Med J 1970;3:731-4.
14. Wolff M, Jelkmann W. Clinical applicability of the determination of erythropoietin. In: Pagel H, Weiss CH, Jelkmann W, editors. Pathophysiology and pharmacology of erythropoietin. Berlin: Springer, 1992:99-107.
15. Broadus AE, Mahaffey JE, Bartter FC, Neer RM. Nephrogenous cyclic adenosine monophosphate as a parathyroid function test. J Clin Invest 1977;60:771-83.
16. Karlberg BE, Tolagen K. Relationships between blood pressure, age, plasma renin activity and electrolyte excretion in normotensive subjects. Scand J Clin Lab Invest 1977;37:521-8.
17. Osswald H, Greven J. Effects of adrenergic activators and inhibitors on kidney function. In: Szekeeres L, editor. Adrenergic activators and inhibitors; part II: handbook of experimental pharmacology; vol 54/II. Berlin: Springer, 1981:243-88.
18. Gross DM, Fisher JW. Effects of terbutaline, a synthetic beta adrenoceptor agonist, on in vivo erythropoietin production. Arch Int Pharmacodyn 1978;236: 192-201.
19. Jelkmann W, Beckman B, Fisher JW. Enhanced effects of hypoxia on erythropoiesis in rabbits following beta-2 adrenergic activation with albuterol. J Pharmacol Exp Ther 1979;211:99-103.
20. Gould AB, Goodman S, DeWolf R, Onesti G, Swartz C. Interrelation of the renin system and erythropoietin in rats. J Lab Clin Med 1980;96:523-34.
21. Osswald H, Gleiter CH, Mühlbauer B. Therapeutic use of theophylline to antagonize the renal effects of adenosine. Clin Nephrol 1995;43(suppl 1):S33-7.
22. Eckardt KU. Erythropoietin: oxygen-dependent control of erythropoiesis and its failure in renal disease. Nephron 1994;67:7-23.
23. Brown MJ, Brown DC, Murphy MB. Hypokalemia from beta-2 receptor stimulation by circulating epinephrine. New Engl J Med 1983;399:1414-9.
24. Clausen T, Flatman JA. β-2 adrenoceptors mediate the stimulating effect of adrenaline in active electrogenic Na-K transport in rat soleus muscle. Br J Pharmacol 1980;68:749-55.
25. Kurtz A, Jelkmann W, Pfeilschifter J, Bauer C. Role of prostaglandins in hypoxia-stimulated erythropoietin production. Am J Physiol 1985;249:C3-8.
26. Kurtz A, Jelkmann W, Pfuhl A, Malmström K, Bauer C. Erythropoietin production by fetal mouse liver cells in response to hypoxia and adenylate cyclase stimulation. Endocrinology 1986;118:567-72.
27. Gleiter CH. Posttransplant erythrocytosis: a model for the investigation of the pharmacological control of renal erythropoietin production? Int J Clin Pharmacol Ther 1996;34:489-92.
28. Goodfriend TL, Elliott ME, Catt KJ. Angiotensin receptors and their antagonists. N Engl J Med 1996; 334:1649-54.
29. Beynon G. The influence of the autonomic nervous system in the control of erythropoietin secretion in the hypoxic rat. J Physiol (Lond) 1977;266:347-60.