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Endothelium-Derived Relaxing Factor Is Important in Mediating the High Output State in Chronic Severe Anemia

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Objectives. **We evaluated the endothelial and vascular smooth muscle function in patients with chronic severe anemia to determine whether increased basal nitric oxide levels contribute to the systemic vasodilation and high cardiac output seen in these patients.**

Background. **Patients with chronic severe anemia have a high output state due to a low systemic vascular resistance. However, the cause of the low vascular resistance is unclear. Because hemoglobin is a potent inhibitor of endothelium-derived relaxing factor, we postulated that in chronic severe anemia, low circulating hemoglobin results in reduced inhibition of endothelium-derived relaxing factor. The basal endothelium-derived relaxing factor activity therefore increases, and this contributes significantly to the low systemic vascular resistance and the hyperdynamic state seen in this condition.**

Methods. **Hemodynamic variables and forearm blood flow (using plethysmography) were measured in eight patients with chronic severe anemia before (hematocrit 16 ± 2% [mean ± SD]) and within 24 h of red blood cell transfusion (n = 6, hematocrit 30 ± 1%) and in six control subjects. The effect on baseline blood flow of blocking endothelium-derived relaxing factor activity with N^G-monomethyl-L-arginine was investigated. In addition, the effects of both endothelium-dependent and endothelium-independent vasodilators on forearm blood flow were tested.**

Results. **Baseline forearm blood flow was markedly increased in untreated patients (6.5 ± 1.2 ml/min per 100 ml) compared with that in control subjects (2.8 ± 0.7 ml/min per 100 ml, $p < 0.0001$, 95% confidence interval [CI] for difference −5 to −2.5). Red blood cell transfusion significantly reduced blood flow in the anemic patients to 3.5 ± 1.1 ml/min per 100 ml ($p < 0.001$, 95% CI for difference −4.9 to −1.9), which was not significantly different from that in control subjects; increased systemic vascular resistance (796 ± 141 to 1,230 ± 151 dynes·s·cm^{-5}, $p < 0.001$); and decreased cardiac output (4.9 ± 0.6 to 3.5 ± 0.5 liters/min per m^2, $p < 0.001$). N^G-monomethyl-L-arginine (16 μmol/min), a specific inhibitor of endothelium-derived relaxing factor, reduced forearm blood flow by an equal amount ($p = 0.9$, 95% CI for difference −0.7 to 0.8) in control subjects (0.98 ± 0.39 ml/min) and treated patients (1.03 ± 0.8 ml/min) but caused a threefold greater decrease in flow (2.9 ± 0.9 ml/min) in untreated patients ($p = 0.0003$, 95% CI for difference between untreated patients and control subjects 1.1 to 2.7). These findings suggest increased basal endothelium-derived relaxing factor activity in patients with anemia. Stimulated forearm blood flows (both endothelium dependent and endothelium independent) were similar in all groups, confirming normal endothelial and smooth-muscle function.**

Conclusions. **These findings support the hypothesis that enhanced basal endothelium-derived relaxing factor activity makes an important contribution to the low systemic vascular resistance in chronic severe anemia.**

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Patients with chronic severe anemia have a high output state due to a low systemic vascular resistance, which is rapidly corrected after treatment (1,2). Although its pathogenesis remains unclear, low systemic vascular resistance has important implications. We have shown (2,3) that low systemic vascular resistance and not myocardial dysfunction is the major factor that mediates salt and water retention in various syndromes of high output congestive heart failure. Two major factors have been suggested to contribute to the low systemic vascular resistance in anemia: reduced viscosity and peripheral vasodilation. The cause of peripheral vasodilation has remained unexplained. In recent years, endothelium-derived relaxing factor or nitric oxide has been shown to play an important role in the regulation of vascular tone and arterial blood pressure (4,5). Because hemoglobin is a potent inhibitor of endothelium-derived relaxing factor (6), we postulated that in chronic severe anemia low circulating hemoglobin results in reduced inhibition of endothelium-derived relaxing factor. The basal endothelium-derived relaxing factor activity therefore increases, and this accounts for the generalized vasodilation and the high output state (7). In this report, we present data to support this hypothesis.

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Methods

Patients. The study was carried out at the Dayanand Medical College and Hospitals, Ludhiana, India, in eight male patients (mean [±SD] body surface area 1.55 ± 0.1 m^2) with chronic severe anemia who presented with symptoms of fatigue and shortness of breath (New York Heart Association functional class III). The jugular venous pressure was not elevated, but most patients had mild ankle edema. Chest radiographic findings were normal. The electrocardiogram (ECG) showed nonspecific ST segment and T wave changes. Anemia was due to hookworm infection in three, chronic bleeding piles in two, idiopathic aplastic anemia in one and nutritional deficiency in two. Routine clinical chemistry, serum creatinine levels, liver function tests and serum albumin levels were normal. None of the patients had received any treatment for anemia or heart failure. Six patients were restudied after rapid transfusion (4.5 ± 0.5 U) of packed red blood cells. Six age-matched normal male subjects (body surface area 1.54 ± 0.06 m^2) were studied as control subjects. The study was approved by the Dayanand Medical College and Hospitals Human Studies Committee in July 1992, and all subjects gave written informed consent to the procedure.

Protocol. After initial forearm blood flow measurements, the anemic patients underwent a hemodynamic study. They then received transfusion of packed red blood cells over the next 12–16 h to increase their hematocrit to ~30%. Forearm blood flow studies and hemodynamic measurements were repeated at the end of transfusion at an average of 24 h after the first study. Hemodynamic measurements were not made in the control subjects, and forearm blood flow was studied only once in these subjects.

Forearm blood flow. Studies were performed in the morning in a quiet temperature-controlled room with the subjects laying supine. An 18-gauge cannula was inserted into the brachial artery of the nondominant arm, and forearm blood flow (ml/100 ml forearm volume per min) was measured in that arm using a mercury-in-rubber strain gauge plethysmograph (model EC5; D.E. Hokanson) (8,9). All flow measurements were made during intraarterial infusion of either 5% dextrose in water or drug at 1 ml/min. Blood pressure was recorded from the intraarterial catheter and heart rate from the ECG monitor during each measurement.

After obtaining baseline measurements with 5% dextrose, we measured forearm blood flow during infusion of either an endothelium-dependent vasodilator (methacholine) or an endothelium-independent vasodilator (sodium nitroprusside). Methacholine was infused in two cumulative doses of 0.3 and 1.5 μg/min. Sodium nitroprusside was infused at 1 and 5 μg/min. These doses have been shown to produce comparable increases in blood flow in normal subjects (9). Each dose was infused for 3 min, and forearm blood flow was measured during the last minute of the infusion. A 20-min rest period was allowed between infusion of the two drugs to allow flow to return to the basal level, and a control measurement was obtained before infusion of the second drug. After testing the responses to methacholine and nitroprusside, a further 20-min period was allowed for return of flow to basal values. The arginine analogue N^G-monomethyl-L-arginine, an inhibitor of nitric oxide (5), was then infused at 4 and 16 μmol/min (infusion rate 1 ml/ml) for 4 min each, and during the last minute of each infusion flow measurements were repeated. At the end of these measurements, N^G-monomethyl-L-arginine infusion was continued and the effects of 1.5 μg/min methacholine and 5 μg/min sodium nitroprusside were tested, with rest periods between the drugs. The sequence of administration of methacholine and sodium nitroprusside before and after infusion of N^G-monomethyl-L-arginine was randomized and the subjects were not aware of which drug was being infused.

Hemodynamic variables. Right heart catheterization was performed with a Swan-Ganz thermodilution balloon catheter. Arterial pressure was measured from the intraarterial brachial cannula. Pressures were measured with Hewlett-Packard 1290C quartz transducers and a Hewlett-Packard 7835A monitor. Cardiac output was determined by thermodilution (model SP 1445, Gould).

Statistics. Results are presented as mean value ± SD. Differences in basal flow between the control and the two anemic groups were analyzed using the unpaired *t* test; differences between the untreated and treated anemic groups were compared using the paired *t* test. The effect of multiple comparisons was adjusted using the Bonferroni correction. The effects of drug interventions (multiple doses of N^G-monomethyl-L-arginine, methacholine and nitroprusside) in various groups were compared using the two-way fixed-effects univariate analysis of variance for repeated measurements, and the p values were corrected with the Greenhouse-Geisser correction. For comparisons between the patients (untreated or treated) and control subjects, we used one between-group factor (group) and one within-group factor (drug dose with multiple levels). For comparisons between the patient groups (untreated vs. treated), two within-group factors were used (group with two levels and drug dose with multiple levels). The interaction term (group × dose) was used to assess the differences in the effect of an intervention among the various groups. All the analyses were done using the multivariate analysis of variance module in a commercial statistical program (STATISTICA, StatSoft Inc., 1994); $p < 0.01$ was considered significant.

Results

The patients and normal control subjects were of similar age (33 ± 15 vs. 33 ± 9 years, respectively). Hemoglobin and hematocrit (4.8 ± 0.7 g/dl and 16 ± 2%) were significantly lower in patients than in control subjects (13.0 ± 0.5 g/dl and 40 ± 1%, $p < 0.001$). After blood transfusion, hemoglobin and hematocrit increased significantly in the patients (9.6 ± 0.7 g/dl and 30 ± 1.0%, $p < 0.001$) but remained lower than that in the control subjects ($p < 0.001$).

Table 1. Basal and Stimulated Forearm Blood Flow (mean ± SD) in Patients With Chronic Severe Anemia Before and After Treatment and in Normal Control Subjects

	Untreated Anemia (n = 8)	Treated Anemia (n = 6)	Control Subjects (n = 6)
Hemoglobin (g/dl)	4.8 ± 0.7*†	9.6 ± 0.7*	13.0 ± 0.5
Hematocrit (%)	16 ± 2*†	30 ± 1*	40 ± 1
Hemodynamic variables			
Heart rate	86 ± 14	68 ± 7	60 ± 12
Mean right atrial pressure (mm Hg)	3 ± 1	1 ± 1	
Mean pulmonary artery pressure (mm Hg)	11 ± 3	8 ± 2	
Mean pulmonary wedge pressure (mm Hg)	5 ± 3	4 ± 2	
Mean arterial pressure (mm Hg)	74 ± 8*†	85 ± 7*	94 ± 4
Cardiac output (liters/min per m^2)	4.9 ± 0.6†	3.5 ± 0.5	
Systemic vascular resistance (dynes·s·cm^{-5})	796 ± 141†	1,230 ± 151	
Forearm blood flow (ml/min per 100 ml vol)			
Baseline flow	6.5 ± 1.2*†	3.5 ± 1.1‡	2.8 ± 0.7
Peak flow with			
Mch 0.3 μg/min§	11.1 ± 3	9.6 ± 3.4	7.6 ± 4
Mch 1.5 μg/min§	19.7 ± 5.5	18.6 ± 5.6	14.4 ± 6.6
SNP 1.0 μg/min§	10.7 ± 2.1	7.0 ± 2.3	6.6 ± 1.6
SNP 5.0 μg/min§	19.1 ± 5.0	18.0 ± 5.9	13.5 ± 4.7
L-NMMA 4 μM/min‖	5.0 ± 0.9	3.0 ± 1.0	2.2 ± 0.5
L-NMMA 16 μM/min‖	3.6 ± 0.8	2.5 ± 0.9	1.8 ± 0.4
L-NMMA 16 μM/min + Mch 1.5 μg/min¶	12.7 ± 4.7	10.6 ± 3.7	7.8 ± 4.2
L-NMMA 16 μM/min + SNP 5.0 μg/min¶	17.9 ± 6.4	14.3 ± 4.1	11.5 ± 3.4
Change in flow (peak − baseline) with			
Mch 0.3 μg/min§	4.6 ± 2.7	6.1 ± 2.7	4.8 ± 1.6
Mch 1.5 μg/min§	13.2 ± 4.9	15.1 ± 4.8	11.7 ± 6.8
SNP 1.0 μg/min§	4.2 ± 2.1	3.5 ± 1.9	3.8 ± 1.8
SNP 5.0 μg/min§	12.6 ± 4.0	14.5 ± 5.0	10.7 ± 5.0
L-NMMA 4 μM/min‖	−1.5 ± 0.8	−1.0 ± 1.1	−0.6 ± 0.2
L-NMMA 16 μM/min‖	−2.9 ± 0.9	−1.0 ± 0.8	−1.0 ± 0.4
L-NMMA 16 μM/min + Mch 1.5 μg/min¶	6.2 ± 4.5	7.0 ± 3.2	5.1 ± 4.2
L-NMMA 16 μM/min + SNP 5.0 μg/min¶	11.4 ± 5.5	10.8 ± 3.2	8.7 ± 3.8

*$p < 0.001$ versus control. †$p < 0.001$ versus treated. ‡p = NS versus control. §All (group × drug) interaction among groups, p = NS by analysis of variance. ‖Untreated versus control or treated (group × drug) interaction, $p < 0.001$; treated versus control, p = NS. ¶p = NS among all groups. Data presented are mean value ± SD. L-NMMA = N^G-monomethyl-L-arginine; Mch = methacholine; SNP = sodium nitroprusside.

Hemodynamic variables (Table 1). Rest heart rate was 86 ± 14 beats/min; right atrial pressure (3 ± 1 mm Hg), mean pulmonary artery pressure (11 ± 3 mm Hg) and mean pulmonary wedge pressure (5 ± 3 mm Hg) were within normal limits. Cardiac output was high (4.9 ± 0.6 liters/min per m^2) but mean arterial blood pressure (74 ± 8 mm Hg) and systemic vascular resistance (796 ± 141 dynes·s·cm^{-5}) were low. After blood transfusion, heart rate (68 ± 7 beats/min, $p < 0.05$) and cardiac output (3.5 ± 0.5 liters/min per m^2; $p < 0.001$) decreased, and systemic vascular resistance (1,230 ± 151 dynes·s·cm^{-5}, $p < 0.001$) increased.

Forearm blood flow studies. The primary a priori hypothesis in this study was that an excess of basal endothelium-derived relaxing factor is important in the pathogenesis of reduced systemic vascular resistance. This was tested by comparing the effects of N^G-monomethyl-L-arginine and correction of anemia on baseline blood flow.

Basal forearm blood flow (Fig. 1, Table 1). Basal forearm blood flow in the anemic subjects was 6.5 ± 1.2 ml/100 ml forearm volume per min, more than twice that seen in the control subjects (2.8 ± 0.7 ml/100 ml forearm volume per min, $p < 0.0001$, 95% confidence interval [CI] for difference −5 to −2.5). Blood transfusion significantly reduced blood flow in the anemic patients to 3.5 ± 1.1 ml/100 ml forearm volume per min (p = 0.002, 95% CI for difference −4.9 to −1.9), and this value was not significantly different from that the control subjects (p = 0.19, 95% CI for difference −1.8 to 0.4).

Effect of N^G-monomethyl-L-arginine. N^G-monomethyl-L-arginine caused a dose-dependent decrease in basal forearm blood flow in all three groups (Fig. 1 [top], Table 1). Although the dose response to N^G-monomethyl-L-arginine was similar in the treated and control groups (p = 0.96 for absolute flow and p = 0.78 for change in flow or delta flow), the untreated group showed a significantly greater decrease in forearm blood flow than either the treated group (p = 0.0003 for absolute flow and p = 0.04 for delta flow) or control subjects (p = 0.00001 for absolute flow and p = 0.007 for delta flow). Thus, with 16 μmol/min N^G-monomethyl-L-arginine, forearm blood flow decreased by an equal amount (p = 0.9, 95% CI −0.7 to 0.8) in both control subjects (0.98 ± 0.39 ml/min) (Fig. 1 [bottom])

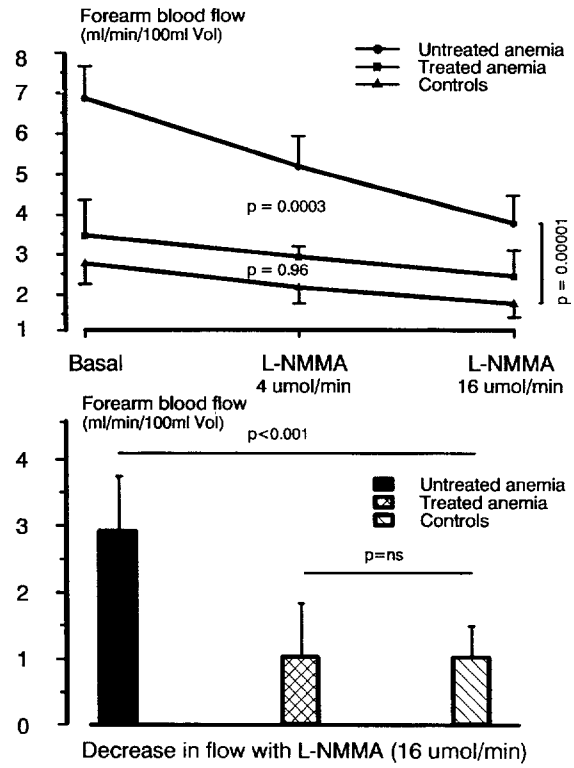

Figure 1. Dose-dependent decrease in basal forearm blood flow with 4 and 16 μmol/min of N^G-monomethyl-L-arginine (L-NMMA) in treated and untreated patients with chronic severe anemia (n = 6) and in normal control subjects (**top**). **Bars** (**bottom**) show absolute decreases from baseline in basal forearm blood flow with 16 μmol/min of N^G-monomethyl-L-arginine in the three groups; p values (**top**) are by analysis of variance (group × dose interaction) with Greenhouse-Geisser correction.

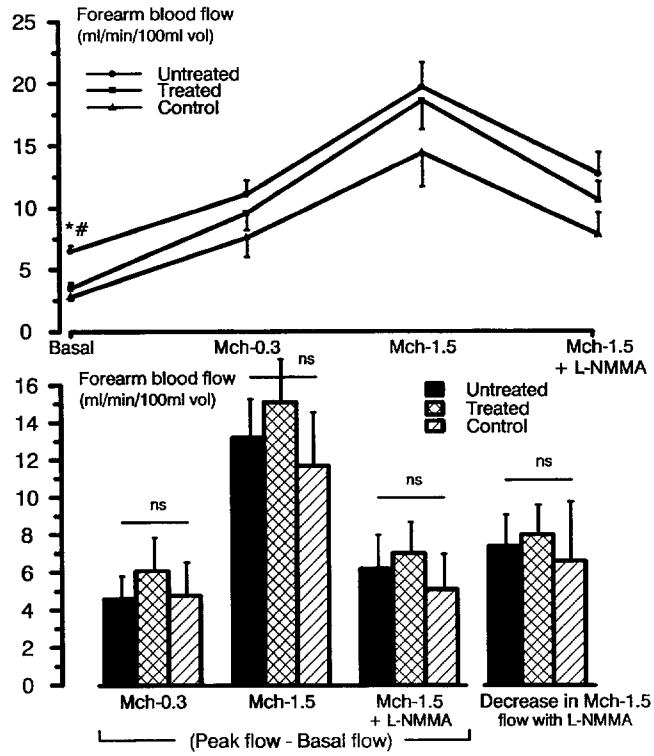

Figure 2. Effect of the endothelium-dependent vasodilator methacholine (Mch) on forearm blood flow in normal control subjects and in patients with chronic severe anemia before and after treatment. **Top,** Basal and peak stimulated flow with methacholine (0.3 and 1.5 μg/min) and the effect of N^G-monomethyl-L-arginine (L-NMMA) (16 μmol/min) on the methacholine-1.5–stimulated flow. **Bottom,** Increase (peak − basal) in flow with methacholine (0.3 and 1.5 μg/min) and methacholine 1.5 plus N^G-monomethyl-L-arginine. The last group of **bars** shows the decrease in methacholine-1.5–stimulated blood flow after administration of N^G-monomethyl-L-arginine (16 μmol/min). *p < 0.001 for baseline flow, untreated versus control; #p < 0.001 for baseline flow, untreated versus treated.

and treated patients (1.03 ± 0.8 ml/min) Fig. 1 [bottom]. In contrast, the same dose of N^G-monomethyl-L-arginine caused a nearly threefold greater decrease in flow (2.9 ± 0.9 ml/min) (Fig. 1 [bottom]) in the untreated patients (p = 0.0003, 95% CI for difference between untreated and control subjects 1.1 to 2.7). Both doses of N^G-monomethyl-L-arginine had no effect on the systemic arterial blood pressure. For this reason the forearm vascular resistance data are not shown because they mirrored the blood flow changes.

Effects of endothelium-dependent and endothelium-independent vasodilators on stimulated forearm blood flow (Table 1). An ancillary interest of this study, not primarily related to the central hypothesis, was to investigate the endothelial and vascular smooth-muscle function in these patients to see whether this contributes to the differences in blood flow. This was done by testing the effects of multiple doses of endothelium-dependent and endothelium-independent vasodilators.

Both methacholine (Fig. 2 [top], Table 1) and sodium nitroprusside (Table 1) caused a dose-dependent increase in blood flow in control subjects and in untreated and treated anemic patients. Although absolute basal flows were different, the increases in flow with the two doses of methacholine (0.3 and 1.5 μg/min) (Fig. 2 [bottom]) and sodium nitroprusside were similar in the three groups (interaction between group × methacholine: p = 0.34 between untreated and control subjects, p = 0.43 for treated vs. control subjects and p = 0.73 for untreated vs. treated groups; interaction between group × sodium nitroprusside: p = 0.40 between untreated and control subjects, p = 0.16 for treated vs. control subjects and p = 0.69 for untreated vs. treated groups). The doses of methacholine and sodium nitroprusside used in these experiments had no effect on arterial blood pressure.

Effect of N^G-monomethyl-L-arginine on methacholine- and sodium nitroprusside-stimulated forearm blood flow (Table 1). N^G-monomethyl-L-arginine infusion (16 μmol/min) caused a significant reduction in the methacholine (1.5 μg/min)-stimulated blood flow in all three groups (Fig. 2 [top]). The reductions in methacholine-stimulated flow caused by N^G-monomethyl-L-arginine infusion were similar in the untreated anemic patients (7 ± 5 ml), treated anemic patients (8 ± 3.4 ml) and control subjects (6.7 ± 6 ml) (untreated vs. control

subjects p = 0.9, 95% CI for difference −7.5 to 6.7; untreated vs. treated p = 0.9, 95% CI for difference −6.2 to 7, treated vs. controls p = 0.7, 95% CI for difference −8.8 to 6; Fig. 2 [bottom]). In contrast, N^G-monomethyl-L-arginine caused only a minimal decrease in the sodium nitroprusside-stimulated flow which too was no different among the three groups.

Discussion

The present study investigated only those patients with chronic severe anemia who did not have evidence of congestive heart failure because heart failure could itself alter endothelial responses (9). Hemodynamic measurements in these patients were classic of a hyperdynamic state with high cardiac output and low systemic vascular resistance (1,2). The hyperdynamic circulation was accompanied by an increased forearm blood flow and reduced forearm vascular resistance. Rapid correction of anemia with packed cell transfusion over 24 h reduced cardiac output, increased systemic vascular resistance and corrected the hyperdynamic state. The forearm blood flow and forearm vascular resistance became normal.

Possible mechanisms for vasodilation in severe anemia. The mechanisms responsible for the low systemic vascular resistance in chronic severe anemia remain unknown (1,2). Low viscosity due to reduced hematocrit contributes to but cannot entirely explain the low systemic vascular resistance (7,10). Tissue hypoxia is not a direct cause of low systemic vascular resistance, as partial pressure oxygen is normal in anemia and reducing the arterial oxygen content in dogs by inducing methemoglobinemia to levels seen in chronic severe anemia does not affect the systemic vascular resistance (11). Hemoglobin is a potent inhibitor of endothelium-derived relaxing factor (6). There is also evidence that hemoglobin affects vascular resistance in vivo: Infusion of stroma-free hemoglobin causes an immediate and pronounced increase in systemic vascular resistance in hemorrhagic shock (12), a condition in which systemic vascular resistance is already high. This effect is in contrast to a decrease in systemic vascular resistance seen with the use of non-blood volume expanders (12). Is hemoglobin in red blood cells also accessible to endothelium-derived relaxing factor in the vascular lumen? A number of lines of evidence suggest that hemoglobin in the intact red blood cell does influence luminal endothelium-derived relaxing factor. First, endothelium-derived relaxing factor is highly diffusable across membranes and hemoglobin has a great affinity for endothelium-derived relaxing factor (13). Second, Gillespie and Sheng (14) have shown that hemoglobin in intact red blood cells is as effective as free hemoglobin in blocking endothelium-dependent vasodilation. Finally, whole blood with a hemoglobin concentration as low as 1 g/dl can block some of the circulating nitric oxide (15). Therefore, we postulated that the low circulating hemoglobin in patients with chronic severe anemia results in reduced inhibition of vascular endothelium-derived relaxing factor, which then contributes to the vasodilation and the high output state.

Our findings support this hypothesis. In the untreated anemic patients, increased forearm blood flow and low forearm vascular resistance were rapidly corrected by both endogenous (hemoglobin) and exogenous (N^G-monomethyl-L-arginine) inhibitors of endothelium-derived relaxing factor. The effect of N^G-monomethyl-L-arginine was dose dependent, and the higher dose reduced the forearm blood flow to the same extent as seen by increasing hemoglobin to 9 g/dl. The degree of reduction in forearm blood flow with N^G-monomethyl-L-arginine is a measure of the contribution made by endothelium-derived relaxing factor to basal vascular tone (16); a greater decrease in blood flow with N^G-monomethyl-L-arginine implies a higher concentration at the vascular surface (17). N^G-monomethyl-L-arginine (16 μmol/min) caused a similar (~1 ml/min) decrease in basal blood flow in control subjects and treated patients (Fig. 1 [bottom]). In contrast, the same dose of N^G-monomethyl-L-arginine caused a threefold greater decrease (2.9 ml/min) in flow in untreated patients. This suggests that the extra flow (~2 ml/min) reduced by the same dose of N^G-monomethyl-L-arginine in the untreated patients was probably caused by an excess of endothelium-derived relaxing factor that N^G-monomethyl-L-arginine was able to block. Even during N^G-monomethyl-L-arginine infusion, forearm blood flow in untreated patients (3.6 ± 0.8 ml/min) remained ~1 ml/min higher than that in the treated patients (2.5 ± 0.9 ml/min). This amount of forearm blood flow could be attributed to non–endothelium-derived relaxing factor-dependent mediators and gives an estimate of the contribution made by factors such as viscosity and other non-endothelium-derived relaxing factor mechanisms. However, it could be argued that the concentration of N^G-monomethyl-L-arginine used in this study was not sufficient to block all the excess nitric oxide and that higher concentrations might have reduced basal forearm flow further, to levels seen in treated patients. Although this would further favor the endothelium-derived relaxing factor hypothesis, it is unlikely that a higher concentration of N^G-monomethyl-L-arginine would have decreased flow further because the same concentration of N^G-monomethyl-L-arginine (16 μmol/min) reduced methacholine (1.5 μg/min)-stimulated flow by a much greater amount (19.7 ± 5.5 to 12.7 ± 4.7 ml/min) in the untreated patients, suggesting that the dose of N^G-monomethyl-L-arginine used in our study was sufficient to block most of the basal circulating endothelium-derived relaxing factor. Thus, the residual increase in flow is most likely non–endothelium-derived relaxing factor-dependent. These findings suggest that enhanced endothelium-derived relaxing factor activity, because of its reduced inhibition by low circulating hemoglobin, contributes substantially to the low systemic vascular resistance in anemia. However, it is unclear whether these patients also have increased synthesis and release of nitric oxide. High blood flow increases shear stress and therefore nitric oxide release (18), but low hematocrit has the opposite effect on shear stress. Therefore the net effect of anemia on the flow-mediated nitric oxide release is difficult to assess, and our study was not designed to address this.

Endothelial and smooth-muscle function in severe anemia. Although the basal forearm blood flow was significantly increased in the untreated patients, both endothelium-dependent and endothelium-independent vasodilators caused a further increase in flow almost identical to that seen in normal subjects or treated patients, albeit from a higher baseline level (Fig. 2 [bottom], Table 1). These data are consistent with the findings in simulated septicemic shock, a condition associated with increased nitric oxide in which the arteriolar response to endothelium-dependent vasodilators remains normal unless accompanied by structural endothelial damage (19). This suggests that both the endothelial function and the ability of vascular smooth muscle to respond to guanylate cyclase-mediated vasodilation are normal in patients with chronic severe anemia. Although this would explain the similar increases in stimulated flow in all groups, we were surprised that the anemic group did not have a higher stimulated flow. There was a trend toward higher stimulated flows but the wide standard deviation resulted in a lack of a statistically significant difference.

Conclusions and implications. Low systemic vascular resistance, which is the hallmark of chronic severe anemia and other conditions with a hyperdynamic circulation, such as cor pulmonale, may have important pathogenetic implications (2,3). We have shown that salt and water retention in the syndromes of both low and high output congestive heart failure is due to reduced renal blood flow as a result of neurohumoral activation (2,3,20). The stimulus for neurohumoral activation appears to be a threat to arterial blood pressure (21). In low output congestive heart failure blood pressure is threatened because of reduced cardiac output. However, in high output congestive heart failure cardiac output is normal or increased, and blood pressure is threatened because of low systemic vascular resistance. The present study suggests that patients with chronic severe anemia have increased endothelium-derived relaxing factor activity due to its reduced inhibition by low hemoglobin, and this contributes significantly to the low systemic vascular resistance.

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