

Hemodynamic Effects of Hydroxocobalamin in Conscious Dogs

Bruno Riou, M.D.,* Jean-Louis Gérard, M.D.,† Christophe Drieu La Rochelle, Pharm. D.,‡
Raymond Bourdon, Ph.D.,§ Alain Berdeaux, M.D., Ph.D.,¶ Jean-François Giudicelli, M.D., Ph.D.¶

Hydroxocobalamin has been shown to be a rapid and powerful antidote in acute cyanide poisoning and to prevent cyanide poisoning during sodium nitroprusside administration. However, its hemodynamic effects remain unknown. The authors therefore investigated the effects in chronically instrumented conscious dogs ($n = 8$) that were randomly given hydroxocobalamin (20, 70, and 140 $\text{mg} \cdot \text{kg}^{-1}$) or saline. Determination of peak cobalt plasma concentrations showed that 20 and 70 $\text{mg} \cdot \text{kg}^{-1}$ hydroxocobalamin correspond to "therapeutic doses," whereas 140 $\text{mg} \cdot \text{kg}^{-1}$ corresponds to a supratherapeutic dose. Hydroxocobalamin did not modify heart rate, mean arterial pressure, left ventricular (LV) end-diastolic pressure, and PR and QT intervals, regardless of the dose administered. The largest dose (140 $\text{mg} \cdot \text{kg}^{-1}$) induced a decrease in the maximum increase of LV pressure ($-7 \pm 3\%$; $P < 0.05$), maximum aortic blood flow acceleration ($-17 \pm 5\%$; $P < 0.05$), and cardiac output ($-19 \pm 6\%$; $P < 0.05$), whereas systemic resistance increased ($+41 \pm 9\%$; $P < 0.05$). In six other dogs, local administration of hydroxocobalamin (0.5, 1.5, and 5.0 $\text{mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) confirmed that, in large doses, this drug has direct vasoconstrictor properties affecting both conductance (decrease in iliac artery diameter: $-2.5 \pm 0.8\%$) and resistance (decrease in iliac artery blood flow: $-19.5 \pm 3.4\%$) vessels. Thus, hydroxocobalamin should be a safe cyanide antidote, considering the lack of hemodynamic effects within the therapeutic range of doses. (Key words: Antidotes, cyanide: hydroxocobalamin. Toxicity, cyanide.)

IN THE PAST, most cases of cyanide poisoning resulted from either suicide or occupational hazards. More recently, new sources of cyanide toxicity, such as smoke inhalation¹ or use of sodium nitroprusside (SNP), have been recognized. Overdosage with SNP may result in cyanide poisoning because cyanide is the major metabolite of SNP degradation.² The ideal cyanide antidote remains

debatable: nitrites decrease oxygen transport,³ and the antidotal action of sodium thiosulfate—a source of sulfur for hepatic rhodanese—develops slowly.⁴ Moreover, it has been shown that liver damage, which results in rhodanese inactivation, does not modify the acute toxicity of cyanide.⁵ Consequently, although sodium thiosulfate actually prevents SNP toxicity, it might be less useful with treatment of acute cyanide poisoning.

Hydroxocobalamin—a cobalt-containing compound that combines with cyanide to form cyanocobalamin (vitamin B₁₂)—has been demonstrated to prevent SNP toxicity⁶ and to be a safe, rapid, and efficacious cyanide antidote in experimental^{7,8,**} and clinical studies.^{9,10} In the past, hydroxocobalamin has not been widely used because of the absence of a commercially available form containing a high dose (4 to 5 g) of hydroxocobalamin. Recently, the Pharmacie Centrale des Hôpitaux de Paris has designed a special vial containing a pure hydroxocobalamin solution for emergency intravenous administration, which has been used successfully in humans in many cyanide-poisoning cases in France.^{9,10} Cobalt-containing compounds have a high affinity for cyanide, but inorganic salts are very toxic†† and cobalt edetate induces deleterious cardiovascular effects.¹¹ The cardiovascular effects of high doses of hydroxocobalamin remain unknown. Indeed, previous experimental studies in cyanide-poisoned animals did not separate the dramatic improvement of hemodynamic conditions related to the reversal of cyanide effects from the cardiovascular effects of hydroxocobalamin. We therefore investigated the cardiovascular effects of hydroxocobalamin in nonpoisoned, conscious, chronically instrumented dogs. We used conscious rather than anesthetized animals to better analyze the pharmacologic effects of hydroxocobalamin, because surgical trauma and anesthesia profoundly alter hemodynamic state, especially the autonomic control of heart rate and myocardial contractility.¹²

Materials and Methods

SURGICAL PROCEDURE

Animal care conformed to the Helsinki Declaration, and the study was approved by our institution. This study

* Assistant Professor, Département d'Anesthésie-Réanimation, C. H. U. Pitié-Salpêtrière, Paris.

† Assistant Professor, Département d'Anesthésie-Réanimation, C. H. U. Côte de Nacre, Caen.

‡ Research Fellow, Laboratoire de Pharmacologie, Université Paris-Sud.

§ Professor of Biochemistry, Laboratoire de Toxicologie, Hôpital Fernand Widal, Paris.

¶ Professor of Pharmacology, Laboratoire de Pharmacologie, Université Paris-Sud.

Received from the Laboratoire de Pharmacologie, Université Paris Sud, Le Kremlin-Bicêtre; Département d'Anesthésie-Réanimation, C.H.U. Pitié-Salpêtrière, Paris; Département d'Anesthésie-Réanimation, C.H.U. Côte de Nacre, Caen; and Laboratoire de Toxicologie, Hôpital Fernand Widal, Paris, France. Accepted for publication November 2, 1990. Supported in part by INSERM CRL 882002. Dr. B. Riou was supported by the Fondation pour la Recherche Médicale and the Fonds d'Etude du Corps Médical des Hôpitaux de Paris. Presented in part at the Annual Meeting of the American Society of Anesthesiologists, New Orleans, Louisiana, October 14-18, 1989.

Address reprint requests to Dr. Riou: Département d'Anesthésie-Réanimation, C.H.U. Pitié-Salpêtrière, 47-83 Boulevard de l'Hôpital, 75651 Paris Cedex 13, France.

** Riou B, Baud FJ, Astier A, Barriot P, Lecarpentier Y: In vitro demonstration of the antidotal efficacy of hydroxocobalamin in cyanide poisoning. *J Neurosurg Anesthesiol* 2:296-304, 1990

†† Paulet G: Etat actuel du traitement de l'intoxication cyanhydrique. *Arch Mal Prof* 45:182-192, 1984

involved two parts: the hemodynamic effects of hydroxocobalamin, and iliac artery vasomotion during local administration of hydroxocobalamin.

Hemodynamic Study

Nine adult mongrel dogs, of either sex, weighing 20–32 kg (mean, 24 ± 4 kg), were chronically instrumented, as previously described.¹³ Anesthesia was induced with sodium pentobarbital ($30 \text{ mg} \cdot \text{kg}^{-1}$); muscle relaxation was achieved with pancuronium ($0.2 \text{ mg} \cdot \text{kg}^{-1}$); and tracheal intubation and mechanical ventilation (Harvard Apparatus; Harvard Instruments, Boston, MA) were instituted. Anesthesia was maintained with sodium pentobarbital, as required (3-h period). Under sterile surgical conditions, a thoracotomy was performed in the left fifth intercostal space and the lung gently retracted. Heparin-filled Tygon catheters were implanted in the descending aorta, pulmonary artery, and left atrium. The heart was supported by a pericardial cradle, and a miniature high-fidelity pressure transducer (Konigsberg P7A, Konigsberg Company, Pasadena, CA) was inserted through the left ventricular (LV) apex into the cavity. A precalibrated electromagnetic flow probe (Skalar Instruments, Delft, the Netherlands), of appropriate size (20–22 mm) to ensure a snug fit, was placed around the ascending aorta. The catheters and transducer and flow probe leads were secured, tunneled subcutaneously, and exteriorized between the scapulae through a small incision. All instrumentation was carefully checked for function before and after wound closure. The chest wall was closed in layers and the pneumothorax evacuated by a chest tube with suction drainage. A tissue jacket protected the catheters and the instruments for the remainder of the experiment. The catheters were flushed daily with saline and kept filled with a concentrated heparin solution. Cefazolin (1 g) was administered intravenously before and after surgery. During the 8 days postoperatively, ampicillin was administered subcutaneously. No animal was investigated less than 15 days after surgery and only when general appearance was normal. During this recovery period, animals were trained to lie quietly on their right sides on the tables in the laboratory.

The experiments were conducted on separate days, with a minimal time interval of 48 h. Hydroxocobalamin (20, 70, or $140 \text{ mg} \cdot \text{kg}^{-1}$) or saline was randomly administered through the pulmonary artery catheter with the use of a motor-driven syringe-type pump (model 907, Harvard Instruments). The volume injected was adjusted to $1.4 \text{ ml} \cdot \text{kg}^{-1}$ and infused over a 15-min period. Hemodynamic parameters were recorded before and 1, 3, 5, 10, 15, 30, 45, and 60 min after the onset of infusion.

Iliac Artery Vasomotion Study

Six female mongrel dogs, weighing 18–22 kg (mean, 20 ± 1 kg), were chronically instrumented to investigate

the effects of locally injected hydroxocobalamin on the conductance and resistance vessels of the posterior limb.¹⁴ Changes in iliac artery diameter reflect changes in conductance vessels, whereas changes in iliac artery blood flow are thought to reflect changes in resistance vessels. Under sterile conditions and after induction of anesthesia as stated above, the distal aorta and iliac bifurcation were exposed by a midline laparotomy. Two heparin-filled Tygon catheters were implanted in the terminal aorta, one of them through a small arterial branch. A 10-MHz pulsed Doppler ultrasonic flow transducer was implanted on an external iliac artery. Ultrasonic dimension transducers (piezoelectric crystals) were attached to Dacron® backing and implanted on opposing adventitial surfaces of the iliac artery, 1.5–2 cm proximal to the flow probe. During instrumentation, crystal alignment was ensured by monitoring the signal on an oscilloscope. Care was taken to avoid excessive dissection around the iliac vessels.

To test the vasomotion of the vessels, norepinephrine $0.05 \text{ } \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ and nitroglycerin $1 \text{ } \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ were administered locally into the distal aorta through one of the implanted catheters, with the use of a motor-driven syringe pump. These concentrations were selected because they had been shown to elicit almost maximal responses for mean external iliac diameter changes, without simultaneously inducing modifications in systemic hemodynamics, *i.e.* arterial pressure and heart rate.¹³ Then, hydroxocobalamin was administered in the three following cumulative doses: 0.5, 1.5, and $5.0 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$. The intermediate dose was the total dose ($7.5 \text{ mg} \cdot \text{kg}^{-1}$) chosen to approximate one twentieth of the largest dose administered during the hemodynamic study ($140 \text{ mg} \cdot \text{kg}^{-1}$), as previously reported.¹⁴ All drugs were infused for 5 min at a constant infusion rate of $1 \text{ ml} \cdot \text{min}^{-1}$, regardless of the dose administered, as previously reported.¹⁴

MEASUREMENT TECHNIQUES

The electrocardiogram was recorded with the use of surface electrodes (lead II). Aortic and left atrial pressures were measured with Statham P231d strain gauges (Statham Instruments, Oxnard, CA) that were zeroed and calibrated against a mercury manometer. The Konigsberg® micromanometer was calibrated *in vitro* with a mercury manometer and was cross-correlated *in vivo* with measurements obtained from the left atrial and aortic catheters. Cardiac output minus coronary blood flow (referred to below as cardiac output) was monitored continuously with the use of an electromagnetic flowmeter with incorporated nonocclusive zero (Transflow 601® system; Skalar Instruments, The Netherlands). LV rate of tension development ($\text{LVdP} \cdot \text{dt}^{-1}$) was derived from LV pressure signal with the use of an electronic differentiator (Gould

Inc., Cleveland, OH). The first derivative of phasic aortic blood flow (Acc) was also recorded with an identical differentiator. Mean aortic blood flow was derived from phasic aortic blood flow with the use of an integrator (Gould). Mean aortic blood pressure was divided by cardiac output to yield systemic resistance (SR), neglecting the right atrial pressure. Cardiac output was divided by heart rate to yield stroke volume (SV). The Doppler flow transducer was connected to a Doppler flowmeter (Model 100; Triton Technology Inc., San Diego, CA). Blood flow was calculated with the use of a calibration factor relating velocity to flow, which was determined from timed collections of blood during a terminal experiment. The leads of each piezoelectric crystal were connected to an ultrasonic amplifier (Sonomimeter 100.2[®]; Triton Technology). The tracings were monitored continuously on a 10-MHz oscilloscope (OS 3000; Gould Inc., Cleveland, OH). While changes in transmission time were recorded, the distance between the two crystals was measured and it corresponded to external vessel diameter.¹⁴

Continuous low-speed ($1 \text{ mm} \cdot \text{s}^{-1}$) recordings were made on a multichannel electrostatic recorder (ES 1000; Gould). At the indicated measurement intervals, high-speed ($50 \text{ mm} \cdot \text{s}^{-1}$) recordings were made.

HYDROXOCOBALAMIN

Hydroxocobalamin was a gift from the Unité de Production Industrielle de la Pharmacie Centrale des Hôpitaux de Paris (Nanterre, France). The preparation used was a sterile vial containing a pure solution of hydroxocobalamin (5 g in 100 ml). This commercial preparation is now used in case of acute cyanide poisoning in humans in France^{1,9} and was recently accepted by the Food and Drug Administration. However, to reduce volume loading with the highest dose of hydroxocobalamin in this study ($140 \text{ mg} \cdot \text{kg}^{-1}$), a special vial was designed that contained a more concentrated solution (10 g in 100 ml). Peak plasma hydroxocobalamin concentrations were estimated by measurement of plasma cobalt concentrations at the end of the infusions: arterial blood was drawn on dry heparin and immediately centrifuged, and plasma was separated and stored at -18°C . Plasma cobalt concentrations were measured by inductively coupled plasma emission spectroscopy, as previously described.^{‡‡} The limit of detection was $0.1 \mu\text{mol} \cdot \text{l}^{-1}$ and the coefficient of variation 2.5%.

STATISTICAL ANALYSIS

Comparison of control values between groups was performed with the use of a one-way analysis of variance. A

repeated-measures analysis of variance, followed by a Dunnett's test,¹⁵ was used to compare all parameters. Data are means \pm standard error of the mean. Mean percentage changes from control values, which are given in parentheses in the Results section ("Hemodynamic Study" and "Iliac Artery Vasomotion Study"), refer to the maximum mean response recorded. All *P* values were two-tailed, and a *P* value less than 0.05 was necessary to reject the null hypothesis.

Results

Generalized urticaria appeared in one dog after the administration of $140 \text{ mg} \cdot \text{kg}^{-1}$ hydroxocobalamin. This adverse reaction was associated with an increase in heart rate and arterial blood pressure as the animal experienced itching. However, no cardiovascular collapse occurred, and complete cutaneous and hemodynamic recovery was observed within 1 h. This reaction was significantly decreased when a lower dose ($70 \text{ mg} \cdot \text{kg}^{-1}$) was tested 48 h later. This dog was thus excluded from the analysis of the hemodynamic effects of hydroxocobalamin. In the remaining dogs used in the hemodynamic study ($n = 8$) and iliac vasomotion study ($n = 6$), no side effects of hydroxocobalamin were observed.

HEMODYNAMIC STUDY

As shown in table 1, no statistical differences were observed between groups for the control values of each hemodynamic parameter before administration of hydroxocobalamin (20, 70, and $140 \text{ mg} \cdot \text{kg}^{-1}$) and saline. The hemodynamic effects of hydroxocobalamin depended on the dose administered.

At $20 \text{ mg} \cdot \text{kg}^{-1}$, hydroxocobalamin did not exhibit any hemodynamic effects (fig. 1). At $70 \text{ mg} \cdot \text{kg}^{-1}$, the only significant hemodynamic change that was found was a trend toward an increase in systemic resistance ($P < 0.05$), but, at a given time, no differences reached statistical significance (fig. 1).

At the highest dose ($140 \text{ mg} \cdot \text{kg}^{-1}$) of hydroxocobalamin, decreases in $\text{LVdP} \cdot \text{dt}^{-1}$ ($-7 \pm 3\%$; $P < 0.05$), maximum aortic blood flow acceleration (Acc, $-17 \pm 5\%$; $P < 0.05$), cardiac output ($-19 \pm 6\%$; $P < 0.05$), and SV ($-15 \pm 6\%$; $P < 0.05$) were observed, without any change in left ventricular end-diastolic pressure (LVEDP) (fig. 1). As a result of unchanged mean arterial pressure and decreased cardiac output, systemic resistance increased significantly ($41 \pm 9\%$; $P < 0.05$) (fig. 1). The decreases in Acc and $\text{LVdP} \cdot \text{dt}^{-1}$ reached their maximum after 45 min. Hydroxocobalamin did not modify the PR and QT duration, regardless of the dose administered (data not shown).

The mean values of plasma cobalt concentrations after hydroxocobalamin administration are shown in table 2.

‡‡ Bourdon R: Fondements théoriques des méthodes spectroscopiques appliquées au dosage des composés inorganiques dans les liquides biologiques. Rev Fr Lab 177:37-71, 1988

TABLE 1. Hemodynamic and Electrocardiographic Parameters before Administration of Hydroxocobalamin or Saline in Conscious Dogs

	Saline	Hydroxocobalamin (mg · kg ⁻¹)		
		20	70	140
HR (min ⁻¹)	86 ± 7	93 ± 6	88 ± 6	85 ± 5
MAP (mmHg)	83 ± 3	83 ± 2	81 ± 3	80 ± 2
LVdP · dt ⁻¹ (mmHg · s ⁻¹)	2,195 ± 140	2,156 ± 101	2,143 ± 69	2,067 ± 86
LVEDP (mmHg)	7 ± 1	7 ± 1	8 ± 1	7 ± 1
CO (l · min ⁻¹)	2.7 ± 0.2	2.9 ± 0.2	2.9 ± 0.3	2.7 ± 0.2
Acc (l · s ⁻²)	12.0 ± 1.0	12.6 ± 1.0	12.2 ± 1.1	10.4 ± 0.9
SV (ml)	32 ± 2	32 ± 2	34 ± 2	32 ± 2
SR (mmHg · min · l ⁻¹)	31.2 ± 2.2	29.2 ± 2.0	29.2 ± 2.5	31.2 ± 2.3
PR interval (ms)	120 ± 4	125 ± 3	118 ± 3	118 ± 2
QT interval (ms)	272 ± 18	270 ± 16	255 ± 13	272 ± 17

Data are mean ± SEM (n = 8); no statistical differences between groups.

HR = heart rate; MAP = mean arterial blood pressure; LVdP · dt⁻¹

= left ventricular rate of tension development; LVEDP = left ventricular end-diastolic pressure; CO = cardiac output; Acc = aortic blood flow acceleration; SV = stroke volume; SR = systemic resistance.

ILIAC ARTERY VASOMOTION STUDY

Control values of mean iliac artery blood flow and mean diameter before administration of hydroxocobalamin, nitroglycerin, and norepinephrine are shown in table 3. No statistical differences were observed between groups. In-

fusion of nitroglycerin (1 µg · kg⁻¹ · min⁻¹) increased mean iliac artery blood flow and mean external diameter, whereas infusion of norepinephrine (0.05 µg · kg⁻¹ · min⁻¹) had opposite effects (figs. 2 and 3). Increasing doses of hydroxocobalamin that did not modify systemic hemodynamics (*i.e.*, heart rate and arterial pressure) were

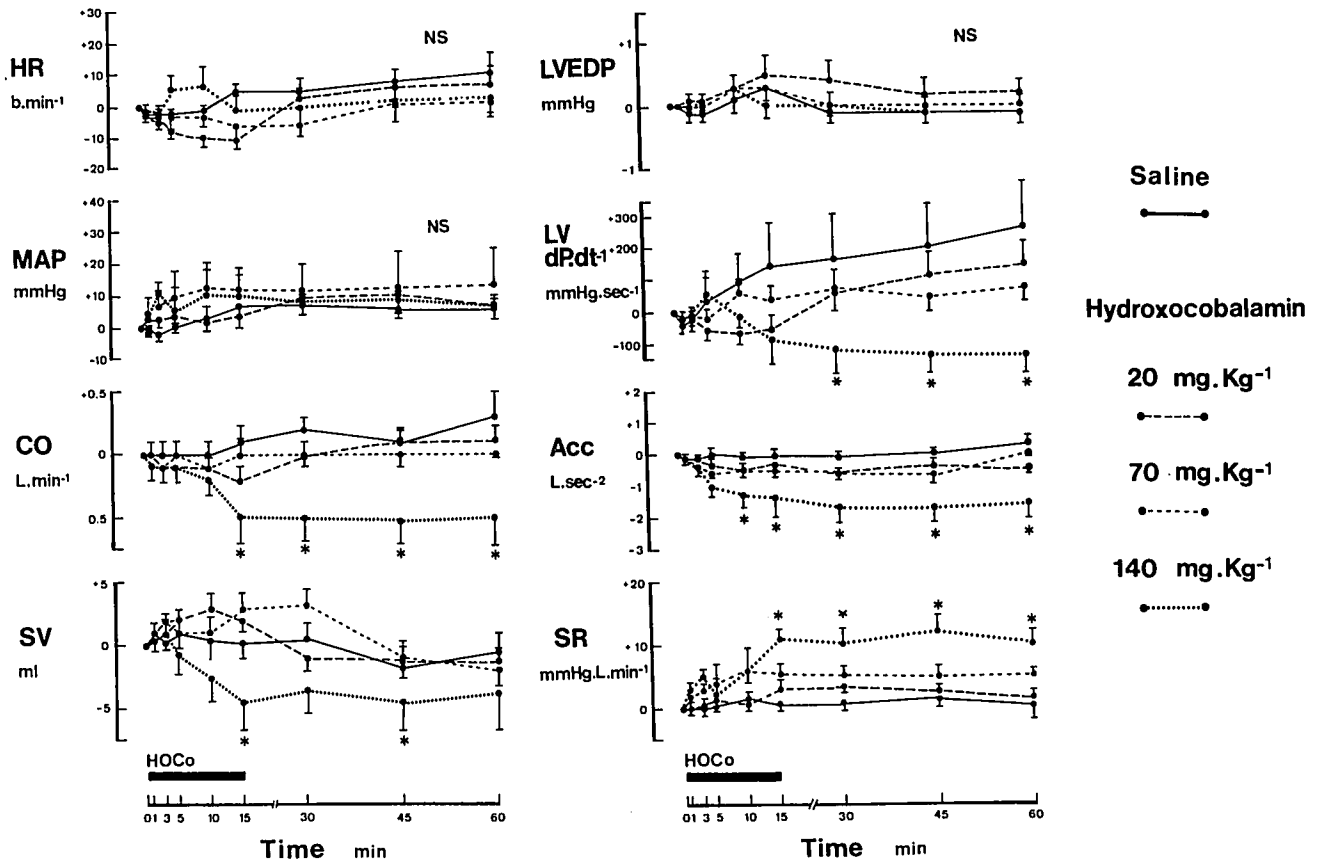


FIG. 1. Effects of hydroxocobalamin (HOCo) on heart rate (HR), mean arterial pressure (MAP), cardiac output (CO), stroke volume (SV), left ventricular end-diastolic pressure (LVEDP), maximum rise of left ventricular pressure (LVdP · dt⁻¹), maximum aortic blood flow acceleration (Acc), and systemic resistance (SR) in conscious dogs (n = 8). Data are mean changes (±SEM) in absolute values from control. *P < 0.05 as compared to saline; NS = no significant differences between groups.

TABLE 2. Cobalt Plasma Concentrations After Hydroxocobalamin Administration

	Hydroxocobalamin (mg · kg ⁻¹)		
	20	70	140
Cobalt (μmol · l ⁻¹)	138 ± 15	448 ± 49	859 ± 119

Data are mean ± SEM.

TABLE 3. Iliac Artery External Diameter and Flow before Administration of Hydroxocobalamin, Nitroglycerin, and Norepinephrine, in Conscious Dogs

	Hydroxocobalamin	Nitroglycerin	Norepinephrine
Mean iliac external diameter (mm)	5.40 ± 0.36	5.27 ± 0.33	5.27 ± 0.38
Mean iliac blood flow (ml · min ⁻¹)	87 ± 9	88 ± 9	96 ± 13

Data are mean ± SEM (n = 6). No statistical differences between groups.

administered locally. The smallest doses of hydroxocobalamin (0.5 and 1.5 mg · kg⁻¹ · min⁻¹) did not significantly affect either mean iliac artery external diameter or blood flow. Only the largest doses of hydroxocobalamin (5 mg · kg⁻¹ · min⁻¹) induced significant vasoconstriction, as reflected by a decrease in mean iliac artery blood flow (-19 ± 3%; P < 0.05) (fig. 2) and mean external diameter

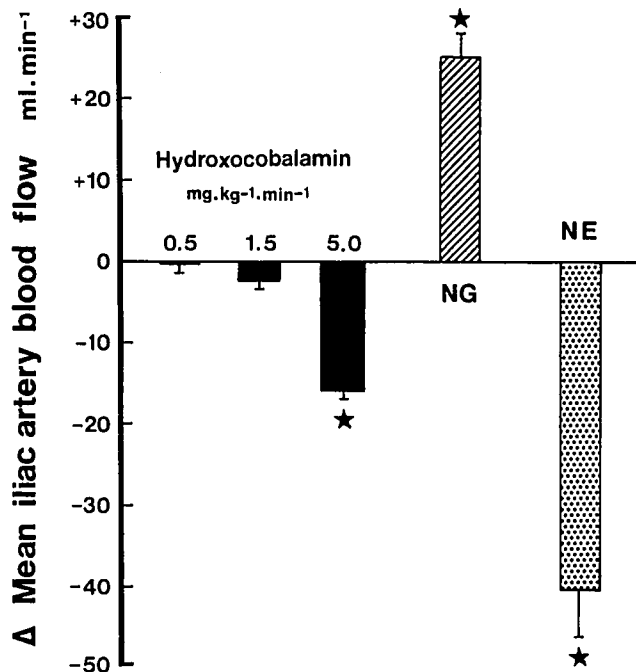


FIG. 2. Effects of various doses of hydroxocobalamin, 1 μg · kg⁻¹ · min⁻¹ nitroglycerin (NG), and 0.05 μ · kg⁻¹ · min⁻¹ norepinephrine (NE) on mean iliac artery blood flow. Data are expressed as mean changes (±SEM) from control values. *P < 0.05 from the corresponding control values.

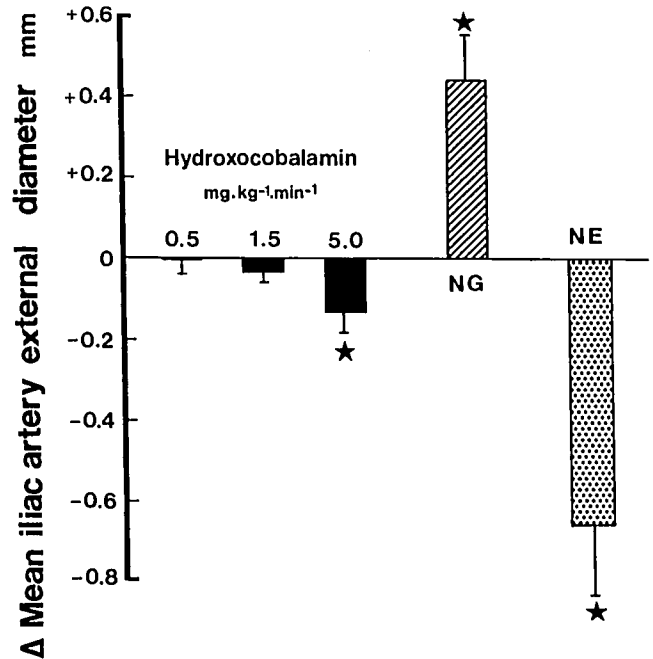


FIG. 3. Effects of various doses of hydroxocobalamin, 1 μg · kg⁻¹ · min⁻¹ nitroglycerin (NG), and 0.05 μg · kg⁻¹ · min⁻¹ norepinephrine (NE) on mean iliac artery external diameter. Data are expressed as mean changes (±SEM) from control values. *P < 0.05 from the corresponding control values.

(-2.5 ± 0.8%; P < 0.05) (fig. 3). At 5 mg · kg⁻¹ · min⁻¹ hydroxocobalamin, the response of conductance vessels (10% of the mean decrease in iliac diameter with norepinephrine) was less than that of the resistance vessels (20% of the mean decrease in iliac blood flow with norepinephrine).

Discussion

Plasma cobalt concentrations were assumed to reflect plasma hydroxocobalamin concentrations, because the biotransformation of hydroxocobalamin is slow and probably of minor magnitude at these high doses.¹⁶ After administration of 20 and 70 mg · kg⁻¹ hydroxocobalamin, mean plasma cobalt concentrations (table 2) were within the range recorded in humans after therapeutic administration of hydroxocobalamin.¹ Therefore, 20 and 70 mg · kg⁻¹ may actually be considered "therapeutic" doses of hydroxocobalamin in cyanide poisoning, whereas 140 mg · kg⁻¹ should be considered a suprathreshold dose. Nevertheless, such comparison must be cautiously performed because differences in pharmacokinetics and, therefore, therapeutic concentrations, may exist between dogs and humans. It should be pointed out that 20 mg · kg⁻¹ is ten times the dose previously used by Cottrell et al.⁶ in preventing SNP toxicity in humans.

The principal result from the current study is that hydroxocobalamin within the therapeutic range of doses

appears to be devoid of hemodynamic effects (except for a slight but statistically significant increase in systemic resistance at $70 \text{ mg} \cdot \text{kg}^{-1}$). No side effects were observed at these doses. After the largest dose, we observed generalized urticaria without cardiovascular collapse in only one dog. This adverse reaction was less significant 48 h later, when a smaller dose was administered, suggesting a nonspecific histamine release. Indeed, anaphylactic shock has been reported rarely after administration of very low doses of hydroxocobalamin.¹⁷ After the largest dose of hydroxocobalamin was administered, an increase in systemic resistance was observed (fig. 1). At the same time, no significant changes in blood pressure or heart rate were observed, and, consequently, reflexly mediated vasoconstriction is unlikely. The hypothesis of a direct vasoconstrictor effect of hydroxocobalamin was thus investigated after local administration of the drug into the iliac artery, at doses that did not modify systemic hemodynamics. Nevertheless, the doses administered locally are difficult to compare with the doses used in the hemodynamic study. However, the highest dose of hydroxocobalamin induced a decrease in both mean iliac artery blood flow and mean iliac artery external diameter, indicating that the drug elicits direct vasoconstriction on both conductance and resistance arterial vessels. Hydroxocobalamin has a hemic structure and is known to bind to cyanide and oxidants¹⁶; it is well known that heme and hemoproteins, such as hemoglobin, exhibit a vasoconstrictor effect through the binding of endogenous nitric oxide.^{18,19} Thus, although the chemical reactions between nitric oxide and hydroxocobalamin remain unknown, one cannot exclude that the direct vasoconstrictor effects of large doses of hydroxocobalamin could partially result from the binding of endogenous nitric oxide. Additional *in vitro* studies are required to test this hypothesis.

The largest dose of hydroxocobalamin ($140 \text{ mg} \cdot \text{kg}^{-1}$) decreases cardiac output, $\text{LVdP} \cdot \text{dt}^{-1}$, and maximum aortic blood flow acceleration (fig. 1). Aortic blood flow acceleration has been shown to correlate closely with LV ejection fraction²⁰ and is a more reliable index of contractility than $\text{LVdP} \cdot \text{dt}^{-1}$ because it depends to a lesser degree on the ventricular loading conditions than does $\text{LVdP} \cdot \text{dt}^{-1}$.²¹ The current results therefore might indicate that large doses of hydroxocobalamin decrease cardiac contractility. These results agree with those of a previous *in vitro* study suggesting that high concentrations (1 mM) of hydroxocobalamin might slightly decrease the intrinsic myocardial contractility.⁸ Nevertheless, it must be pointed out that an increase in LVEDP that should have been associated with a decrease in contractility did not occur in the current study. Thus, the hypothesis cannot be ruled out that the increase in systemic resistance *per se*, without a specific decrease in contractility, could have been responsible for the decrease in cardiac function; the

exact effect of hydroxocobalamin on intrinsic myocardial contractility remains to be determined.

A change in venous return is unlikely to occur because no significant changes in LVEDP were observed at any dose. However, because LV pressure, and not volume, was measured in the current experimental model during the end-diastolic period, a modification in preload cannot be completely ruled out.²²

Some remarks should be included to assess the clinical relevance of our results. It is well-known that dogs possess high parasympathetic tone²³ and differences in intrinsic myocardial contractility.²⁴ Inasmuch as the situation differs in humans, the cardiovascular effects observed after the largest dose of hydroxocobalamin might not be identical in humans. However, the lack of hemodynamic effects of hydroxocobalamin within the therapeutic range of doses closely conforms to our clinical experience in patients without cyanide poisoning.¹⁰ Conscious rather than anesthetized dogs were used to better study the pharmacologic effects of hydroxocobalamin on an intact cardiovascular system.^{12,13} The effects of hydroxocobalamin might not be identical in anesthetized animals. However, because no significant effects were observed within the therapeutic range of concentrations, this limitation is probably of minor importance.

The lack of hemodynamic effects of hydroxocobalamin within the therapeutic range of doses dramatically contrasts with other cobalt-containing cyanide antidotes.^{11,††} The therapeutic management of acute cyanide poisoning requires administration of pure oxygen, mechanical ventilation,²⁵ and cyanide antidote. However, the ideal cyanide antidote remains debatable.²⁶ During SNP overdose or after smoke inhalation injury, when cyanide poisoning is only suspected but not yet confirmed because cyanide blood concentrations are not known, a rapid, efficacious, and safe antidote is of paramount importance. Hydroxocobalamin has been shown to be a rapid and powerful cyanide antidote both *in vitro*^{7,8,**} and *in vivo*.^{9,10} The lack of significant hemodynamic effects of hydroxocobalamin suggests that it is also a safe antidote. Consequently, hydroxocobalamin could be used in acute cyanide poisoning during SNP administration or smoke inhalation injury, even when cyanide poisoning is only clinically suspected.^{10,27}

References

1. Baud FJ, Barriot P, Toffis V, Riou B, Astier A: Cyanide poisoning in fire victims. *Intensive Care Med* 14:S289, 1988
2. Michenfelder JD: Cyanide release from sodium nitroprusside in the dog. *ANESTHESIOLOGY* 46:196-201, 1977
3. Moore SJ, Norris JC, Walsh DA, Hume AS: Antidotal use of methemoglobin forming cyanide antagonists in concurrent carbon monoxide/cyanide intoxication. *J Pharmacol Exp Ther* 242: 70-73, 1987
4. Friedberg KD, Shukla UR: The efficiency of aquocobalamin as

- an antidote in cyanide poisoning when given alone or combined with sodium thiosulfate. *Arch Toxicol* 33:103-113, 1975
5. Rutkowsky JV, Roebuck BD, Smith RP: Liver damage does not increase the sensitivity of mice to cyanide given acutely. *Toxicology* 38:305-314, 1986
 6. Cottrell JE, Casthely P, Brodie JD, Patel K, Klein A, Turndorf H: Prevention of nitroprusside-induced cyanide toxicity with hydroxocobalamin. *N Engl J Med* 298:809-811, 1978
 7. Mushett CW, Kelley KL, Boxer GE, Rickards JC: Antidotal efficacy of vitamin B12a (Hydroxocobalamin) in experimental cyanide poisoning. *Proc Soc Exp Biol Med* 81:234-237, 1952
 8. Benabid AL, Decors M, Remy C, Le Bas JF, Confort S, Leviel JL: ³¹P nuclear magnetic resonance in vivo spectroscopy of the metabolic changes induced in the awake rat brain during KCN intoxication and its reversal by hydroxocobalamin. *J Neurochem* 48:804-808, 1987
 9. Brouard A, Blaisot B, Bismuth C: Hydroxocobalamin in cyanide poisoning. *J Toxicol Clin Exp* 7:155-168, 1987
 10. Riou B, Baud FJ, Bismuth C: L'hydroxocobalamin, Les Antidotes. Edited by Baud FJ, Barriot P, Riou B. Paris, Masson, 1991 (in press)
 11. Klimmek R, Fladerer H, Szinicz L, Weger N, Kiese M: Effects of 4-dimethylaminophenol and Co2EDTA on circulation, respiration, and blood homeostasis in dogs. *Arch Toxicol* 42:75-84, 1979
 12. Vatner SF: Effects of anesthesia on cardiovascular control mechanisms. *Environ Health Perspect* 26:193-206, 1978
 13. Gérard JL, Berdeaux A, Giudicelli JF: Cardiac and hemodynamic profile of the new cardiotonic agent, DPI 201-106, in the conscious dog. *Eur J Pharmacol* 165: 39-49, 1989
 14. Young MA, Vatner SF: Enhanced adrenergic constriction of iliac artery with removal of endothelium in conscious dogs. *Am J Physiol* 250:H892-H897, 1986
 15. Dunnett CW: New tables for multiple comparisons with a control. *Biometrics* 20:482-491, 1964
 16. Hillman RS: Vitamin B12, folic acid, and the treatment of megaloblastic anemias, *The Pharmacological Basis of Therapeutics*. 7th edition. Edited by Gilman AG, Goodman LS, Rall TW, Murad F. New York, MacMillan Publishing, 1985, pp 1323-1337
 17. Auzépy P, Veissière JF, Deparis M: Choc anaphylactique dû à l'hydroxocobalamin. *Presse Med* 3:152, 1974
 18. Craven PA, DeRubertis FR: Restoration of the responsiveness of purified guanylate cyclase to nitrosoguanidine, nitric oxide, and related activators by heme and heme proteins. *J Biol Chem* 253: 8433-8443, 1978
 19. Connor HE, Feniuk W: Role of endothelium in haemoglobin-induced contraction of dog basilar artery. *Eur J Pharmacol* 140: 105-108, 1987
 20. Lasker SM, Thys DM, Hillel Z, Ali J: Maximal aortic blood flow acceleration and its relationship to left ventricular ejection fraction during general anesthesia (abstract). *ANESTHESIOLOGY* 71: A79, 1989
 21. Noble MIM, Trenchard D, Guz A: Left ventricular ejection in conscious dog. *Circ Res* 19:139-147, 1966
 22. Gilbet JC, Glantz SA: Determinants of left ventricular filling and the diastolic pressure-volume relation. *Circ Res* 64:827-852, 1989
 23. Randall WC: *Neural Regulation of the Heart*. New York, Oxford University Press, 1977, pp 15-129
 24. Fabiato A, Fabiato F: Calcium-induced release of calcium from the sarcoplasmic reticulum of skinned cells from adult human, dog, cat, rabbit, rat, and frog hearts and from fetal and newborn rat ventricles. *Ann NY Acad Sci* 307:491-522, 1978
 25. Bismuth C, Cantineau JP, Pontal P, Baud F, Garnier R, Poulos L, Bolo A: Priorité de l'oxygénation dans l'intoxication cyanhydrique. *J Toxicol Med* 4:107-121, 1984
 26. Marrs TC: *The choice of cyanide antidotes, Clinical and Experimental Toxicology of Cyanides*. Edited by Ballantyne B, Marrs TC. Bristol, Wright, 1987, pp 383-401
 27. Hall AH, Rumack BH: Hydroxocobalamin/sodium thiosulfate as a cyanide antidote. *J Emerg Med* 5:115-121, 1987