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Protective Effect of Stroma-free Methemoglobin during Cyanide Poisoning in Dogs

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Background: **During fire exposure, cyanide toxicity can block aerobic metabolism. Oxygen and sodium thiosulfate are accepted therapy. However, nitrite-induced methemoglobinemia, which avidly binds cyanide, decreases oxygen-carrying capacity that is already reduced by the presence of carboxyhemoglobin (inhalation of carbon monoxide in smoke). This study tested whether exogenous stroma-free methemoglobin (SFmetHb) can prevent depression of hemodynamics and metabolism during canine cyanide poisoning.**

Methods: **In 10 dogs (weighing 18.8 ± 3.5 kg) anesthetized with chloralose-urethane and mechanically ventilated with air, baseline hemodynamic and metabolic measurements were made. Then, 137 ± 31 ml of 12 g% SFmetHb was infused into five dogs (SFmetHb group). Finally, the SFmetHb group and the control group (n = 5, no SFmetHb) received an intravenous potassium cyanide infusion (0.072 $mg \cdot kg^{-1} \cdot min^{-1}$) for 20 min. Oxygen consumption ($\dot{V}_{O_2}$) was measured with a Datex Deltatrac (Datex Instruments, Helsinki, Finland) metabolic monitor and cardiac output ($\dot{Q}T$) was measured by pulmonary artery thermodilution.**

Results: **From baseline to cyanide infusion in the control group, $\dot{Q}T$ decreased significantly ($p < 0.05$) from 2.9 ± 0.8 to 1.5 ± 0.4 l/min, mixed venous P_{CO_2} ($P\bar{v}_{CO_2}$) tended to decrease from 35 ± 4 to 23 ± 2 mmHg, $P\bar{v}_{O_2}$ increased from 43 ± 4 to 62 ± 8 mmHg, $\dot{V}_{O_2}$ decreased from 93 ± 8 to 64 ± 19 ml/min, and lactate increased from 2.3 ± 0.5 to 7.1 ± 0.7 mM. In the SFmetHb group, cyanide infusion did not significantly change these variables. From baseline to infused cyanide, the increases in blood cyanide (4.8 ± 1.0 to 452 ± 97 μM) and plasma thiocyanate cyanide (18 ± 5 to 65 ± 22 μM) in the SFmetHb group were significantly greater than those increases in the control group. SFmetHb itself caused no physiologic changes, except small decreases in heart rate and $P\bar{v}_{O_2}$. Peak SFmetHb reached 7.7 ± 1.0% of total hemoglobin.**

Conclusions: **Prophylactic intravenous SFmetHb preserved cardiovascular and metabolic function in dogs exposed to significant intravenous cyanide. Blood concentrations of cyanide, and its metabolite, thiocyanate, revealed that SFmetHb trapped significant cyanide in blood before tissue penetration. (Key words: Gases: carbon monoxide. Heart: cardiovascular function. Metabolism: cellular aerobic. Toxicity: cyanide; smoke inhalation; thiocyanate. Pharmacology: nitrites; thiosulfate.)**

A major cause of death in house fires in the United States is inhalation of toxic compounds, especially carbon monoxide and cyanide. Fire victims may inhale smoke containing toxic amounts of hydrogen cyanide gas.[1–5] Hydrogen cyanide is produced in fires by the thermal decomposition of nitrogenous materials, including natural fibers (wool and silk) and synthetic polymers (polyurethane and polyacrylonitrile).[3,6,7] Cyanide binds to intracellular cytochrome oxidase, the last cytochrome in oxidative phosphorylation, to block cellular aerobic metabolism[6,8,9] and decrease the tissue utilization of oxygen.

Standard treatment includes the administration of oxygen, sodium thiosulfate, and sodium or amyl nitrite.[5] Treatment with oxygen during cyanide poisoning is well established[10–12] and is essentially devoid of side effects. Sodium thiosulfate, which increases the enzymatic conversion of cyanide to thiocyanate,[1,2,9] also is commonly used during cyanide poisoning.[5]

Sodium or amyl nitrite is administered to induce intraerythrocyte methemoglobinemia, which avidly

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binds cyanide.[5] However, nitrite-induced methemoglobinemia to treat cyanide poisoning from fires is complicated by the presence of carbon monoxide, a common incomplete combustion product in smoke.[1] Carbon monoxide converts oxyhemoglobin to carboxyhemoglobin[3] and shifts the oxyhemoglobin dissociation curve to the left,[6] which decreases the oxygen-delivering capacity to the tissues. In fact, studies have suggested a synergistic effect of carbon monoxide and cyanide on oxygen metabolism in the body, such that lower concentrations of each gas are more toxic when they are present together.[4,6,7,13,14]

Thus, the induction of endogenous methemoglobinemia with nitrite may be dangerous when oxygen-carrying capacity is already reduced by the presence of carboxyhemoglobin.[1,2,9,15,16] In addition, the formation of adequate methemoglobin can take 30–70 min[5,16] with significant variability among patients. Finally, eventual elimination of cyanide bound as cyanmethemoglobin depends on the conversion of cyanide to thiocyanate,[17] a reaction hastened by sodium thiosulfate.

Alternatively, the infusion of exogenous stroma-free methemoglobin solution (SFmetHb) during cyanide poisoning is appealing. On intravenous injection, methemoglobin is instantly available to bind cyanide without any reduction in oxygen-carrying capacity. In rats,[17] SFmetHb effectively treated the otherwise lethal effects of cyanide poisoning, but circulatory or gas exchange functions were not studied.

However, in previous studies of combined cyanide and carbon monoxide in the dog,[1,2] we demonstrated that critical recovery of cardiovascular and metabolic function (except lactic acidosis) occurred within 15 min of cessation of cyanide exposure. Thus, in a real-life situation of cyanide toxicity such as a house fire, extraction of the victim from the cyanide exposure would facilitate recovery of critical cardiovascular and metabolic function probably before a further antidote could be administered. Alternatively, we reasoned that the prophylactic administration of SFmetHb could prevent toxicity of subsequent exposure to cyanide by chelating and trapping cyanide in the blood before it could reach the tissues. Clinical scenarios, in which prophylaxis against potential cyanide exposure is attractive, include rescue workers entering a fire or industrial accident and soldiers at risk from chemical warfare. Accordingly, in this study, we test the hypothesis that SFmetHb can prevent the depression of cardiovascular and metabolic function that occurs in a canine model of cyanide poisoning, by binding and trapping cyanide in the blood before it can reach the intracellular compartment and block aerobic metabolism.

Materials and Methods

General Preparations

This study was conducted in accordance with the American Physiologic Society's Guiding Principles in the Care and Use of Animals and was approved by the institutional Animal Care Committee. Ten dogs (18.8 ± 3.5 kg) were anesthetized with 160 mg/kg intravenous chloralose and 800 mg/kg urethane. Further maintenance doses of chloralose (20 mg/kg) and urethane (100 mg/kg) were administered as necessary. After tracheal intubation, the lungs were mechanically ventilated (Harvard respirator, Model 613, South Natick, MA) with air and the animal was positioned supine for the remainder of the experiment. Tidal volume (311 ± 56 ml) and frequency (20.5 ± 2.0 min^{-1}) were adjusted to maintain Pa_{CO_2} near 32 mmHg. The exhaled port of the ventilator was connected to the input of the Deltatrac metabolic monitor (Datex Instruments, Helsinki, Finland).

A catheter was inserted in a femoral vein for administration of drugs and normal saline. Another catheter was placed in the femoral artery for sampling of arterial blood and measurement of arterial blood pressure. Through the right external jugular vein, a thermistor-tipped flotation catheter was positioned in a pulmonary artery branch (by pressure monitoring) for mixed venous blood sampling and measurements of pulmonary artery, pulmonary wedge pressures, and thermodilution cardiac output (Model 9510A Edwards cardiac output computer, Irvine, CA). Through the left external jugular vein, another flotation catheter was positioned in the right side of the heart for administration of the cyanide infusion.# Vascular pressures were measured with Gould transducers (model P23, Gould, Oxnard, CA) and displayed on a polygraph recorder.

Experimental Protocol

Before the experimental protocol began, sodium bicarbonate was infused (about 2 mEq/kg) to facilitate a physiologic baseline arterial *p*H level (7.43 ± 0.07);

In one treatment dog, cyanide was infused through the distal port of the pulmonary artery catheter and pancuronium was administered.

Table 1. Selected Measurements in the Control Group (n = 5) and SFmetHb Group (n = 5) of Dogs at Baseline, after Intravenous Administration of Stroma-free Methemoglobin in the SFmetHb Group, and at the End of the Cyanide Infusion

	Control Group		SFmetHb Group		
	Baseline	CN	Baseline	SFmetHb	CN
Psa (mmHg)	126 ± 23	101 ± 23	142 ± 13	145 ± 11	146 ± 11
HR (min^{-1})	122 ± 17	126 ± 36	163 ± 41	136 ± 44†	166 ± 37
Ppa (mmHg)	12.8 ± 0.8	24.2 ± 5.5*	10.2 ± 4.1	12.4 ± 6.0	16.2 ± 9.6*
pH_v	7.43 ± 0.03	7.39 ± 0.08	7.41 ± 0.09	7.39 ± 0.09	7.39 ± 0.07
$\dot{V}_{CO_2}$ (ml/min)	83 ± 8	89 ± 19	83 ± 33	82 ± 34	92 ± 41†
metHb (% total Hb)	2.1 ± 1.2	1.8 ± 1.7	0.6 ± 0.4	7.7 ± 1.0†	2.9 ± 0.9*
Blood [CN] (μM)	2.2 ± 2.0	113 ± 33*	4.8 ± 1.0	2.6 ± 0.4†	452 ± 97*
Plasma [CN] (μM)			3.3 ± 2.4	3.2 ± 3.9	612 ± 111†
Plasma [SCN] (μM)	27.6 ± 11.0	45.7 ± 16.9*	17.6 ± 4.9	17.1 ± 6.0	65.3 ± 22.1†

Values are mean ± SD.

Psa = systemic arterial blood pressure; HR = heart rate; Ppa = pulmonary arterial blood pressure; pHv = venous blood pH (n = 4 in control group); $\dot{V}_{CO_2}$ = pulmonary CO_2 elimination; metHb = methemoglobin (percent of total hemoglobin, n = 4 in control group); blood [CN] = cyanide concentration; plasma [SCN] = thiocyanate concentration (n = 4 in SFmetHb group).

*Significant difference ($P < 0.05$) from baseline.

†Significant difference ($P < 0.05$) from other stages.

thereafter, no further sodium bicarbonate was administered.

For the SFmetHb group, baseline measurements consisted of blood temperature, hemodynamics, oxygen consumption ($\dot{V}_{O_2}$), carbon dioxide production ($\dot{V}_{CO_2}$), and minute ventilation ($\dot{V}E$), and simultaneous samples of arterial and mixed venous blood. Then, SFmetHb (137 ± 31 ml, 12 g%) was slowly infused into the femoral vein. After 15 min, the measurement sequence was repeated (SFmetHb stage). Then, the cyanide infusion began and the measurement sequence was repeated after 20 min of cyanide infusion (cyanide stage). The control group of animals followed a similar protocol except that SFmetHb was not administered.

The commercially prepared bovine stroma-free hemoglobin (Biopure Corporation, Boston, MA) was stored at −20° C. After thawing, it was incubated with an equimolar amount of sodium nitrite for 1 h during gentle stirring. Then, the SFmetHb was dialyzed through 12–14,000 M.W. pore membrane (Specta/Por, Thomas Scientific, Swedesboro, NJ) four times during 48 hours in a bath of sterile normal saline for cleansing and to remove any traces of residual sodium nitrite. Conversion of hemoglobin to methemoglobin was confirmed by spectrophotometric measurement at 630 nm (Spectronic 601, Milton Roy, Rochester, NY).

Potassium cyanide was prepared each experimental day. Two drops of 0.1 N NaOH were added to alkalinize 10 ml 0.9% sodium chloride (NaCL) before adding potassium cyanide powder. For each dog, we prepared a potassium cyanide solution that delivered 0.072 $mg \cdot kg^{-1} \cdot min^{-1}$ when infused at 1 ml/min.[11] We infused this cyanide solution through the catheter positioned in the right heart.[1,2]

Data Analysis

The pH level, P_{CO_2}, and P_{O_2} of blood samples were measured at 37°C in a blood gas analyzer (Nova 5, Nova Biomedical, Waltham, MA) and corrected to body temperature.[18] Fractions of oxyhemoglobin, carboxyhemoglobin, and methemoglobin and total hemoglobin concentration were measured by cooximetry (model IL 482, Instrumentation Laboratory, Lexington, MA). To measure lactate, blood samples were processed by reagent methods (Diagnostic Reagents, Sigma Chemical, St. Louis, MO) and ultraviolet light absorption (340 nm) was measured on a spectrophotometer (model 300N, Gilford Instrument, Oberlin, OH). Minute ventilation ($\dot{V}E$), oxygen consumption ($\dot{V}_{O_2}$), and carbon dioxide production ($\dot{V}_{CO_2}$) were measured with the metabolic monitor (Deltatrac), which employed a constant flow generator and the Haldane transformation to calculate differences between inspired and expired flows. According to standard convention, $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ were expressed as standard temperature and pressure (dry), while $\dot{V}E$ was reported as body temperature and pressure (saturated).

To measure blood cyanide concentration,[19] the hydrogen cyanide in the headspace above acidified blood

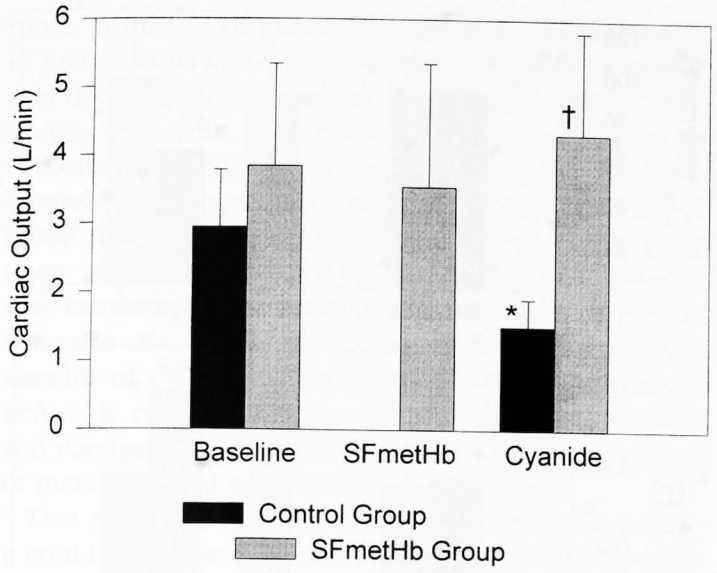

Fig. 1. Cardiac output (mean ± SD, n = 5) in the control and stroma-free methemoglobin groups of dogs at baseline, after intravenous administration of stroma-free methemoglobin in the stroma-free methemoglobin group, and at the end of the cyanide infusion. *Significant difference ($P < 0.05$) from baseline. †Significant difference ($P < 0.05$) from the stroma-free methemoglobin measurement.

was detected by gas chromatography (model 5790, Hewlett-Packard, Avondale, PA). Plasma was separated from blood by centrifugation. Then, plasma thiocyanate concentration was measured by a colorimetric technique,[20] using a spectrophotometer at 520 nm. In the SFmetHb group, we also measured cyanide concentration in the plasma.

We used Student's paired *t* test (control group) or repeated-measures analysis of variance (SFmetHb group) to test each variable for differences among stages.[21] If populations did not have normal distributions or equal variances about the mean, nonparametric tests were employed (Wilcoxon signed rank test and Friedman repeated measures analysis of variance on ranks, respectively). For a significant F statistic ($P < 0.05$), the differing stages were identified by the Student-Newman-Keuls multiple comparison test. Data are reported as mean ± SD.

Results

The administration of SFmetHb to the SFmetHb group caused no physiologic changes in cardiovascular and metabolic variables (within the statistical constraints of n = 5), with the exception of small decreases in heart rate (table 1) and $P\bar{v}_{O_2}$ (fig. 2, middle). Peak measured SFmetHb reached 7.7 ± 1.0% of total hemoglobin (table 1). After administration of SFmetHb, its renal excretion during the experiment was evident by the appearance of dark urine. The decrease in percent oxyhemoglobin (89.5% ± 1.7% to 84.0% ± 2.2%) was mostly caused by the added exogenous methemoglobin.

At the end of the cyanide infusion in the control group (fig. 1), $\dot{Q}_T$ decreased significantly ($P < 0.05$) to 1.5 ± 0.4 l/min, from the baseline value of 2.9 ± 0.8

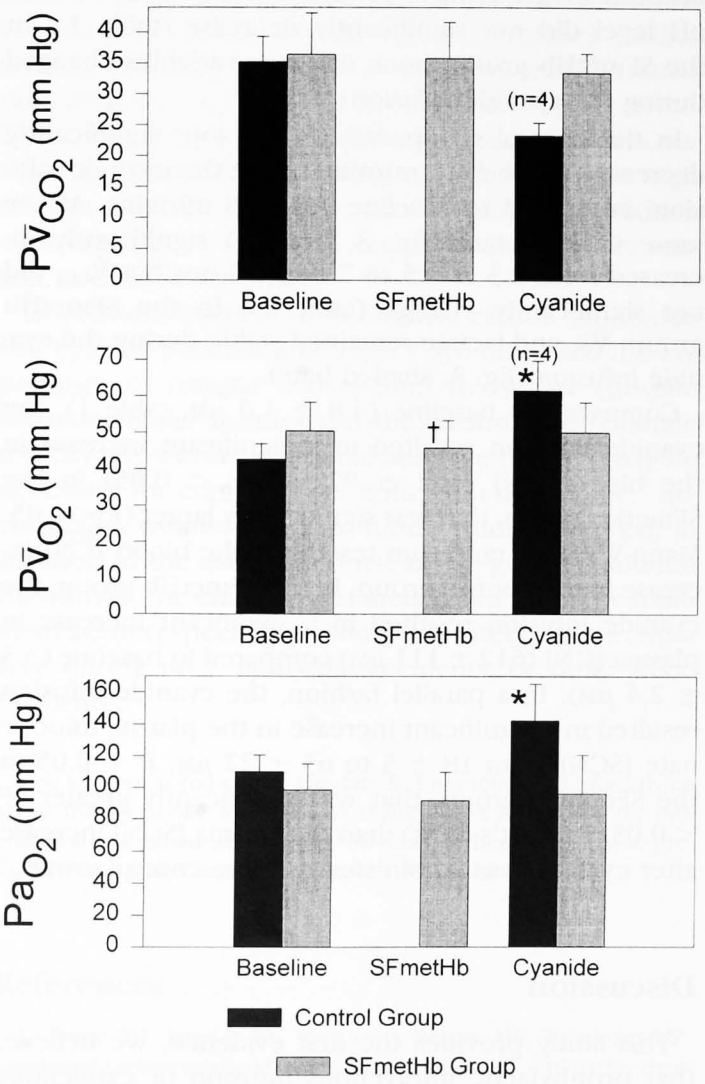

Fig. 2. Mixed venous P_{CO_2} and P_{O_2} ($P\bar{v}_{CO_2}$ and $P\bar{v}_{O_2}$, respectively) and arterial blood P_{O_2} (Pa_{O_2}) (mean ± SD, n = 5) in the control and stroma-free methemoglobin groups of dogs at baseline, after intravenous administration of stroma-free methemoglobin in the stroma-free methemoglobin group, and at the end of the cyanide infusion. *Significant difference ($P < 0.05$) from baseline. †Significant difference ($P < 0.05$) from the other measurements in the stroma-free methemoglobin group.

l/min. While arterial blood pressure and heart rate did not significantly change (table 1), pulmonary artery pressure increased significantly during the cyanide infusion (24.2 ± 5.5 mmHg), compared to baseline (12.8 ± 0.8 mmHg). In contrast, in the SFmetHb group, $\dot{Q}_T$ did not decrease below baseline measurements during the cyanide infusion (fig. 1, shaded bars).

Blood gas data are displayed in figure 2. In the control group, compared to baseline, the cyanide infusion tended to decrease $P\bar{v}_{CO_2}$ from 35 ± 4 to 23 ± 2 mmHg and significantly increased $P\bar{v}_{O_2}$ from 43 ± 4 to 62 ± 8 mmHg. Arterial P_{O_2} also increased during the cyanide infusion in the control group (lower panel). Venous *p*H level did not significantly decrease (table 1). In the SFmetHb group, none of these variables changed during the cyanide infusion.

In the control group, $\dot{V}_{O_2}$ (fig. 3, top) significantly decreased to 64 ± 19 ml/min during the cyanide infusion, compared to baseline (93 ± 8 ml/min). At the same time, lactate (fig. 3, bottom) significantly increased from 2.3 ± 0.5 to 7.1 ± 0.7 mM but $\dot{V}_{CO_2}$ did not significantly change (table 1). In the SFmetHb group, $\dot{V}_{O_2}$ and lactate remained stable during the cyanide infusion (fig. 3, shaded bars).

Compared to baseline (4.8 ± 1.0 μM, table 1), the cyanide infusion resulted in a significant increase in the blood [CN] (452 ± 97 μM, $P < 0.05$) in the SFmetHb group, that was significantly larger ($P < 0.05$, Mann-Whitney rank sum test) than the blood [CN] increase in the control group. In the SFmetHb group, the cyanide infusion resulted in a significant increase in plasma [CN] (612 ± 111 μM) compared to baseline (3.3 ± 2.4 μM). In a parallel fashion, the cyanide infusion resulted in a significant increase in the plasma thiocyanate [SCN] from 18 ± 5 to 65 ± 22 μM, $P < 0.05$ in the SFmetHb group, that was significantly greater ($P < 0.05$, Student's *t* test) than the plasma [SCN] increase after cyanide was administered in the control group.

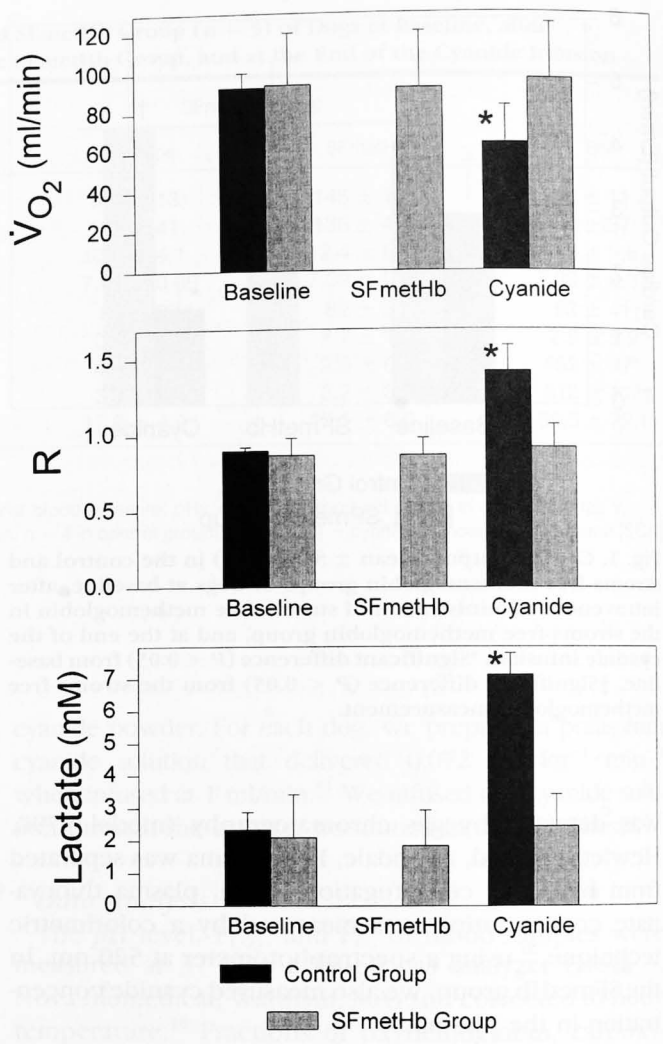

Fig. 3. Oxygen consumption ($\dot{V}_{O_2}$), respiratory quotient ($R = \dot{V}_{CO_2}/\dot{V}_{O_2}$), and venous lactate concentration (mean ± SD, n = 5) in the control and stroma-free methemoglobin groups of dogs at baseline, after intravenous administration of stroma-free methemoglobin in the stroma-free methemoglobin group, and at the end of the cyanide infusion. *Significant difference ($P < 0.05$) from baseline.

Discussion

This study provides the first evidence, we believe, that prophylactic intravenous infusion of exogenous SFmetHb (0.9 g/kg) preserved cardiovascular and metabolic function in dogs exposed to a significant amount of intravenous cyanide, without compromising oxygen-carrying capacity in the blood. In contrast, animals that did not receive SFmetHb had significant percent decreases in $\dot{Q}_T$ (48%) and $\dot{V}_{O_2}$ (32%), and a significant increase in venous lactate by 4.8 mM, during the same cyanide exposure. Previous studies in rats have showed that, after cyanide infusion, survival was significantly improved by administration of SFmetHb,[16,17] but cardiovascular and metabolic function were not studied.

Furthermore, the infusion of SFmetHb itself had little effect on any cardiovascular or metabolic variable. The observed decrease in heart rate during the SFmetHb infusion (table 1) has been reported in spontaneously contracting neonatal rat myocardiocytes exposed to bovine SFmetHb.[22]

The ferric heme group of methemoglobin avidly

binds cyanide[23] and forms the rationale for induction of endogenous methemoglobinemia, usually by inhalation of amyl nitrite or infusion of sodium nitrite.[5] But, during fires with smoke inhalation and exposure to carbon monoxide, conversion of hemoglobin to methemoglobin decreases the oxygen-carrying capacity of blood that may already be compromised by the presence of carboxyhemoglobin.[1,2] Instead, we propose that intravenous administration of exogenous bovine SFmetHb to our study dogs trapped a significant amount of cyanide in the intravascular compartment before it could reach the intracellular compartment and paralyze aerobic metabolism, as evidenced by lack of metabolic and cardiovascular depression.

That SFmetHb trapped cyanide in the blood before it could reach the tissues is evident in the intravascular measurements of cyanide and its metabolite, thiocyanate. The total blood concentrations of cyanide were higher in the SFmetHb-treated animals than the control dogs because the measurement of blood cyanide concentration, which forces all cyanide into the gaseous phase,[19] includes cyanide in all blood components, including SFmetHb in plasma. Indeed, high plasma cyanide concentration in the SFmetHb group reflects trapping of cyanide by SFmetHb in the vascular compartment. The lower amounts of blood cyanide in the control animals, which did not receive SFmetHb, reflects more tissue uptake of the toxin.

Furthermore, thiocyanate is the normal metabolite of cyanide in the body.[2] Thiosulfate can be a sulfur donor in the rhodanese-catalyzed reaction to metabolize cyanide to thiocyanate.[24,25] Plasma SCN concentrations were greater in the SFmetHb-treated dogs presumably because the cyanide, trapped in the intravascular compartment, was available for detoxification by the rapidly equilibrating physiologic pool of cyanide-reactive "sulfane" sulfur.[2,24,25] In the control group, once cyanide entered the cellular compartment and penetrated the mitochondria, the generally extracellular locations of cyanide antidotes (such as SFmetHb or thiosulfate[2,26]) limit their effectiveness.

We selected a cyanide-binding dose of SFmetHb that was 2.4 times greater than the molar cyanide dose administered to the animal, to maximize chelation of cyanide in the blood compartment,[27] without excess dosage of SFmetHb. To significantly increase animal survival in rats,[17] a much greater equivalence molar binding ratio (SFmetHb:CN) was used (9.2–36), suggesting a generous margin of safety if excess SFmetHb is administered.

The urinary half-life elimination of SFmetHb solutions is about 3–5 h.[17] Accordingly, in the prophylaxis of cyanide poisoning, stroma-free cyano-methemoglobin is relatively rapidly excreted in urine to provide a one-step therapeutic method to inactivate and eliminate cyanide from the body.

Exogenous mammalian SFmetHb can be relatively easily produced and stored.[17,28] Indeed, a major challenge in the use of SFmetHb as a blood substitute has been preventing its oxidation to methemoglobin — that reaction is easily catalyzed in the laboratory. Lyophilization of hemoglobin preparations[29] adds further potential for storage and stability. To demonstrate that intravenous SFmetHb is safe in humans requires studies seeking potential side effects on glomerular filtration rate, immunoreactivity, reticuloendothelial system, *etc.* Then, we speculate that SFmetHb might be administered preemptively to emergency personnel at high risk for cyanide exposure, including rescue workers entering fires or industrial accidents and soldiers subject to chemical warfare.

In previous models of combined carbon monoxide and cyanide poisoning in dogs,[1,2] we discussed the importance of oxygen and sodium thiosulfate (despite its extracellular location) in the treatment of cyanide toxicity. However, additional antidote therapy may be necessary for complete detoxification of cyanide.[2] Accordingly, we also envision future studies that test, in addition to the established use of oxygen and sodium thiosulfate, the efficacy of SFmetHb as a third-line treatment agent (especially pre-hospital) after cyanide exposure during fires, industrial accidents, or other toxic exposure.

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