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| <b>14. ABSTRACT</b><br>Current antidotes for cyanide poisoning must be administered by intravenous injection, which would not be practical for treating mass casualties as could occur in a major industrial accident or a terrorist attack. Thus, a need exists for alternative modes of administering cyanide antidotes, and we are comparing three different administration modes: intramuscular injection via an autoinjector, intraosseous injection, and inhalational delivery. We have found that all three modes can rescue animals from exposure to lethal cyanide doses, and now need to determine which administration mode would be the most practical for treating a large number of cyanide-poisoned persons.   |                         |                                 |  |  |   |
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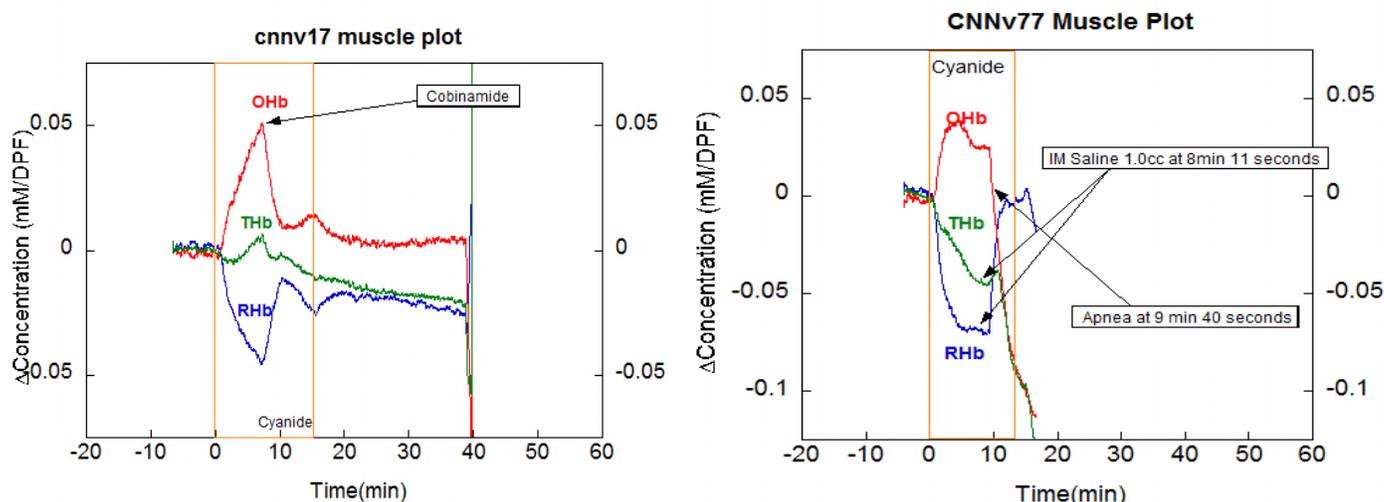
## **INTRODUCTION**

Cyanide is a rapidly acting poison, and, thus, antidotes must be administered quickly; clearly, the fastest way to deliver a drug to the systemic circulation is via intravenous injection. However, even under the best of circumstances, starting an intravenous line takes several minutes, and even more time will likely be required in cyanide-poisoned victims, since they may be hypotensive with collapsed peripheral veins. Thus, intravenous antidote administration would not be practical in the setting of mass casualties from cyanide exposure. Of other possible routes of drug administration, three stand out as potentially very useful to treat a large number of cyanide-poisoned people: intramuscular injection via an autoinjector, intraosseous injection, and inhalational delivery. We are comparing each of these three drug delivery modes to intravenous injection in two different species—rabbits and pigs. Each delivery mode has advantages and disadvantages. Intramuscular injection via an autoinjector is very quick, can be performed through clothing, can be done via self-administration, and has well developed technology. However, a limited volume can be injected, and muscle blood flow is relatively low under resting conditions and can be severely compromised during hypotension as occurs in cyanide poisoning. Intraosseous injection provides access to the systemic circulation as rapidly as intravenous injection, does not require finding a vein, and can be accomplished in a clothed hypotensive person. Disadvantages of intraosseous injection are that it is technically more difficult and time-consuming than intramuscular injection, cannot be conducted in a self-administration mode, and absorption can be potentially reduced by peripheral vasoconstriction. Inhalational delivery has advantages of self-administration, and very rapid absorption not compromised by peripheral vasoconstriction. Disadvantages of inhalational delivery are that the subject needs to be breathing, significant amounts of drug can be lost in the upper airways, and current inhalers deliver only small quantities of drug.

## **BODY**

### **Intramuscular Injection with Autoinjector**

The major provider of autoinjectors in the United States is Meridian Medical Technologies (MMT), now a subsidiary of Pfizer Pharmaceuticals. We established a Cooperative Agreement with MMT to provide 120 autoinjectors for this project. Given the large size of Pfizer and its many lawyers, this required much negotiation between MMT and the University of California, San Diego. Unfortunately, due to recent internal problems at MMT-Pfizer, the autoinjectors will not be delivered for at least six more months (estimated delivery date is April, 2014). In the meantime, we used the commercially-available Stratis Needle-free Injector produced by Pharmajet, Golden, Colorado. We performed experiments in rabbits, and found just as good results injecting cobinamide with this injector as with conventional needle and syringe (Figure 1, next page). We would expect an autoinjector with a needle to perform considerably better. These studies were performed via the subcontract to Drs. Matthew Brenner and Sari Mahon at the University of California, Irvine.

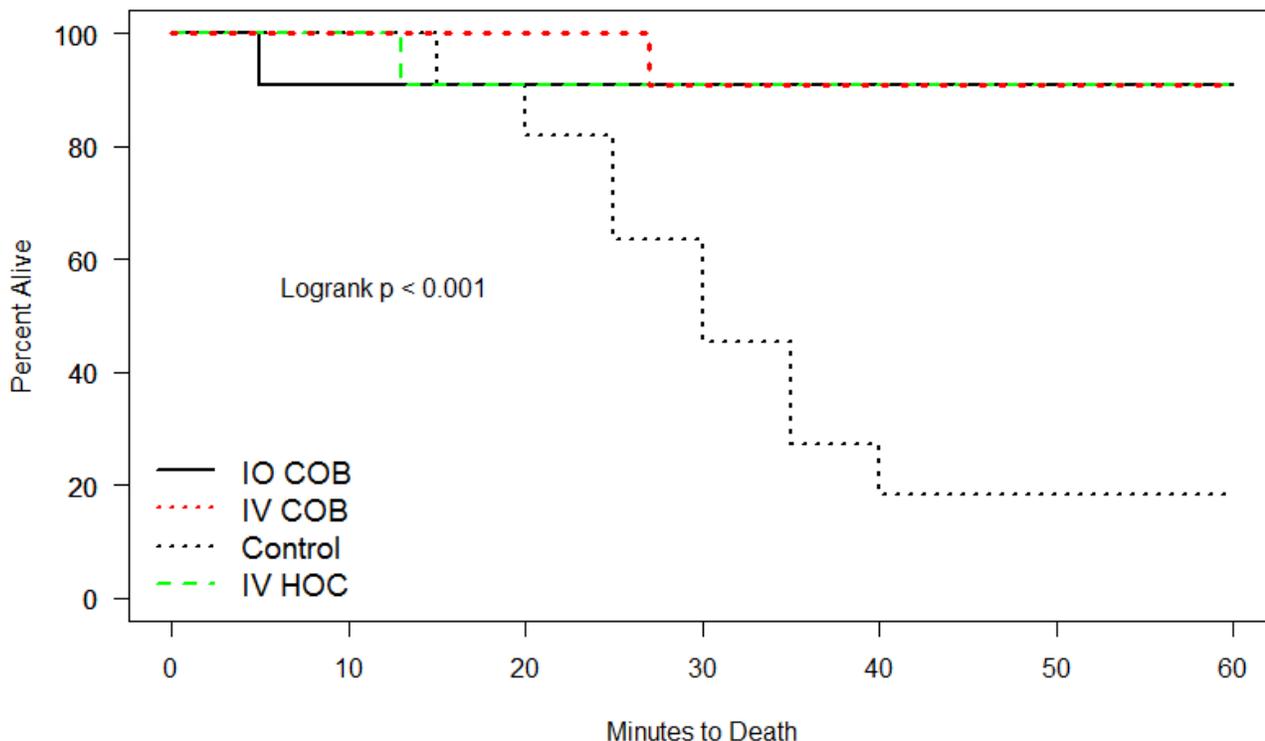


**Fig. 1. Intramuscular Injection of Cobinamide Using an Autoinjector Rescues Cyanide-poisoned Rabbits.** Anesthetized non-ventilated New Zealand white rabbits received a lethal dose of cyanide. Tissue oxyhemoglobin (OHb, red lines), deoxyhemoglobin (RHb, blue lines), and total hemoglobin (THb, green lines) were measured by diffuse optical spectroscopy. The increase in oxyhemoglobin and decrease in deoxyhemoglobin concentrations during sodium cyanide infusion (which is the interval between the vertical orange lines) is due to the inability of tissues to extract oxygen from circulating blood, leaving more hemoglobin in the oxygenated state. At the time the oxy- and deoxyhemoglobin concentrations showed the greatest increase and decrease, respectively, the animals received an intramuscular injection via a needless autoinjector of either cobinamide (left panel) or saline (right panel). In the cobinamide-treated animal, the oxy- and deoxyhemoglobin concentrations rapidly returned towards normal and the animal survived until the time of euthanasia at 40 min after starting the cyanide infusion. This is to be contrasted to the control animal in which the oxyhemoglobin concentration fell dramatically until the animal died at about 17 min after starting the cyanide infusion.

### Intraosseous Injection

We have administered cobinamide via intraosseous injection to both rabbits (Drs. Brenner and Mahon) and pigs (Dr. Vikhyat Bebartha at University of Texas, San Antonio). We found that this administration mode rescued animals from lethal cyanide doses as effectively as when the antidote was given by intravenous injection. Results in pigs are shown in Figure 2 (next page). As part of these experiments, we compared cobinamide to hydroxocobalamin and found that cobinamide was five times more potent than hydroxocobalamin, i.e., 12.5 mg/kg of cobinamide was equivalent to 65 mg/kg hydroxocobalamin.

## 60 Minute Survival by Cyanide Treatment Groups



**Fig. 2. Intraosseous Injection of Cobinamide Rescues Pigs from Cyanide Poisoning.** Cyanide was given by continuous intravenous injection to 50 kg Yorkshire pigs until one minute beyond the onset of apnea, i.e., apnea plus one minute. The animals then received saline by intraosseous injection (Control), 12.5 mg/kg cobinamide (COB) by intraosseous or intravenous injection, or 65 mg/kg hydroxocobalamin (HOC) by intravenous injection. The intraosseous injection was into the tibial plateau using a standard intraosseous injection device. Animals were randomly assigned to each group. A sample size of 11 animals per group was selected based on obtaining a power of 80%, an alpha of 0.05, and an effect size of  $\geq 0.25$  difference (one standard deviation) in mean time to spontaneous breathing. Time to spontaneous breathing and survival were compared using rank methods. Baseline weights (53, 51, 51 kg), time to apnea (10:54, 10:07, 9:49 min), and cyanide dose at apnea (1.8, 1.7, 1.7 mg/kg) were similar. At the time of antidote injection, mean blood cyanide (1.7, 1.7, 1.84 mcg/ml) and lactate concentrations (3.5, 3.5, 3.1 mmol/L), and reduction in mean arterial pressure MAP from baseline (29%, 28%, 36% decrease) were similar. Two of 11 animals in the saline control group survived (18% survival) compared to 10 of 11 surviving in both the intravenous and intraosseous cobinamide groups (91% survival) ( $p < 0.001$  difference between saline- and cobinamide-injected animals). Survival in the intravenous hydroxocobalamin group was also 91%. Time to spontaneous breathing after antidote was similar (intravenous 1:48 min, and intraosseous 1:47 min). Blood cyanide concentrations became undetectable after cobinamide infusion in both groups. No statistically significant differences were detected between the intraosseous and intravenous cobinamide groups for cardiac output, MAP, or minute ventilation, or in lactate (1.3 vs 1.8 mmol/L) and pH (7.44 vs 7.41) at 60 min. We conclude that intraosseous cobinamide is as effective as intravenous cobinamide for treating cyanide-poisoned pigs.

### Inhalational Delivery

Dr. Chen Tsai at the University of California, Irvine has further developed an ultrasonic nebulizer to deliver cyanide antidotes by inhalation (Figure 3, next page). It is a small, pocket-sized device ( $8.6 \times 5.6 \times 1.5 \text{ cm}^3$ ) that contains a nozzle, electronic driver, cell-phone battery, piezoelectric micro pump, drug reservoir, and liquid feed system. It can deliver flow rates of up to 0.2 ml/min, allowing a cyanide antidote to be given in about five minutes. We have shown that giving cobinamide by this device can successfully rescue rabbits from lethal cyanide doses. During the past year, an improved nozzle platform was designed and fabricated. The new platform is considerably smaller in size and capable of incorporating a pair of centimeter-sized nozzles that will facilitate a higher delivery rate for a single antidote or delivery of separate antidotes such as cobinamide and sulfanegen. Dr. Tsai recently had a paper accepted at the annual meeting of the Institute of Electrical and Electronics Engineers (IEEE) describing this new ultrasonic nebulizer (see below).

**Fig. 3. Ultrasonic Nebulizer Prototype.** The device is nebulizing cobinamide, which is seen as a fine red spray emanating from the device.



### KEY RESEARCH ACCOMPLISHMENTS

Intramuscular injection of cobinamide using an autoinjector successfully rescues rabbits from lethal cyanide exposure

Intraosseous injection of cobinamide successfully rescues rabbits and pigs from lethal cyanide exposures

Inhalational delivery of cobinamide using a new state-of-the-art ultrasonic nebulizer successfully rescues rabbits from lethal cyanide exposure

### REPORTABLE OUTCOMES

Two reportable outcomes were generated during the last year: a manuscript describing intraosseous injection of cobinamide in pigs was submitted and a paper describing the ultrasonic nebulizer was published as part of the annual meeting of the IEEE.

1. Bebarta, V, Tanen, D. Boudreau, S.M., Castaneda, M.G. Tone, T., and Boss, G.R. Intraosseous versus intravenous cobinamide in treating acute cyanide toxicity and apnea in a swine (*Sus Scrofa*) model. Manuscript submitted.
2. Tsai, C.S., Mao, R.W., Zhu, Y. Chien, E., Maduzia, J., Tsai, S.C., Brenner, M. Mahon, S., Mukai, D. Lee, J., Yoon, D., Berney, T., Boss, G., and Patterson, S.E. Hand-Held High-Throughput Ultrasonic Monodisperse Aerosol Inhalers for Detoxification of Massive Cyanide Poisoning. IEEE Proceedings, *International Ultrasonics Symposium*, Prague, Czech Republic, 2013.

### CONCLUSION

We have shown that cyanide antidotes can be administered by intramuscular injection using a needleless autoinjector, by intraosseous injection, and by inhalational delivery. By all three modes, animals can be rescued from lethal doses of cyanide. During the next year, we plan to test a more conventional needle-delivery autoinjector for intramuscular administration and to further develop the ultrasonic nebulizer for inhalational delivery.

### REFERENCES

Not applicable.

### APPENDICES

The two works reported above are included.

# Hand-Held High-Throughput Ultrasonic Monodisperse Aerosol Inhalers for Detoxification of Massive Cyanide Poisoning

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**Abstract**— Detoxification of massive cyanide (CN) poisoning by inhalation of antidotes is recognized to be superior to intravenous (IV) or intra muscular (IM) treatment with regard to ease of administration, self-administration, and rapidity of onset. However, there are currently no effective, portable, high-throughput inhalers that can be produced in large quantities and distributed for such purpose. A hand-held inhaler has been realized using silicon-based ultrasonic nozzle to produce high-throughput of monodisperse cobinamide antidote solution for detoxification of CN poisoning in a rabbit model.

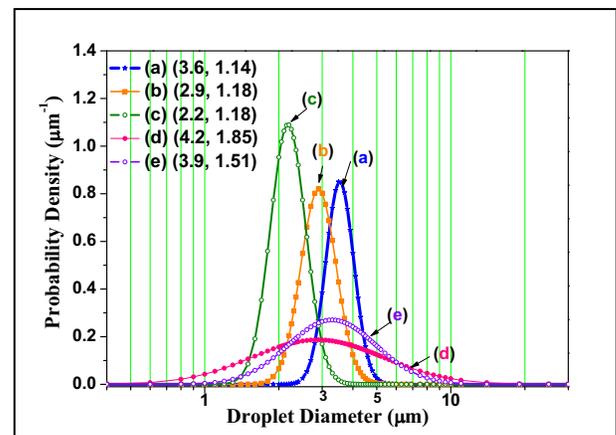
**Keywords**- cyanide poisoning and detoxification, cobinamide antidote, Fourier-horn ultrasonic nozzles, monodisperse aerosol inhaler

## I. INTRODUCTION

Currently, all effective cyanide (CN) antidotes must be administered intravenously (IV). This is not possible for mass CN poisoning resulting from disasters such as terrorist attack and major fires. There is currently no available intramuscular (IM) treatment or agents that can be applied rapidly for the mass CN poisoning either. Meanwhile, inhalation modes may be superior with regard to ease of administration, self-administration, and rapidity of onset. However, current commercial inhalers or nebulizers all suffer from polydisperse (broad-size) aerosol distribution and/or low throughput, making it difficult to deliver sufficient amount of drugs to the lung rapidly and precisely. Thus, there is no effective portable, high-throughput, low-power inhalers that can be produced in large quantities and distributed for such purposes.

Aerosol particles (or droplets) greater than  $5\mu\text{m}$  in mass median aerodynamic diameter (MMAD) or mass median diameter (MMD) impact primarily in the oropharynx and thus do not enter the respiratory system. Particles between  $5$  and  $1\mu\text{m}$  (the “respirable” fraction) enter the respiratory system [1,

2] and deposit in progressively smaller airways [2]. Particles between  $3$  and  $1\mu\text{m}$  deposit optimally in the alveolar region [3-5], while particles smaller than  $1\mu\text{m}$  remain airborne and are exhaled. Droplet size distribution, as measured by geometrical standard deviation (GSD), is also an important determinant of inhaled drug delivery. Human deposition images from the same patient inhaling from two different wet nebulizers both with MMAD below  $5\mu\text{m}$  but with different size distributions (GSD  $>4.0$  versus  $3.0-4.0$ ) illustrate how small changes in the polydispersity or GSD of the aerosol distributions result in markedly different deposition patterns [6, 7].



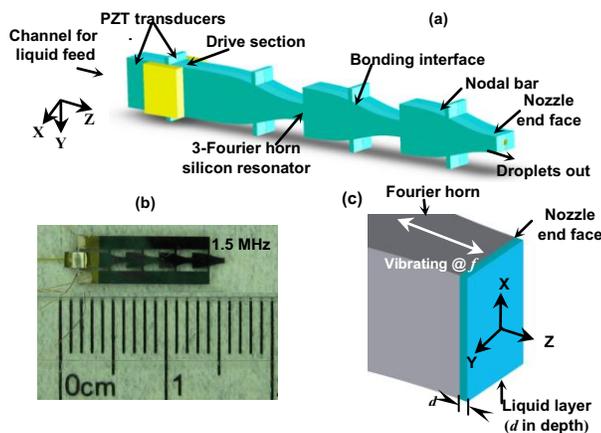
**Fig. 1** (a) 1.5 MHz nozzle with water ( $3.6\mu\text{m}/1.14$ ), (b) 2.0 MHz nozzle with water ( $2.9\mu\text{m}/1.18$ ), (c) 2.0 MHz nozzle with alcohol ( $2.2\mu\text{m}/1.18$ ), and commercial nebulizers (d) Omron NE-U22V ( $4.2\mu\text{m}/1.85$ ) and (e) Pari eFlow ( $3.9\mu\text{m}/1.51$ ). Note: Numbers in parenthesis designate NMD and GSD which stand for number mean diameter and geometrical standard deviation, respectively.

As shown in Fig. 1 plots (d) and (e), even the most advanced vibrating mesh technology-based ultrasonic

nebulizers produced very broad drop-size distributions. In contrast, the MHz multiple-Fourier horn ultrasonic nozzle reported recently [8-10] has demonstrated its capability of producing high-throughput micrometer-sized monodisperse droplets (see plots (a) to (c) of Fig. 1) at very low electrical drive power and thus fulfilling the unmet needs. This paper reports utilization of a hand-held inhaler with 1.5 MHz 4-Fourier horn nozzle to produce high-throughput of aerosolized monodisperse cobinamide antidote solution for detoxification of CN poisoning in a rabbit model.

## II. SILICON-BASED ULTRASONIC NOZZLE

Figure 2(a) shows the silicon-based multiple-Fourier horn ultrasonic nozzle that enables controlled excitation of single-mode MHz Faraday waves and production of micrometer-sized monodisperse droplets from the nozzle end face. Fig. 2(b) shows photographs of the 1.5 MHz four-Fourier horn nozzle used in this study. The nozzle was designed to vibrate in a single longitudinal vibration mode at the single resonance frequency ( $f$ ) of the multiple-Fourier horns [8]. Electrical activation of the PZT transducers at this resonance frequency creates a standing acoustic wave through the nozzle body in the direction perpendicular to the nozzle end face [Z-axis in Figs. 2(a) and 2(c)] with a maximum vibration displacement ( $h$ ) on the end face. The greatly enhanced  $h$  due to the multiple-Fourier horns in resonance (with a displacement gain of  $2^n$  for a  $n$ -Fourier-horn nozzle) [8, 9] facilitates the critical excitation displacement ( $h_{cr}$ ) required to form Faraday waves on the free surface of the planar liquid layer resting on the nozzle end face and, subsequently, initiates temporal instability of the waves, resulting in the ejection of monodisperse droplets at low electrical drive power. Specifically, high-throughput of aerosolized micrometer-sized monodisperse cobinamide antidote solution was produced for the CN detoxification experiments.



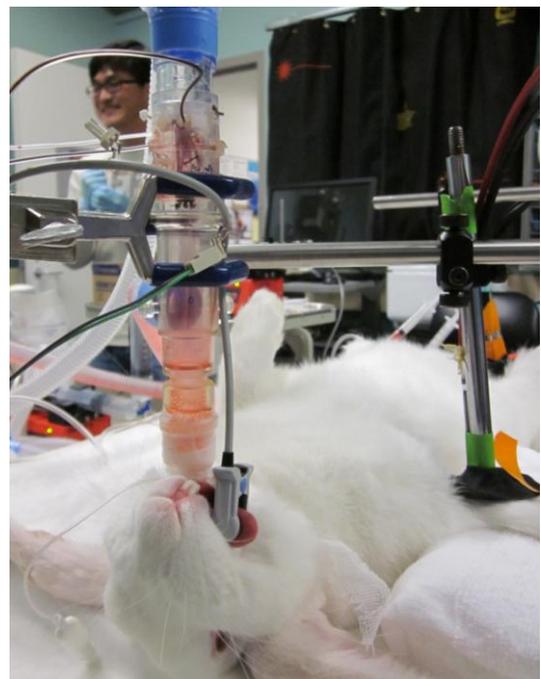
**Fig. 2** (a) MHz silicon ultrasonic nozzle with central channel dimensions of  $150\mu\text{m} \times 150\mu\text{m}$  for 1.5 MHz four-Fourier horn nozzle, and the corresponding end face dimensions of  $482\mu\text{m} \times 1060\mu\text{m}$ . (b) Photograph of the 1.5 MHz nozzle; (c) Geometry of nozzle end face and liquid layer  $d$  in depth.

## III. CYANIDE DETOXIFICATION EXPERIMENTS WITH RABBITS

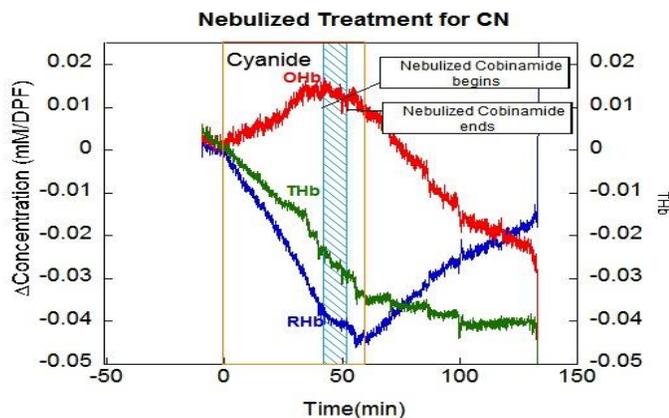
We proceeded with the animal experiments using the 1.5 MHz nozzle just described with relatively low throughput (0.15 ml/min) of cobinamide antidote (100 mM or  $\sim 100$  mg in saline solution) [11-13]. Four rabbits were studied using CN infusion continuously for 60 min as shown in Fig. 3. Nebulized cobinamide was administered beginning 40 min into the CN infusion and continuing for 10 min. As is evident from Fig. 4, the rate deterioration and tissue oxygen extraction defect was immediately stabilized as the nebulization started. The process was further reversed after the CN infusion was discontinued at 60 min. Cobinamide was readily seen in the plasma samples drawn serially following initiation of the cobinamide nebulization (Fig. 5). These results clearly show the significant effect of nebulized cobinamide for reversing CN poisoning even at low dose ( $\sim 100$  mg) and thus, demonstrate the high potential of the hand-held high-throughput ultrasonic monodisperse aerosol inhalers for detoxification of massive CN poisoning.

## IV. CONCLUSIONS

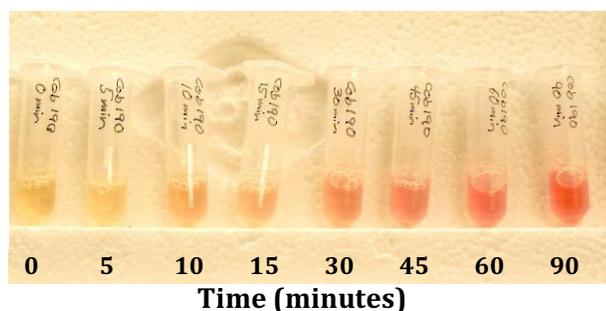
Significant effect of aerosolized cobinamide for reversing CN poisoning even at low dose ( $\sim 100$  mg) has demonstrated the high potential of a hand-held MHz ultrasonic monodisperse aerosol inhaler for detoxification of massive CN poisoning. Furthermore, the micrometer-sized ( $2.2$  to  $4.6\mu\text{m}$ ) monodisperse aerosols produced at high throughput and very low electrical drive power ( $<1.0$  W) will have broad applications to delivery of both inhalation solution and suspension drugs to the lung.



**Fig. 3** Rabbit Model Experiment



**Fig. 4** Diffuse optical spectroscopy (DOS) measurements of oxyhemoglobin (OHb) and deoxyhemoglobin (RHb) during induction of cyanide poisoning and reversal using monodisperse aerosol cobinamide administration. OHb increases during cyanide poisoning due to inability of tissue to extract oxygen. As antidote drug is absorbed, OHb returns to normal rapidly.



**Fig. 5** Appearance of active drug, cobinamide, in the plasma of rabbits following trans-pulmonary drug administration. In other words, cobinamide is seen as CN toxicity has been reversed with aerosol administration

#### ACKNOWLEDGMENT

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