We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,300

Open access books available

172,000

International authors and editors

190M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com

Application of CO-oximeter for Forensic Samples

Hiroshi Kinoshita, Naoko Tanaka, Ayaka Takakura,
Mostofa Jamal, Asuka Ito, Mitsuru Kumihashi,
Shoji Kimura, Kunihiro Tsutsui, Shuji Matsubara and
Kiyoshi Ameno

Additional information is available at the end of the chapter

<http://dx.doi.org/10.5772/intechopen.71182>

Abstract

CO-oximeter is routinely used in clinical practice, and it has been applied in the field of forensic medicine. It is a simultaneous and nondestructive technique for the analysis of total hemoglobin (Hb) and various Hb species, such as oxyhemoglobin, reduced hemoglobin, carboxyhemoglobin, and methemoglobin. It automatically measures the proportion of each species of Hb and oxygen contents. This is an easy, rapid, and convenient way as the laboratory test. Since there are many advantages such as no necessity of sample preparation, easy handling, and portability, it may provide valuable information for forensic diagnosis. In the present paper, we discuss about the diagnostic application of CO-oximeter in the field of forensic medicine.

Keywords: CO-oximeter, forensic diagnosis, carbon monoxide poisoning, hypothermia, methemoglobin

1. Introduction

CO-oximeter is widely used in clinical practice [1–5]. It would be measurable total hemoglobin (Hb) and various Hb species, such as oxyhemoglobin (O₂Hb), reduced hemoglobin (HHb), carboxyhemoglobin (COHb), and methemoglobin (MetHb), simultaneously. This is an easy, rapid, and convenient way as the laboratory test, and it provides valuable information for clinical diagnosis. It is widely used in clinical laboratory, emergency department, intensive care unit, or cardiac catheterization laboratory for the evaluation of general status including the ability of oxygenation or ventilation [1–5].

It has been reported that CO-oximeter is applied in a field of forensic diagnosis [6–30]. In the present chapter, we discuss about the diagnostic application of CO-oximeter in the field of forensic medicine.

2. Principle of the CO-oximeter

The CO-oximeter is a spectrophotometer that determines hemoglobin derivatives in blood by measuring absorbance at selected wavelength [1, 2, 31, 32]. The Hb solutions obey the Lambert-Beer Law, and the absorbance measured at selected wavelength is the sum of the absorbance of each Hb derivative [31–36]. The wavelength is selected by the combination of absorption maxima and isosbestic points [37]. The concentration of four Hb derivatives (O_2Hb , HHb, COHb, and MetHb) is determined by measuring absorbance at four wavelengths [33].

The CO-oximeter is included in the routine toxicological examination in daily forensic practice, as it is not necessary for the sample pretreatment or any reagent.

3. Forensic application of CO-oximeter

Since the O_2Hb in the postmortem heart blood was usually very low (under 10%) in most of the cases, postmortem blood gas analysis is less valuable for interpretation of cause of death [13]. However, the composition of Hb provides valuable information for forensic diagnosis.

We have been using the AVOX4000 (AVOX; International Technidyne Corporation, NJ, USA), which monitors seven wavelengths (488.4, 520.1, 562.4, 585.2, 597.5, 621.7, and 671.7 nm) in the visible region for the determination of various Hb species [24]. This portable CO-oximeter (**Figure 1**) requires 50 μ l of blood for single measurement, and it may be a valid option in case of difficult blood sampling due to severe blood loss. Since there are many advantages such as no necessity of sample preparation, easy handling, and portability, it is suitable for forensic practice. It automatically analyzes the proportion of each species of Hb and oxygen contents.

3.1. Carbon monoxide (CO) poisoning

CO is an odorless, colorless and nonirritable gas, mainly produced by incomplete combustion of fuels or carbon compounds [38, 39]. CO is second most common cause of death among non-medical poisonings in United States [40], and the leading cause of poisoning death in Japan [41, 42]. It includes accidental or suicidal poisoning, and the postmortem investigation for CO poisoning and its related death are important for forensic practice.

CO binds to hemoglobin and forms COHb (represented as a percentage of the total Hb) following inhalation of CO gas [39, 43, 44]. As the affinity of CO for Hb is 200–300 times greater than that for oxygen, the toxicity of CO is mainly thought to be the decrease the capacity of oxygen transport, and it causes impairment of oxygen supply in tissue level [39, 43–46]. In a recent study, it may be involved interference with ferroproteins such as myoglobin and cytochrome oxidases [43, 45, 46].

Figure 1. Portable oximeter (AVOX 4000).

CO-Hb (%)	Clinical symptoms
<1-2	Normal range (due to endogenous production)
<10	Smoker's blood (no symptom)
10–20	Headache
20–40	Headache, nausea, vomiting
40–	Severe symptoms
50–60	Coma, convulsions
60–	Cardiorespiratory depression or failure, often fatal

Table 1. Level of carboxyhemoglobin (COHb) and symptoms.

Table 1 shows the relationship between toxic symptoms and COHb levels [39, 46]. However, it is not an absolute reference value, and large individual difference was observed in fatal level. Severe symptoms such as convulsion, deep coma, and cardiovascular failure are observed around 50% of COHb level. The fatal COHb levels are more than 50–60%, and its values are important for the diagnosis of fatal CO poisoning [46]. However, lethal level has large variation. Elderly people may die at relatively low concentration in some cases [46]. It may be involved to pathological status such as anemia, coronary artery disease, and respiratory insufficiency [46]. Autopsy findings indicate that blood, organs, and muscle will be cherry red

color, as a result of COHb formation. Other findings such as pulmonary edema and generalized organ congestion are also observed [46].

The application of oximeter in fatal CO poisoning case has been reported [6, 7, 10–13, 15–20, 22–29]. Various methods such as spectrophotometric method and gas chromatography have been also employed for the identification and quantification of CO [43, 47]. There was a good correlation between the COHb values obtained by AVOX and by the conventional method [23]. No arterial-venous difference of COHb concentration was observed at the level less than 75% of COHb [23] and in animal experiments [48].

In a forensic practice, we sometimes treat various kinds of denatured blood samples such as from the putrefied bodies or thermo-coagulated one. As the COHb is relatively stable under the storage in cool and dark conditions, it would be accurately measurable less than 2 years under the storage in fridges [22, 49], and it is possible for rough estimation of COHb levels in thermo-coagulated blood with CO oximeter [6, 12]. In recent study, it has been reported that splenic blood, which is obtained by manual squeezing, is applicable for alternative matrix for COHb measurement using AVOX [29].

3.2. Fire-related cases

The victims by fire will die not only from the thermal injury but also from inhalation of the toxic substances such as CO, cyanide, nitric oxide, phosgene, and others and reduction of the atmospheric oxygen [46]. When the organic material burn but access of oxygen is limited in fire, large amount of CO is produced by the incomplete combustion. The COHb level in fire-related cases is an important aspect [46]. The presence of CO in circulating blood and carbon particle in the air passages indicates that the victim was alive after the fire began [46]. It is a valuable indicator in fire-related cases. The COHb levels in blood of the fire victim depend on various factors such as CO concentration in atmosphere, time of exposure, and oxygen contents [46].

It has been reported that marked arteriovenous and centropерipheral difference of COHb were observed in the group of above ca.70% of COHb [11]. It seems to be that inhalation of CO-rich air immediately causes acute heart failure [11]. On the other hand, COHb levels in victim were lower in flash fires or open-air petrol involved cases. The quick measurement of COHb using CO-oximeter in victim of fire-related case provides valuable information for forensic diagnosis.

3.3. Hypothermia

There is little or no diagnostic findings in cases of fatal hypothermic death [14, 28, 30, 46, 50–55]. It has been reported that the blood in left cardiac chamber is bright red compared to that in right cardiac chamber [28, 30, 50, 51, 53, 56]. This color difference between left and right heart blood is a common characteristic sign of hypothermic death. This finding was observed in approximately 95% of hypothermic death cases [30, 50, 53]. This color difference is formed by many factors such as decrease of body temperature, binding of oxygen to Hb, and inhalation of cold air before death [30, 50]. The blood in left heart has usually higher oxygen contents than

that in right heart. The lower body temperature keeps the antemortem composition of Hb following death, and it also enhances the oxygen binding to Hb [30, 50, 53].

The O₂Hb saturation level could increase as a result of cardiopulmonary resuscitation or administration of oxygen. We have to exclude the following cases such as subjected to body rewarming, long postmortem interval, and received cardiopulmonary resuscitation, for forensic diagnostic application of CO-oximeter [30].

It has been proposed that the diagnostic criterion of hypothermic death, designating O₂Hb in left cardiac blood $\geq 36\%$ as a basic condition, with the difference in the O₂Hb saturation level between left and right heart blood $\geq 13\%$ or O₂Hb saturation ratio between left and right heart blood ≥ 1.8 , as a complementary condition [30]. This finding reflects the final balance of oxygen uptake and consumption in the dying process, and the pathophysiological status of the victim would be obtained by the application of CO-oximeter for forensic diagnosis.

3.4. Evaluation of MetHb

MetHb is a form of Hb in which ferric iron (Fe³⁺) is carried in its heme group [57]. It is formed by the exposure to oxidizing agents such as nitrates, nitrites, or chlorates [57–59]. MetHb may also arise from genetic, dietary, or idiopathic etiologies [57–59]. It causes impairment of O₂ and CO₂ transport, leading to tissue or cellular hypoxia [57–59]. High levels of MetHb have been observed in cases of fire and poisoning by various oxidizing agents such as vehicle exhaust (containing nitric oxide and nitrogen dioxide), nitrate, and chlorate [60–64]. We should also take into consideration about the stability of MetHb. The formation of MetHb by postmortem oxidation of heme-protein has been reported [8]. On the other hand, high COHb containing blood is considered to have heat resistant properties, and the formation of MetHb is lower [65]. Spontaneous reduction of MetHb in blood sample due to the enzyme activity has also been reported [66]. We have to consider them for the interpretation of the MetHb value.

Measurement of MetHb using the conventional spectrophotometric method [67] is relatively complicated procedure. On the other hand, CO-oximeter is routinely used in clinical practice [2, 3, 5] and has also been applied in forensic practice [8, 64]. **Table 2** shows

MetHb (%)	Clinical symptom
<1–2	Normal range (no symptom)
10–15	Cyanosis
20–	Headache, dyspnea, tachycardia, tachypnea
40–50	Mental derangement, metabolic acidosis
50–	Coma, convulsion
70–	Death

Table 2. Level of methemoglobin (MetHb) and symptoms.

the relationship between toxic symptoms and MetHb concentration [57–59, 68]. The blood MetHb concentration is less than 1–2% in normal healthy subjects, and fatal concentration of MetHb in blood has been reported higher than 70% [57–59, 68]. Blood MetHb concentration provides useful toxicological information for forensic diagnosis. From these results, additional toxicological examination for oxidizing agent may be requested to the forensic toxicologist.

4. Conclusion and future perspective

We have discussed about the application of CO-oximeter in forensic practice. The postmortem oximetric profiles may be considered to reflect the final balance of oxygen uptake and consumption in the dying process [13]. Those data may be valuable for interpretation in some cause of death and provides valuable information for forensic diagnosis. Further applications in the fields of forensic practice can be expected.

Acknowledgements

This work was supported by JSPS KAKENHI Grant-in-Aid for Scientific Research (C) Number 15 K08873.

Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

Author details

Hiroshi Kinoshita^{1*}, Naoko Tanaka¹, Ayaka Takakura¹, Mostofa Jamal¹, Asuka Ito¹, Mitsuru Kumihashi¹, Shoji Kimura¹, Kunihiro Tsutsui², Shuji Matsubara³ and Kiyoshi Ameno¹

*Address all correspondence to: kinochin@med.kagawa-u.ac.jp

1 Department of Forensic Medicine, Faculty of Medicine, Kagawa University, Miki, Kagawa, Japan

2 Health Sciences, Faculty of Medicine, Kagawa University, Miki, Kagawa, Japan

3 Community Health Care Education Support Center, and Postgraduate Clinical Education Center, Kagawa University Hospital, Miki, Kagawa, Japan

References

- [1] Zijlstra WG, Buursma A, Zwart A. Performance of an automated six-wavelength photometer (Radiometer OSM3) for routine measurement of hemoglobin derivatives. *Clinical Chemistry*. 1988;**34**:149-152
- [2] Mahoney JJ, Vreman HJ, Stevenson DK, Van Kessel AL. Measurement of carboxyhemoglobin and total hemoglobin by five specialized spectrophotometers (CO-oximeters) in comparison with reference methods. *Clinical Chemistry*. 1993;**39**:1693-1700
- [3] Gong AK. Near-patient measurements of methemoglobin, oxygen saturation, and total hemoglobin: Evaluation of a new instrument for adult and neonatal intensive care. *Critical Care Medicine*. 1995;**23**:190-201
- [4] Touger M, Gallagher EJ, Tyrell J. Relationship between venous and arterial carboxyhemoglobin levels in patients with suspected carbon monoxide poisoning. *Annals of Emergency Medicine*. 1995;**25**:481-483
- [5] Bailey SR, Russell RN, Martinez A. Evaluation of the avoximeter: Precision, long-term stability, and use without heparin. *Journal of Clinical Monitoring*. 1997;**13**:191-198
- [6] Freireich AW, Landau D. Carbon monoxide determination in postmortem clotted blood. *Journal of Forensic Sciences*. 1971;**16**:112-119
- [7] Okada M, Okada T, Ide K. Utilization of a CO-oximeter in the medico-legal field. *Nihon Houigaku Zasshi*. 1985;**39**:318-325
- [8] Okada M, Okada T, Kawaguchi N, Ide K. Studies of methemoglobin production in the blood of dead burn victims. *Nihon Houigaku Zasshi*. 1986;**40**:124-128
- [9] Ohshima T, Takayasu T, Nishigami J, Lin Z, Kondo T, Nagano T. Application of hemoglobin analysis by CO-oximeter to medico-legal practice with special reference to diagnosis of asphyxia. *Nihon Houigaku Zasshi*. 1992;**46**:382-388
- [10] Higuchi T, Noguchi K, Maeda H. An evaluation of analyzed data of hemoglobin derivatives by CO-oximeter in medico-legal autopsy. *Nihon Houigaku Zasshi*. 1992;**46**:416-418
- [11] Maeda H, Fukita K, Oritani S, Nagai K, Zhu BL. An evaluation of post-mortem oxymetry in fire victims. *Forensic Science International*. 1996;**81**:201-209
- [12] Oritani S, Nagai K, Zhu BL, Maeda H. Estimation of carboxyhemoglobin concentrations in thermo-coagulated blood on a CO-oximeter system: an experimental study. *Forensic Science International*. 1996;**83**:211-218
- [13] Maeda H, Fukita K, Oritani S, Ishida K, Zhu BL. Evaluation of post-mortem oxymetry with reference to the causes of death. *Forensic Science International*. 1997;**87**:201-210
- [14] Shimizu K, Mizukami H, Fukushima T, Sasaki M, Shiono H. Use of a CO-oximeter for forensic diagnosis of hypothermia. *Nihon Houigaku Zasshi*. 1998;**52**:196-201

- [15] Lee CW, Tam JCN, Kung LK, Yim LK. Validity of CO-oximetric determination of carboxyhaemoglobin in putrefying blood and body cavity fluid. *Forensic Science International*. 2003;**132**:153-156
- [16] Brehmer C, Iten PX. Rapid determination of carboxyhemoglobin in blood by Oximeter. *Forensic Science International*. 2003;**133**:179-181
- [17] Watanabe N, Terazawa K, Sakaiharu M. Blood storage for forensic hemoglobin analysis using CO-oximeter. *Hokkaido Igaku Zasshi*. 2003;**78**:289-295
- [18] Watanabe N. Medico-legal application of hemoglobin analysis using CO-oximeter. *Hokkaido Igaku Zasshi*. 2003;**78**:557-566
- [19] Olson KN, Hillyer MA, Kloss JS, Geiselhart RJ, Apple FS. Accident or arson: Is Co-oximetry reliable for carboxyhemoglobin measurement postmortem? *Clinical Chemistry*. 2010;**56**: 515-520
- [20] Tanaka N, Ameno K, Jamal M, Ohkubo E, Kumihashi M, Kinoshita H. Application of oximeter AVOX 4000 for the determination of CO-Hb in the forensic practice. *The Research and Practice in Forensic Medicine*. 2010;**53**:39-43
- [21] Tanaka N, Ameno K, Jamal M, Kumihashi M, Kinoshita H. Application of oximeter AVOX 4000 in the forensic practice (report 2): Diagnosis for hypothermia. *The Research and Practice in Forensic Medicine*. 2011;**54**:205-209
- [22] Tanaka N, Ameno K, Jamal M, Kumihashi M, Miyatake N, Kinoshita H. Effects of sampling methods and storage on the value of oxyhemoglobin ratio and carboxyhemoglobin ratio. *The Research and Practice in Forensic Medicine*. 2012;**55**:51-55
- [23] Kinoshita H, Tanaka N, Jamal M, Kumihashi M, Ameno K. Evaluation of carboxyhemoglobin (CO-Hb) by oximeter in forensic practice. In: DiLoreto D, Corcoran I, editors. *Carbon Monoxide Source, Uses and Hazards*. New York: Nova Science Publishers, Inc.; 2012. p. 109-116
- [24] Fujihara J, Kinoshita H, Tanaka N, Yasuda T, Takeshita H. Accuracy and usefulness of the AVOXimeter 4000 as routine analysis of carboxyhemoglobin. *Journal of Forensic Sciences*. 2013;**58**:1047-1049
- [25] Fujihara J, Hasegawa M, Kato T, Miura M, Iida K, Kinoshita H, Tanaka N, Takeshita H. A case of drowning lacking typical autopsy findings of carbon monoxide poisoning despite the high CO concentration. *Forensic Toxicology*. 2013;**31**:180-182
- [26] Nakagawa H, Maebashi K, Fukui K, Ochiai E, Iwadate K. Applicability of a new CO oximeter to forensic autopsy cases. *Acta Criminologicae et Medicinae Legalis Japonica*. 2013;**79**:16-21
- [27] Tanaka N, Ameno K, Jamal M, Kumihashi M, Miyatake N, Kinoshita H. Effects of sample dilution on the value of carboxyhemoglobin ratio. *Japanese Journal of Forensic Pathology*. 2014;**20**:39-40

- [28] Kanoto-Nishimaki Y, Saito H, Watanabe-Aoyagi M, Toda R, Iwadate K. Investigation of oxyhemoglobin and carboxyhemoglobin ratios in right and left cardiac blood for diagnosis of fatal hypothermia and death by fire. *Legal Medicine (Tokyo)*. 2014;**16**:321-325
- [29] Tanaka N, Kinoshita H, Jamal M, Takakura A, Kumihashi M, Miyatake N, Ameno K. Squeezed splenic blood sampling as an alternative method for carboxyhemoglobin measurement. *Romanian Journal of Legal Medicine*. 2015;**23**:106-108
- [30] Yajima D, Asari M, Okuda K, Maseda C, Yamada H, Ichimaru C, Matsubara K, Shiono H, Iwase H, Makino Y, Shimizu K. An objective approach using three indexes for determining fatal hypothermia due to cold exposure; statistical analysis of oxyhemoglobin saturation data. *Legal Medicine (Tokyo)*. 2015;**17**:451-458
- [31] Yukawa N, Suzuoka T, Saito T, Forrest ARW, Osawa M, Takeichi S. Data processing in CO-oximeters that use overdetermined systems. *Clinical Chemistry*. 1997;**43**:189-190
- [32] Yukawa N, Suzuoka T, Saito T, Forrest ARW, Osawa M, Takeichi S. Current CO-oximeter. *Forensic Science International*. 1998;**94**:211-215
- [33] Brown LJ. A new instrument for the simultaneous measurement of total hemoglobin, % oxyhemoglobin, % carboxyhemoglobin, % methemoglobin, and oxygen content in whole blood. *IEEE Transactions on Biomedical Engineering*. 1980;**27**:132-138
- [34] Zwart A, Buursma A, van Kampen EJ, Oeseburg B, van der Ploeg PHW, Zijlstra WG. A multi-wavelength spectrophotometric method for the simultaneous determination of five haemoglobin derivatives. *Journal of Clinical Chemistry and Clinical Biochemistry*. 1981;**319**:457-463
- [35] Zwart A, Buursma A, van EJ, Zijlstra WG. Multicomponent analysis of hemoglobin derivatives with reversed-optics spectrophotometer. *Clinical Chemistry*. 1984;**30**:373-379
- [36] Zwart A, van Kampen EJ, Zijlstra WG. Results of routine determination of clinically significant hemoglobin derivatives by multicomponent analysis. *Clinical Chemistry*. 1986;**32**:972-978
- [37] Brunelle JA, Moran RF. A manufacturer replies. *Clinical Chemistry*. 1997;**43**:190-191
- [38] Baselt RC. *Disposition of Toxic Drugs and Chemicals in Man*. 8th ed. Foster City: Biochemical Publications; 2008
- [39] Elenhorn MJ, Barceloux DG. *Medical Toxicology Diagnosis and Treatment of Human Poisoning*. New York: Elsevier; 1988
- [40] Sircar K, Clower J, Shin MK, Bailey C, King M, Yip F. Carbon monoxide poisoning deaths in the United States, 1999 to 2012. *The American Journal of Emergency Medicine*. 2015;**33**:1140-1145
- [41] Ministry of Health, Labour and Welfare. *Vital Statistics of Japan*. Tokyo: Health, Labour and Welfare Statistics Association; 1998-2015.

- [42] Ito T, Nakamura Y. Death from carbon monoxide poisoning in Japan between 1968-2007 through data from vital statistics. *Journal of Japanese Society for Emergency Medicine*. 2010;**13**:275-282
- [43] World Health Organization. *Environmental Health Criteria 213, Carbon Monoxide*. 2nd ed. Geneva: World Health Organization; 1999
- [44] Powers RH, Dean DE. *Forensic Toxicology Mechanism and Pathology*. Boca Raton: CRC Press; 2016
- [45] Tomaszewski C. Carbon monoxide. In: Nelson LS et al., editors. *Goldfrank's Toxicologic Emergencies*. 9th ed. New York, Chicago: McGraw-Hill; 2011. p. 1658-1670
- [46] Saukko P, Knight B. *Knight's Forensic Pathology*. 4th ed. Boca Raton, FL: CRC Press; 2016
- [47] Akane A, Fukui Y. A review on the development of carboxyhemoglobin analysis. *The Research and Practice in Forensic Medicine*. 1985;**28**:185-190
- [48] Lopetz DM, Weingarten-Arams JS, Singer LP, Conway EE. Relationship between arterial, mixed venous, and internal jugular carboxyhemoglobin concentrations at low, medium, and high concentrations in a piglet model of carbon monoxide toxicity. *Critical Care Medicine*. 2000;**28**:1998-2001
- [49] Kunsman GW, Presses CL, Prodriguez P. Carbon monoxide stability in stored postmortem blood samples. *Journal of Analytical Toxicology*. 2000;**24**:572-578
- [50] Shimizu K, Shiono H, Fukushima T, Sasaki M. Diagnosis of fatal hypothermia—Differences in color between blood from the right and left ventricles and prevalence of Wischnewski's Spot. *Acta Criminologicae et Medicinae Legalis Japonica*. 1996;**62**:157-160
- [51] Mizukami H, Shimizu K, Shiono H, Uezono T, Sasaki M. Forensic diagnosis of death from cold. *Legal Medicine (Tokyo)*. 1999;**1**:204-209
- [52] Türk EE, Sperhake JP, Pueschel K, Tsokos M. An approach to the evaluation of fatal hypothermia. *Forensic Science, Medicine, and Pathology*. 2005;**1**:31-35
- [53] Shiono H, Shimizu K. Necropsy and autopsy diagnosis of fatal hypothermia. *The Research and Practice in Forensic Medicine*. 2007;**50**:1-7
- [54] Funayama M. Diagnosis of hypothermia. *Nihon Hōigaku Zasshi*. 2008;**62**:145-154
- [55] Turk EE. Hypothermia. *Forensic Science, Medicine, and Pathology*. 2010;**6**:106-115
- [56] Iwadate K. Death from cold. In: Nagao M et al., editors. *New Essentials of Forensic Medicine*. 5th ed. Tokyo: Ishiyaku Publishers Inc; 2012. p. 189-192
- [57] Wright RO, Lewander WJ, Woolf AD. Methemoglobinemia: etiology, pharmacology, and clinical management. *Annals of Emergency Medicine*. 1999;**34**:646-656

- [58] Blanc PD. Methemoglobinemia. In: Olson KR, editor. *Poisoning & Drug Overdose*. 5th ed. New York: Lange Medical Books/McGraw-Hill; 2007. p. 262-264
- [59] Price DP. Methemoglobin inducers. In: Nelson LS et al., editors. *Goldfrank's Toxicologic Emergencies*. 9th ed. New York, Chicago: McGraw-Hill; 2011. p. 1698-1707
- [60] Saito T, Takeichi S, Osawa M, Yukawa N, Huang X-L. A case of fatal methemoglobinemia of unknown origin but presumably due to ingestion of nitrate. *International Journal of Legal Medicine*. 2000;**113**:164-167
- [61] Suyama H, Morikawa S, Noma-Tanaka S, Adachi H, Kawano Y, Kaneko K, Ishihara S. Methemoglobinemia induced by automobile exhaust fumes. *Journal of Anesthesia*. 2005;**19**:333-335
- [62] Vevelstad M, Morild I. Lethal methemoglobinemia and automobile exhaust inhalation. *Forensic Science International*. 2009;**187**:e1-e5
- [63] Kinoshita H, Yoshioka N, Kuse A, Nishiguchi M, Tanaka N, Jamal M, Kumihashi M, Nagasaki Y, Ueno Y, Ameno K. A fatal case of severe methemoglobinemia presumably due to chlorate ingestion. *Soudní Lékarství*. 2011;**56**:43-44
- [64] Nishiguchi M, Nushida H, Okudaira N, Nishio H. An autopsy case of fatal methemoglobinemia due to ingestion of sodium nitrite. *Journal of Forensic Research*. 2015;**6**:262
- [65] Shigezane J. Effects of heating on methemoglobin contents in blood. *Nihon Houigaku Zasshi*. 1985;**39**:1-5
- [66] Fukui Y, Yamamoto Y, Mastubara K. Reduction with lapse of time of methemoglobin in blood sample. *Nihon Houigaku Zasshi*. 1980;**34**:563-568
- [67] Sato K. A method for determination of methemoglobin in blood containing carboxyhemoglobin. *Nihon Houigaku Zasshi*. 1983;**37**:133-144
- [68] Sato K. Methemoglobin. In: Suzuki O, Watanabe K, editors. *Drugs and Poisons in Humans, A Handbook of Practical Analysis*. Berlin, Heidelberg: Springer-Verlag; 2002. p. 655-657