Letter to the Editor

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Serum ischemia-modified albumin concentration may reflect long-term hypoxia in chronic respiratory disease: a pilot study

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To the Editor,

Hypoxia is usually assessed as a decrease in either partial pressure of oxygen in arterial blood (PaO_2) or percutaneous oxygen saturation (SaO_2).

Those indicators reflect the degree of oxygen concentration in blood at the time of withdrawal or sensor attachment.

On the other hand, patients with respiratory disease often suffer for years. Although sustained hypoxia is harmful, there are no current blood markers reflecting long-term presence and magnitude of hypoxia. If there were a marker that reflects cumulative hypoxia (days or weeks), physicians could assess the severity of hypoxia more efficiently.

Ischemia-modified albumin (IMA) is produced irreversibly by the attack of reactive oxygen species on albumin during ischemia. When pH drops, eight amino acids from the N terminal of albumin reduce their ability to bind transition metals [1]. Because the half-life of human albumin is approximately 2–3 weeks, IMA may reflect these pH changes in tissues [2], in a similar manner to the relationship of serum glucose concentrations and glycated albumin. Applying this reasoning, we hypothesized that IMA may increase in patients with chronic hypoxia, especially during 2–3 weeks prior to the test.

Nineteen respiratory disease patients, 14 males and 5 females, ages 57.7 ± 15.0 years (mean ± standard deviation) were enrolled. There were 12 chronic obstructive pulmonary disease, 3 acute pneumonia and 4 other chronic respiratory disease cases. Subjects with ischemic heart or cerebrovascular diseases were excluded. The patients were recruited from the population attending the Departments of Respiratory Disease and Laboratory Medicine, Showa University Northern Yokohama Hospital, Tsuzuki-ku, Yokohama City. The age- and gender-matched control subjects in the study (n = 24) were selected from a healthy population of hospital staff workers with no history of diabetes, renal disease or acute coronary syndrome. IMA was assayed by the albumin-cobalt-binding test [3] using Versa Max microplate reader and expressed as absorbance arbitrary units (AU). The intra-assay coefficient of variance was <5%. The research protocol was approved by the Institutional Review Board of Showa University Northern Yokohama Hospital, and investigations were performed in accordance with the principles of the Declaration of Helsinki Ethical Guidelines. A blood sample from all subjects was obtained by venipuncture and collected in evacuated tubes, centrifuged at 1600 × *g*, at 4 °C for 7 min, and separated serum was immediately analyzed or frozen at −80 °C until use.

As shown in Figure 1A, average concentration of IMA in respiratory disease patients was 0.48 AU, which was significantly higher than that of healthy adults (0.36 AU, $p = 0.000138$). IMA had a weak regression with SaO_2 ($r = 0.337$) and PaO_2 ($r = 0.343$), ($p < 0.05$). Concentration of IMA decreased after successful treatment of hypoxia such as oxygen inhalation and administration of antimicrobial

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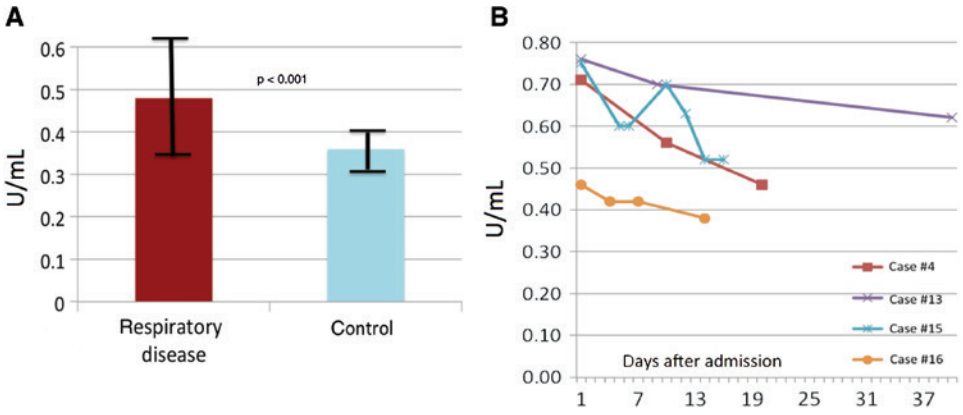

Figure 1: Serum IMA concentration.
Comparison of serum IMA concentration in respiratory disease patients and age-matched healthy control (A). Change of serum IMA concentration after treatment (B).

agents. For example, a 42-year-old female patient (case 4 in Figure 1B) with acute *Streptococcus pneumoniae* pneumonia had an IMA concentration of 0.71 AU and SaO_2 of 92.0% on admission. After successful treatment, she recovered with lower IMA and higher SaO_2 levels, at 10 days (0.56 AU, 96%) and 19 days (0.46 AU, 97.0%) after admission. In a 43-year-old male case with *Chlamydophila pneumoniae* infection (case 16), IMA decreased from 0.46 to 0.38 AU and SaO_2 increased from 95.0% to 97.0% with treatment for 14 days.

Case 15 in Figure 1B was a 43-year-old female patient with pleural effusion and dyspnea due to heart failure. Her SaO_2 level was 70.0%, and PaO_2 was 79.4 mmHg on admission. At first, her dyspnea improved mostly by diuretics and oxygen administration. However, on her eighth hospital day, dyspnea got worse because of pneumonia. Her IMA level increased, and PaO_2 was unstable ranging from 61.2 to 280.8 mmHg over several days. After successful treatment using antimicrobials, she recovered; the PaO_2 became stable, above 90 mmHg in room air, and her IMA decreased.

We previously reported increased serum IMA concentration in neonates with fetal distress [3]. According to our report, neonates who suffered hypoxic condition showed increased level of IMA. This phenomenon was confirmed by Kahveci et al. [4] and Oztekin et al. [5]. As we show in this paper, serum IMA concentration increased in adult patients with hypoxia, compared to subjects without neither hypoxia nor respiratory disease. After successful treatment, the patients with hypoxia showed a gradual decrease in IMA concentration.

Observing leukemia patients, Erkut et al. [6] reported significantly higher IMA concentration in the hypoxic state. According to Joulia et al. [7], change of serum IMA concentration occurs slowly, compared to SpO_2. Using elite divers, they assayed serum IMA concentration and SpO_2 under apnea performances. In contrast to the significant change of SpO_2, IMA concentration did not significantly change after the apnea. Those results suggest serum IMA concentration does not change drastically in acute hypoxemia.

Thus, as we hypothesized, IMA could be a marker of long-term hypoxia that may contribute to detect potential respiratory insufficiency cases that do not yet display showing acutely decreased SpO_2 and PaO_2. Because the assay is a simple colorimetric method, it can be applied to conventional automatic analyzers for emergency diagnosis.

Although the sample number is limited and the mechanism is not well understood, we posit that IMA could be an indicator of long-term hypoxia. More studies are needed to confirm the contention.

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