Background to the development of the pulse oximeter that has been in demand around the world since the start of the COVID-19 pandemic

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Introduction

This fall, I received a letter from Dr. Eiji Shimozawa, who is the editorial chairperson of the Alumni Journal of Department of Surgery II, Hokkaido University, as well as an old acquaintance of mine. In the letter, he suggested that I write an article about the background to the development of the pulse oximeter, which has been the focus for monitoring the respiration of patients with COVID-19, and my relationship with Mr. Takuo Aoyagi, who was a co-researcher and died on July 18, and then post in the *Alumni Journal*. Some readers may think posting an article about a device for measuring oxygen concentration in the *Alumni Journal* of a surgical department is irrelevant; however, I am one of the readers who finds the *Alumni Journal* of Department of Surgery II interesting with its wide variety of topics covered. So, I hope you accept my article as one of the various topics.

In 1960, when I joined the Department of Surgery II, Hokkaido University, I was engaged in medical examinations as a surgical intern. However, after suffering from hepatic disorder, I stayed in Misumai Sanatorium near Sapporo as recommended by the medical office. Since I had time to spare after my surgical internship in the morning, I decided to attend a class led by Professor Seiji Mochizuki of the Research Institute for Applied Electricity, Hokkaido University. As soon as I acquired my driver's license, I started going to Hokkaido University. The Research Institute for Applied Electricity, Hokkaido University was a unique place where specialists in a wide range of fields gathered, from basic science to medical science. I remember that senior doctors at the Department of Surgery II, such as Dr. Ryozo Sawaguchi and Dr. Keisuke Sakai, were co-researching the detection of intracardiac shunts using platinum electrodes, the development of a domestic cardiac pacemaker, the development and application of an electrode blood flow meter, etc. I chose the class of Professor Mochizuki because he was a world-class researcher of oxygen diffusion theory of the lungs, as well as the strictest professor. At that time, the development of a glow discharge expired gas analyzer, demonstration experiments of Mochizuki's theory on oxygen diffusion, and such like were being conducted. Back then, I never imagined that I would be involved in the development of an oxygen saturation measuring device in the future, nor was I aware I was learning from someone who was in charge of oxygen-related subjects in the respiratory physiology of the Japanese physiology system.

One day, I was suddenly summoned by Dr. Akihiko Kuze who was the Director at that time. According to him, the Ministry of Health and Welfare was planning to establish an Intensive Respiratory Care Unit (IRCU) at major sanatoriums nationwide, and since Misumai Sanatorium was selected, he appointed me as a person in charge of selecting required medical equipment. I believe the budget was over 12 million yen at that time. Bennett-type ventilators and blood gas analyzers were quickly decided upon. When I was looking for a respiratory monitor that was not available at other facilities, Mr. Sugiyama, who was the sales manager of Nihon Kohden, told me that a group researching the measurement of cardiac output with the dye injection method using ICG in the company laboratory had found something interesting. The group led by Mr. Aoyagi successfully observed a new pulse wave on the curve with cardiac output measurement, and there was possibility of creating a new oximeter by utilizing the new pulse wave. So, I allocated a budget of 2.5 million yen and had them create a custom-made device. Eventually, an oxygen saturation measurement device based on a new principle was delivered to Misumai, and both Mr. Aoyagi and Mr. Yamaguchi also participated in the first animal experiments and helped me adjust the device. Nihon Kohden also made another prototype of the same device and conducted clinical tests at Sapporo Medical University. However, they put a pause on the pulse oximeter research project after this device. The company restarted the project after clinical applications really took off in the United States. I brought the prototype device to the Physiology Department of the Research Institute for Applied Electricity, Hokkaido University, which had world-class facilities for oxygen research, and continued conducting performance tests and clinical application for patients I was in charge of at the sanatorium. At that time, there were people like Mr. Arai who had excellent crafting skills, Mr. Miura who had excellent glass skills, and Mr. Shindo who was knowledgeable in electricity and computers at the Research Institute. There were many occasions I helped them compose a thesis on applied electricity written in English. On the other hand, they helped me with my experiments and kept me in the best condition. I must say they were my good friends and daily drinking buddies.

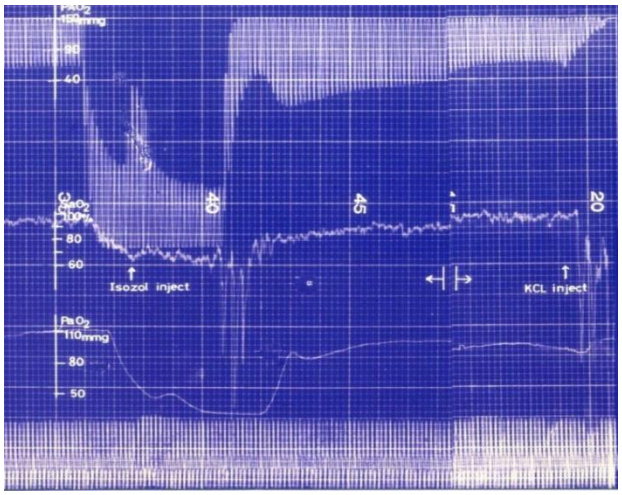

Figure 1. Performance tests of the pulse oximeter conducted at the Physiology Department of the Research Institute for Applied Electricity, Hokkaido University

The top reading indicates continuous recording of expiratory oxygen concentration using a glow discharge oxygen concentration recorder

The middle reading indicates a pulse oximeter recording

The bottom reading indicates the output of oxygen concentration in the femoral arterial blood using a Pt oxygen electrode

(Directly inserted an electrode into the femoral artery)

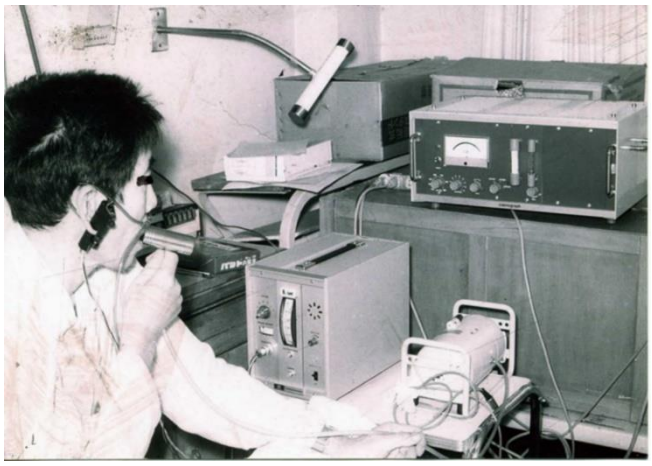

Photo (1) The world's first clinical application of a pulse oximeter conducted in the patient room at Misumai Sanatorium

The patient had respiratory failure after he underwent thoracoplasty for tuberculosis treatment

Figure 1 shows the results of a performance test on the new device used on a dog. The top reading indicates continuous recording of expiratory oxygen concentration using a glow discharge oxygen concentration recorder, the middle reading indicates a pulse oximeter recording, and the bottom reading indicates continuous recording of the partial pressure of oxygen in the artery observed by inserting a platinum electrode into the femoral artery.

Photo (2) Report of the world's first clinical application of a finger-tip type pulse oximeter developed by Minolta Camera

The patient developed hypoxemia after receiving postoperative radiation treatment for an esophageal tumor

The dog suffered from lower inspired oxygen partial pressure, which was triggered by increasing nitrogen gas that the dog inhaled, slightly raising the oxygen concentration in the inspired oxygen. At this moment, the pulse oximeter captured the change faster than the platinum electrode. At a time when there were no medical mass spectrometers, I think the level of the performance tests was considered high on a worldwide scale. The world's first clinical application of a pulse oximeter was conducted in the patient room at Misumai Sanatorium (Photo (1)). The patient underwent thoracoplasty for tuberculosis treatment. Oxygen concentration was continuously measured with a pulse oximeter, and the partial pressure of carbon dioxide was also continuously measured with a capnometer using infrared rays. After we examined the increasing tendency of carbon dioxide concentration during oxygen inhalation, the effect of light exercise and the effect of Diamox administration, we published a research paper in "Respiration and Circulation," Vol. 23, No. 8 in 1975. Later, Professor Severinghaus of the University of California mentioned our paper when he was searching for the roots of pulse oximeter development.

Clinical tests of the world's first finger-tip type pulse oximeter and publication of research paper in the Journal of Japan Surgical Society

In 1977, an employee from Mochida Pharmaceutical and a technician from Minolta Camera visited the medical office of the Department of Surgery, and they asked the medical stuff to clinically evaluate a device they had developed that could measure oxygen concentration through a fingertip. The device and a patient are shown in Photo (2). The patient received radiation

treatment before surgery and suffered from hypoxemia post-surgery. The device was simpler and easier to use, and the output of pulse was stable compared to an earpiece-type one. This clinical result was presented at the 12th Congress of European Society for Surgical Research held in Warsaw in 1977 under the joint names of Dr. Yoshihiko Kubo, Dr. Natsuki Samejima, and me, Nakajima. It was the first clinical application result of a finger-tip pulse oximeter ever reported in the world. I remember when I presented it to a medical conference in Japan, a young anesthesiologist questioned the necessity of the device since there was a blood gas analyzer, and this disappointed me. Whereas in Warsaw, a professor of the Anesthesiology Department in France stood up and praised it as very interesting research.

Since then, as the number of clinical application cases had increased, I published "Experience of using a new pulse-wave type oximeter: for dynamic monitoring of postoperative respiratory failure" with other co-researchers in the *Journal of Japan Surgical Society*, Vol. 41, No. 1. This research paper was later translated into English by Mochida Pharmaceutical and distributed as reference when OXIMET was sold in the United States. I believe this English version of research paper contributed to the massive spread of pulse oximeters in the United States later on.

A letter from Professor Yoshiyuki Honda of Respiratory Physiology, Chiba University

At the end of 1986, I received a letter from Professor Yoshiyuki Honda of Respiratory Physiology, School of Medicine, Chiba University, who was famous for respiratory physiology. In the letter, he wrote that when he was attending the International Congress of Physiological Sciences held in Vancouver, Canada in July of the same year, he spoke with his old acquaintance, Professor Severinghaus of the Department of Anesthesiology, University of California. Apparently, Professor Severinghaus was researching the origin of the pulse oximeter and asked Professor Honda for cooperation.

During the conversation, Professor Severinghaus mentioned someone named Nakajima who discovered a pulse oximeter and worked at Minolta Camera, and his research paper could be found in anesthesia-related magazines, which led Professor Honda to me after he went through the medical magazine *Respiration and Circulation*. During the research, Professor Severinghaus found a handwritten abstract by Mr. Aoyagi in the abstract collection of the first *Japanese Society for Medical Engineering*, which I referenced for my research paper. Since then, Mr. Aoyagi has been recognized as the originator of the pulse oximeter principle, and I have been recognized as the first person to ever conduct a clinical application of the earpiece-type and fingertip-type pulse oximeters and published a research paper.

Photo (3) Photo taken when Professor Severinghaus visited Japan

From the left, Mr. Aoyagi, Professor Severinghaus, Professor Honda and me, Nakajima

Taken in front of the Hilton Tokyo on January 27, 1987

During the research, Professor Severinghaus found a handwritten abstract by Mr. Aoyagi in the abstract collection of the fourth *Japanese Society for Medical Engineering*, which I referenced for my research paper. Since then, Mr. Aoyagi has been recognized as the originator of the pulse oximeter principle, and I have been recognized as the first person to ever conduct a clinical application of the earpiece-type and fingertip-type pulse oximeters and published a research paper.

In 1987, Professor Severinghaus visited Japan to verify the facts. A rare photo of the four of us was taken in front of the Hilton Tokyo (Photo (3)).

In the same year, Professor Severinghaus and Professor Honda published the following paper and concluded:

Severinghaus JW, Honda Y. History of blood gas analysis VII.
Pulse oximetry. J Clin Monit 1987; 3:135-138

ABSTRACT. Pulse oximetry is based on a relatively new concept, using the pulsatile variation in optical density of tissues in the red and infrared wavelengths to compute arterial oxygen saturation without the need for calibration. The method was invented in 1972 by Takuo Aoyagi, a bio-engineer, while he was working on an ear densitometer for recording dye dilution curves. Susumu Nakajima, a surgeon, and his associates first tested the device in patients, reporting in 1975.

A competing device was introduced and also tested and described in Japan. William New and Jack Lloyd recognized the potential importance of pulse

oximetry and developed interest among anesthesiologists and others concerned with critical care in the United States. Success brought patent litigation and much competition.

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How was the principle of the pulse oximeter born?

Mr. Aoyagi died on April 18 of this year in Tokyo just when COVID-19 was beginning to spread. He was born in Niigata in 1936, and joined Shimadzu Corporation after graduating from the Faculty of Engineering, Niigata University. Later, he joined Nihon Kohden where he was involved in the development of circulatory and respiratory ME devices. He was about five years older than me. We used to exchange letters about twice a year. When he and Seisyu Hanaoka were chosen from Asia and named as one of 100 people who have contributed to the development of anesthesiology in the last 100 years in a book "*Notable Names in Anesthesia*" (edited by J. Roger Maltby, published by Sogo Igaku Sha, Co., Ltd), he was extremely excited. If Mr. Aoyagi had not collaborated with our research group, he would never have met Professor Severinghaus and the pulse oximeter research at Nihon Kohden would be buried in history especially with that company's attitude at the time. Rest in peace Mr. Aoyagi.

Traditionally, the Wood-type oximeter was used for medical practices. The Wood-type oximeter was convenient for measuring oxygen saturation since the light absorption of hemoglobin changes significantly when oxygen saturation changes at around 660 nm. Also, a method of calculating oxygen saturation at dual wavelengths using another wavelength of 890 nm was separately used. In order to calculate the absolute value of oxygen saturation at these dual wavelengths based on the Beer-Lambert law, an accurate value of blood volume was required. Thus, Wood tried to calculate oxygen saturation by squeezing the earlobe (ischemia method) in order to obtain an absolute oxygen saturation value. We conducted a comparative experiment between the Wood-type oximeter and a pulse oximeter. The results showed that ischemic operation was complicated and the baseline deviated, making it difficult to measure a stable oxygen saturation with the Wood-type oximeter. Initially, Mr. Aoyagi worked on improving the Wood-type oximeter; however, he came to the same conclusion as ours. After he could not find a way to improve it, he started the development of a cardiac output meter using dye (indocyanine green or ICG). After experimenting with the dye dilution method, he immediately found that light transmitted through tissue pulsated.

Figure 2 shows experiments. A dye (ICG) was injected into a vein, and the change in the amount of transmitted light through an earlobe was measured and the dilution curve observed. At a wavelength of 805 nm, the pulse wave was superimposed on the dye curve as noise. On the other hand, at a wavelength of 930 nm, only a pulse wave was recorded, and no effect of the injected dye was observed. It was experimentally shown that the pulsation portion could be conveniently offset by using signals of both wavelengths, that was, by dividing the absorbance obtained at 805 nm by the absorbance obtained at 930 nm. In addition, as shown in Figure 2 (2), the dye curve was successfully observed without the influence of the pulse wave. From the experiment results, we discovered that the baseline (zero point) could be continuously obtained from the fluctuation of the pulsation wave without the avascularization of the whole earlobe. Shortly after this discovery, from the examination of eliminating the pulse wave component as noise, we realized there was a possibility of measuring continuous oxygen saturation by utilizing the dye information of the pulse wave component, that is, the arterial blood pulsation component. It was December 1972. Professor Severinghaus later showed great interest in the fact that the pulsatile wave, which was considered a noise component when calculating cardiac output, played a major role when calculating oxygen saturation.

Expanding the use of pulse oximeters especially for at-home treatment

I am currently working as the Director of Moriyama Memorial Hospital, which has a convalescent ward for rehabilitation and nine types of at-home support organizations. In recent years, I have investigated the increased use of pulse oximeters at Moriyama Hospital and Moriyama Memorial Hospital (Table (1)). As shown in the table, such use increased 2.3 times in the five years from 2013 to 2018. The use in home care facilities has increased in particular, and it has become common for individuals to have their own pulse oximeter in the home-visit nursing and home-visit rehabilitation sectors. Photo (4) shows the home-visit nurses presenting their own pulse oximeter during their work.

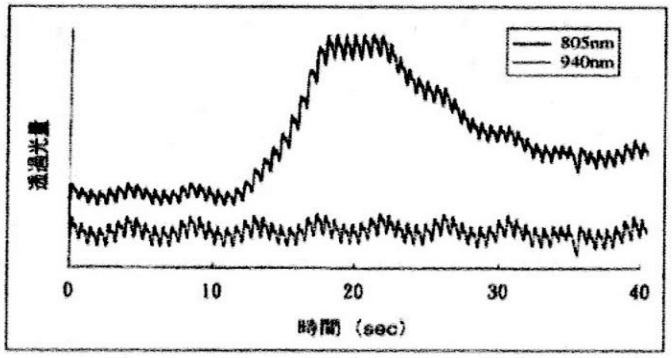
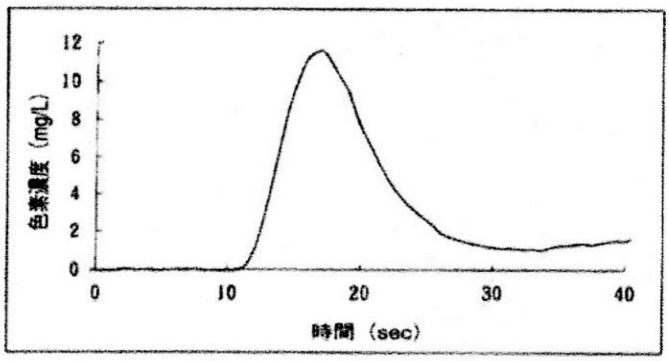


Figure 2 (a) Record of received transmitted light at 805 nm and 904 nm



(b) Chart of calculated dye concentration

パルスオキシメーター保有数

- 森山病院

	年度	外来	病棟	手術室	小計
パルスオキシメーター専用機	2013年	3	10	1	14
	2018年	3	16	1	20
モニター付属器	2013年	3	15	4	22
	2018年	4	25	3	32

- 森山メモリアル病院

	年度	外来	病棟	リハビリ	介護部門（リハビリ）	訪問看護	小計
パルスオキシメーター専用機	2013年	2	2	0	0	6	10
	2018年	0	9	2	28↑	13↑	52
モニター付属器	2013年	0	2	0	0	0	2
	2018年	0	6	0	0	0	6

2013年総計　48台 → 2018年総計　110台↑↑

Table (1) The number of pulse oximeters used at Moriyama Hospital and Moriyama Memorial Hospital

Photo (4) Pulse oximeters carried by nurses when they visit at-home care patients

Acknowledgement of doctors who supported me with the pulse oximeter research

Professor Yoshinobu Osaki of Respiratory Center, Asahikawa Medical University (Present: Assistant Director of Yoshida Hospital, Keiyukai Group) has consistently supported me throughout my pulse oximeter research. He has given me advice and introduced me at various lectures. Professor Osaki has the fingertip-type pulse oximeter made by Minolta Camera mentioned in the research paper. The other day, the Japanese Museum of Anesthesiology in Yokohama requested that this device as a donation, but I politely declined. Pediatric Professor Mutsuo Shibata of Hokkaido Medical University developed an interest in my work after he attended Professor Osaki's lecture. Professor Shibata, who has a rebellious spirit, searched through documents and pointed out how our clinical application report on respiration and circulation, which was the first publication ever made in the world, was undervalued. So, he invited me to speak at the 51st Annual Conference of the Japanese Society of Pediatric Pulmonology held in Sapporo on September 18, 2018. Once again, I reaffirmed how much pulse oximeters are being used for monitoring the respiration of children who it is usually difficult to collect blood samples from. Professor Shibata has also published several books on Senryu (short poetry similar to Haiku), and he sent me one. One of his Senryu called "Cannot find a good reason to give up my dreams" is my favorite.

Epilogue

Pulse oximeters are now gaining in popularity around the world and being deployed in almost every anesthesia care system, intensive care unit, emergency outpatient department, hospitalized patient care, ambulance, as well as at-home care sector. It is an essential device for adjusting oxygen concentration and observing respiratory status, and yet so compact that you can store it in a pocket. Coronavirus, which caused the pandemic, is known to damage capillaries in the lungs and cause early hypoxemia. Thus, use of a pulse oximeter in the early stage of patients with COVID-19 is being urgently called for around the world. I feel fortunate to have been part of the development of such an oxygen monitoring device. Before the pandemic, I used to attend the Alumni of Department of Surgery II, Hokkaido University and studied the leading science of surgery once a year, and I joined the Go Club of Department of Surgery II and played Go with senior doctors a few times a year. Those days are truly missed. I would like to thank Dr.

Shimozawa for giving me the opportunity to share my story, and wish the Alumni of Department of Surgery II, Hokkaido University the best and much success.