Journal of Artificial Organs (2022) 25:287–288
https://doi.org/10.1007/s10047-022-01364-x

OBITUARY

In memory of Dr. Hisateru Takano

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Received: 4 September 2022 / Accepted: 4 September 2022 / Published online: 12 October 2022

The National Cardiovascular Center (NCVC) hospital was opened at Osaka in August 1977, and after 2 years, the research institute was opened in July 1979. I had worked with Dr. Hisateru Takano for about 10 years since the onset of the Research Institute. Dr. Hisao Manabe, the hospital director at the time, told us, "It is extremely serious that heart transplantation in our country is behind the international situation. We have to restart heart transplantation program as early as possible. In parallel, there is a limit to the effectiveness of current assisted circulation, such as IABP, or V-A bypass. So, we need a ventricular assist device (VAD). I would like both of you to develop a clinically available VAD for the patients with extremely severe heart failure."

Dr. Takano had studied abroad in the laboratory of Dr. Tetsuzo Akutsu, who was a pioneer in artificial heart in the world, at the University of Mississippi, between 1969 and 1971. Dr. Akutsu's artificial heart was a pneumatically driven total replacement-type artificial heart (TAH). Its effectiveness was investigated by chronic animal experiments using calves.

After Dr.Takano returned from USA, he presented his research at the annual meeting of the Japanese Society for Artificial Organs. The contents were related to the hemodynamic response of the TAH animal by the treadmill test. As a graduate student at Waseda University, I remembered being very impressive when I heard about Dr. Takano's large-scale experiments. My research theme in the department of mechanical engineering of Waseda graduate school was the development of a sophisticate mock circulatory simulator that could contribute to clinical medicine. This was a joint research project with Tokyo Women's Medical College, where I learned about medical engineering collaboration. After the completion of my PhD, I became a research staff of the NCVC, where I was able to start research with Dr. Takano very smoothly.

Our immediate mission was to develop the original VAD and to evaluate its effectiveness towards clinical application. Prior to the start of our research, Dr. Takano explored several types of artificial hearts in major artificial organ laboratories in USA and he was convinced that an extracorporeal, pneumatically driven diaphragm pump would be the most advantageous pump design as it would take less time to develop for clinical application. As for the material of the pump, we tentatively used silicone rubber. To investigate the hydrodynamic performance of the pump, the prototype pump was incorporated into a mock circuit. As soon as we started driving, an air leak occurred and eventually it was completely broken.

After a lot of improvement, we discussed about chronic animal experiments to evaluate a total performance of our VAD for long-time use. Assuming an adult Japanese, we decided to use a goat weighing about 50 kg, but neither of us had any experience on animal study with goats. Therefore, we asked the anesthesiology department of the hospital for help, but it seems that humans and goats are different, and the experimental goat did not wake up from the anesthesia. At that time in Japan, Professor Kazuhiko Atsumi's group at the Institute of Medical Electronics, University of Tokyo was leading artificial heart research in Japan, and a lot of know-how had been accumulated regarding chronic experiments on goats. Although we received various kind suggestions from them, it was hard to achieve favorable outcome on VAD study in goat. As the opening date of the Research Institute approached, we were nervous. Finally, July came, and we conducted goat experiment just before the opening ceremony. A miracle happened there. The goat woke up after the operation and was able to stand up after removing the respirator. It was the day before the opening ceremony. Among the distinguished guests, we found Professor Atsumi of the University of Tokyo. He was very surprised by our dramatic result. Unfortunately, the hero-goat died suddenly on the following day from a blood clot that had formed between the housing and the diaphragm inside the blood chamber.

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From that time on, the battle how to reduce blood clots began. First, when I was investigating what kind of antithrombotic material to select as the pump material, Dr. Teruo Okano of Tokyo Women's Medical University, who was my classmate of Waseda University, told me that he developed antithrombotic material with a collaboration of Toyobo Company. It is a block co-polymer type polyurethane (TM) material. According to Dr. Okano's doctoral dissertation on engineering submitted to Waseda University, the research results exhibited that antithrombotic properties are obtained by arranging hydrophilic segments and hydrophobic segments in order. It is also possible to modify the mechanical properties of polyurethane by changing the molecular weight of the soft segment.

Then, three different types (TM1, TM3, and TM5) were produced commercially from Toyobo Company. Professor Kozaburo Hayashi of the Bioengineering Department of NCVC Research Institute, who specializes in material engineering, clarified these three differences by his approach. The summarized results were as follows: as TM1 has high stiffness, it was suitable for the pump housing. TM5 was suitable for moving diaphragm due to the most flexible characteristics. Moreover, TM3 was suitable for the coating material on blood contacting surface inside the pump, because TM-3 indicated the most anti-thrombogenic material among the three.

On the other hand, regarding the VAD pump drive, NCVC and Sharp Corporation held in-depth discussions on the reliable hardware of the pneumatic drive system and the software for the automatic control of the pump, which emphasizes safety. We then asked Sharp to create a control-drive unit suitable for clinical use.

Between 1979 and 1982, the number of staff and trainees on the artificial heart team gradually increased. As a result, research has progressed, including improving the pump itself and developing an automatic control system for the efficacy and safety of the NCVC VAD. And we frequently conducted animal experiments assuming safer clinical applications. At that time, it was generally granted that if experiments with large animals were successful to some extent, we were able to start a clinical application (first in human: FIH) by our own responsibility. The history of the clinical application of artificial hearts in Japan began with a sac-type VAD manufactured by the University of Tokyo. It was implanted at Mitsui Memorial Hospital, Tokyo, in 1980. Our FIH was performed at the NCVC hospital in December 1982. In March 1985, the activities of the NCVC artificial heart team were introduced on a Kansai TV program. In it, Dr. Takano was interviewed about FIH (Photo 1).

Dr. Takano said, "We fabricated NCVC-type VADs by ourselves here. As we have had enough experience to implant our VAD into goat, we have confirmed that they are safe, but there should be some differences between goats and heart failure patients. I decided to use it clinically, while I prayed that function of our VAD was doing well just like the goat experiments (Photo 2)."

The reason for this broadcast was that the heart function of a 72-year-old woman was recovered by the VAD and she was able to discharge from the hospital on foot. This was the first successful case among our initial 9 cases at NCVC. Before then, the artificial heart team at NCVC had been blamed, because the outcome was very poor, even though they received a large amount of research fund. Know-how on postoperative infection control was accumulated afterwards, and the clinical outcome gradually improved. The pump, which was initially handmade by NCVC team members, was commercialized by Toyobo. Nationwide clinical trials were conducted organized by NCVC, and in 1992, Toyobo was able to obtain manufacturing approval as well as insurance coverage from the Ministry of Japanese Health, Labor and Welfare (MHLW).

As mentioned above, the contribution of Dr. Takano, who took a major responsibility for the successful development and commercialization of the Japanese-made VAD, was extremely significant. Through this experience, I also learned a lot about the commercializing process of medical devices. So, I am still working as a member of a subcommittee for the development of the medical device field organized by the MHLW.

I would like to once again pray for the repose of Dr. Takano's soul.

Palms together,

Photo 1 Dr. Takano being interviewed.

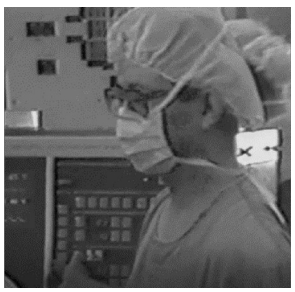

Photo 2 Dr. Takano in the operating theater.