



In memoriam of Dr. Hisateru Takano

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I was deeply saddened when I heard Dr. Hisateru Takano passed away on April 8, 2022, at 81. Although he suffered a COVID-19 infection this February and received intensive treatment with successful recovery records, he regrettably expired acutely during convalescence before discharge. Indeed, we have lost a prominent pioneer in the history of artificial organ development, especially for mechanical circulatory support (MCS).

He was born in 1940 in Osaka City. After graduating from Sumiyoshi Osaka Prefectural High School, he continued his education at Osaka University Medical School (OUMS) in 1959 and graduated in 1965. Following his graduation, he started his career of surgeon at the First Department of Surgery, OUMS, where he joined the cardiac surgery group. Professor Hisao Manabe was presiding as the Chairman, and Dr. Yasunaru Kawashima, an associate professor, led the cardiac surgery team during this period. My relationship with Dr. Takano was built based with one-year junior at the same high school he attended, and I followed his footsteps by also entering OUMS and the First Department of Surgery. Since then, we have worked together in MCS for almost 50 years. Dr. Takano and I mainly shuttled between the National Cardiovascular Center Research Institute (NCVC-RI, Osaka) and OUMS. We shared a keen connection with heart failure treatments from engineering and clinical perspectives and maintained a great friendship, supported by our background as alumni of the high school and OUMS. Therefore, I am deeply and genuinely saddened by this loss.

Considering his life-long career in artificial organ research, it should be mentioned that during his undergraduate days, the first human-to-human heart transplantation (HTx) was notably performed in 1963 at Cape Town by Dr. Christian Barnard, followed by Dr. Wada's attempt in Sapporo, Japan, the following year. Then, in 1966, Dr. Takano

was admitted to the First Department of Surgery, where the Chairman, Prof. Manabe, started preparation for the HTx project by sending young surgeons abroad to have clinical experience in HTx and artificial heart development based on his foresight. Subsequently, in 1969, Professor Yasunaru Kawashima, the successor to Prof. Manabe nominated Dr. Takano as a delegate to the University of Mississippi in the US to join Dr. Tetsuzo Akutsu's laboratory as a research fellow. In this laboratory, an artificial heart program was ongoing, and it had been identified as the key institute for such research in the US. Dr. Takano worked there from 1969 to 1971. During his stay, Dr. Akutsu's laboratory conducted successful hand-made artificial heart implants in calves, which survived more than 10 days, in 1971. After this period, Dr. Takano returned to Osaka and Dr. Akutsu moved to the Texas Heart Institute, where the second artificial heart implant into human was done by Dr. Denton Cooley using Akutsu-Heart in 1981, after which Dr. Akutsu joined NCVC team where he reunited with Dr. Takano.

In Japan, the development of MCS device for managing profound heart failure had started in the early 1980s, which was initiated by a group at the University of Tokyo (UT) headed by Professor Kazuhiko Atsumi, who regrettably passed away in 2019, a counterpart project was also initiated at NCVC by Dr. Takano and Dr. Akutsu. As a result, both groups developed pneumatic-driven extracorporeal pulsatile devices, a UT-type Zeon pump and an NCVC-type Toyobo pump, the latter was designed by Dr. Takano. The name "Toyobo" was derived from the supporting company, Toyobo Inc. Osaka, after Professor Manabe asked the company's President, his friend, to be the manufacturer of this device, thereby enabling the use of their biomaterials. These two domestically produced devices were widely used as the main ventricular assist device (VAD) for the next two decades. The first clinical use of NCVC-VAD was done in 1982 by NCVC cardiac surgery team.

During his time, Dr. Takano worked as the chief of VAD projects at NCVC-RI after moved from OUMS in 1978. Thus, starting with three types of pumps (those with 70-, 40-, and 20-ml stroke volumes), the 70-ml pump was

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approved only for commercially available VAD in 1994. This device was utilized starting for cardiogenic shock patients and extended to cardiomyopathy patients waiting for HTx. Actually, at the HTx restarting year in 1999, two of the initial three patients received HTx at NCVC after the support by Toyobo-VAD.

Regarding the design of this VAD based on the inflow site, the cannula was initially designed for the left atrium. Later, Dr. Takano decided to change to the left ventricle (LV) inflow design with the support of Dr. Takeshi Nakatani, who returned from the Texas Heart Institute where Dr. O.H. Frazier was the chief. Due to this change, the thromboembolic complications from thrombus in LV cavity were significantly reduced, resulting the LV-type Toyobo-VAD to be widely accepted as a bridge device for HTx candidates over the next decade.

In 2002, the Toyobo-VAD production was transferred to NIPRO Inc. (Osaka) and commercially supplied as NIPRO VAD until now, with more than 3000 sets being used for patients with cardiogenic shock and chronic heart failure. As mentioned above, HTx candidates were almost exclusively supported by this VAD until implantable continuous flow VADs were introduced in 2010. Up to now, the total number of heart transplantations reached more than 600 in Japan. As of 2017, Toyobo-VAD had been applied in 110 (28%) out of 400 HTx recipients.

Dr. Takano's group at NCVC-RI also developed smaller sized pumps of 20- and 40-ml stroke volume, after which the 20-ml pump was tested during a clinical trial. At OU, I was privileged to use this pump in children for postoperative cardiogenic shock after complex intracardiac repairs including the Fontan operation in 1988. This experience was valuable for considering the feasibility of using single ventricular support for biventricular failure in postoperative congenital heart diseases. However, these two small devices were not approved for commercial use.

In 1996, Dr. Takano received a PhD as a Doctor of Medical Science from OU based on his main work on the physiological study of a single-left ventricular support for biventricular failure, named a left-sided single artificial heart. The work was published in the *Journal of Thoracic and Cardiovascular Surgery* in 1992 (volume 103: pages 496–503), under the title: Long term circulatory maintenance with a left-sided single artificial heart. Subsequently, this concept was proven by his 2-year-long clinical experience on left-sided VAD support alone during the patient's heart went into persisting ventricular fibrillation. This single-left artificial heart concept was later collaborated by the clinical demand for complex congenital heart operations as mentioned above. The issue of how to mechanically support the compromised single ventricle-circulation after Fontan operation has been currently one of the hot issues in the clinical arena of congenital heart surgery.

In addition to the VAD project, the total artificial heart (TAH) project was initiated in 1987 at NCVC-RI, comprising his team under Dr. Akutu's supervise headed by Dr. Yoshiyuki Taenaka. The prototype of TAH was first designed using a pneumatically driven pump and shifted to an electrohydraulic system with transcutaneous energy transfer and optical telemetry subunits. Subsequently, they started animal implants of this electrohydrolic TAH to calves in 2003, after which successful 70-d support was obtained. However, this project did not reach clinical trials.

Further, his research projects extended to respiratory support, where he designed an integrated artificial heart-lung device combined with a right-sided VAD. Together with Dr. Eisuke Tatsumi, the project developed commercially available small-sized centrifugal pumps and a compact membrane oxygenator for the portable unit to support respiratory failure. Furthermore, in the physiological research on assisted circulation using large animals, particularly during nonpulsatile perfusion, many important papers were published to promote the subsequent nonpulsatile durable device application.

Reviewing his career, his commitment to research work at NCVC-RI started in 1978 after being appointed as the head of artificial organ research division and then as a director in 1983, followed by the appointment as the vice director of NCVC-RI in 1995. Before retirement, he was also appointed as the director of the newly started Advanced Medical and Engineering Research Center in 2004. Then, in 2005, Dr. Takano retired from NCVC after 27 years of hard research and development work, contributing to the internationally well-known progress in MCS and artificial organ development. After that, he moved to NIPRO Inc., joining the Research and Development Institute as the general manager until his death.

It should be applauded that Dr. Takano received many prizes for the development of MCSs, represented by the following prizes: the Osaka Science Prize in 1987, The Medical Prize of the Japanese Medical Association in 2003, and The Medal of Purple Ribbon in 2005. Furthermore, during his career at NCVC, Dr. Takano was appointed as a Professor of Osaka University in 1995, as the NCVC nominated as the affiliate institution to OUMS. Therefore, we are very proud of him for such achievements that were strongly dedicated to heart failure management extended to HTx.

Dr. Takano also contributed to the nation-wide research development of artificial organs as a core member of related academic organizations. For instance, in the Japanese Association for Artificial Organs, he was honored as the President of the 33rd Annual Meeting in 1995. Internationally, he worked as a Trustee and Member of the American Society for Artificial Internal Organs and the International Society for Artificial Organs.

It should also be mentioned that his group at NCVC-RI, represented by Drs. Mituso Umezu, Setuo Takatani,

Takeshi Nakatani, Yoshiyuki Taenaka, and Eisuke Tatsumi, supported his work with great efforts throughout his career. Moreover, Dr. Takano's work in the clinical use of Toyobo-VAD could not be successful without continuous support from the cardiac surgeons of NCVC represented by Drs. Yoshitsugu Kito, Yoshikado Sasako, Fumio Yamamoto, Toshikatu Yagihara, Junjiro Kobayashi and others. He also had continuously warm and strong supports from the leaders of NCVC, by Dr. Tsuyoshi Fujita (Vice Director of NCVC Hospital) and Prof. Manabe, Professor Kawashima and Prof. Soichiro Kitamura of successive Presidents of NCVC.

Dr. Takano happily worked with outstanding coworkers from different professional specialties. Among these collaborators, many professors in artificial organs technologies and related areas have currently emerged as below: Professors M. Umezu of Waseda University, Takehisa Matsuda of Kanazawa Institute of Technology, S. Takatani of Tokyo Medical and Dental University, Toru Masuzawa of Ibaraki University, Yoshiaki Takewa of Asahikawa Medical University, Hirofumi Anai of Oita University Medical School, Tomohiro Nishinaka and Koichi Toda of OUMS, and Takashi Nishimiura of Ehime University Medical School.

Dr. Takano was a warm-hearted person who was always mild and modest, and he was also known for being a principled researcher and leader. Therefore, we sincerely appreciate his endless efforts in connecting artificial organs with organ transplantation. To this end, we will always remember

and appreciate his strong dedication to the current HTx in Japan providing VAD as a key bridge-device under the critical shortage of organ donors.

Finally, we express our sincere condolences to you and your family, and we will miss you.

This message is to be transferred to Dr. Takano's beloved family, his wife (Masako), and three daughters who supported his timeless works.



Photo of Dr. Takano



A picture taken at animal laboratory of NCVC-RI caring a goat supported NCVC-pump by members of Dr. Takano (center) with Dr. Nakatani, Dr. Masuzawa, Dr. Tatsumi and Dr. Taenaka (standing behind, from left to right). The photographs are provided by courtesy of Mrs. Takano.