Kiichi Sagawa Memorial Symposium

Kiichi Sagawa Memorial Symposium

(March 27, 15 : 20–17 : 20, Room A)

1MS1A-1

My Mentor Prof Kiichi Sagawa's Great Contribution to Cardiovascular Physiology

Suga, Hiroyuki (*Okayama Univ Med Sch Former Prof of Physiol, Nat'l Cereb and Cardiovasc Cntr(NCVC)Res Inst Emerit Direct Gen*)

Prof Sagawa published a book "木 の 葉" in 1989 to sum up his cardiovasc physiol life. He thanked Profs K Nishimaru, K Fukuda, and A Guyton for his lucky life as MD at Yokohama Med Sch in 1950, PhD at Tokyo Univ Med Sch in 1958, and postdoc fellow at Mississippi Univ Med Sch in 1959. He then became Assist Prof of the alma mater in 1962, but returned to USA in 1964 to continue his cardiovasc research.

Dr Sagawa moved from Mississippi first to Biomed Engin Depts of Case West Reserv Univ in 1968 and then Johns Hopkins Univ in 1971. I heard this news after I obtained PhD in Tokyo Univ Med Electro Inst. I applied for Prof Sagawa's job offer. This was a very nice chance for me to continue my unique research on cardiac performance quantified by ventricular time-varying elastance (Emax). Although I once returned to Tokyo, Prof Sagawa soon invited me as Assist Prof. I then started to prove my new concept of cardiac energetics (PVA : pressure-volume area) and was able to prove it.

I then heard that Nat'l Cardiovasc Center Res Inst opened in Osaka and fortunately got its lab head first and then dept chief. I continued cardiac mechano-energetic research and established the PVA concept. In 1988, Prof Sagawa nominated me to be a coauthor of his book : Cardiac Contraction and the Pressure-Volume Relationship. I was also nominated to write a Physiolog Rev paper on "Ventricular Energetics" in 1990. Then, I was invited as Physiol Prof of my alma mater and 9 years later as Director General of NCVC for 7 years till retirement age of 65 with no regret.

1MS1A-2

Crossbridge Dynamics in Cardiac Muscle

Saeki, Yasutake (*Department of Physiology, Tsurumi University School of Dental Medicine*)

The time course of myocardial contraction depends on two basic factors, number of active crossbridge and the rate of crossbridge cycling. Many different mechanical parameters had been used as an index of myocardial contractility, such as the maximum velocity of shortening and the rate of tension rise. Changes in these parameters had been generally explained by changes in the number of active crossbridges, and had not been seriously considered in relation to the rate of crossbridge cycling. Crossbridge kinetics of skeletal muscle had been extensively estimated from the transient responses of steadily activated muscle to changes in length or to changes in tension, i.e., from the so-called perturbation analyses. In contrast, systematic analyses on myocardial crossbridge kinetics had lagged behind those on skeletal crossbridge kinetics because of experimental difficulties (will be reviewed). In addition, most studies of force-length and force-velocity relations of heart muscle have focused on muscle function from an empirical or phenomenological point of view rather than on the design of experiments aimed at the crossbridge kinetics. The contractile element has represented as black box to which all active processes were arbitrarily assigned. Investigators have attempted to deduce the function of the black box from assumed arrangements of the black box with varied but ambiguous passive elastic structures. I started my cardiac muscle research 1976 as a Dr. Sagawa's postdoctoral fellow, by applying perturbation techniques on on both steadily activated skinned and intact cardiac muscle to define the crossbridge cycling (will be reviewed).

1MS1A-3

In memory of the late Professor Sagawa : A patho – physiological role of a WD repeat protein, naofen/WDR35

Ishikawa, Naohisa (*Aichi Medical University*)

WD (tryptophan-aspartate)-repeat proteins (WDR), characterized by its structure, i.e., 4-16 times repeats of specific amino acid sequences, have been found in eukaryocytes in all organisms, either plants or animals. Roles of WDR in intracellular signal transduction have been investigated, but no patho-physiological roles have been evaluated in the development of diseases. Naofen, a novel WDR, was cloned from rat spinal cord, the sequences being almost similar to WDR35 in humans. Many evidences obtained from rats indicated that naofen enhanced caspase activities, inducing an apoptosis. Furthermore, naofen increased in hepatocytes of cirrhosis models, and also in the renal tubular and glomerular endothelium of diabetes mellitus. Knockdown of naofen expression in hepatocytes remarkably abolished the caspase activation, bcl-2 reduction and cytochrome C release, suggesting a possible participation of mitochondria pathway in apoptosis mediated by naofen. In addition, an increase in naofen was also found in aortic endothelium of nephrectomy-induced hypertension, but no evidences in spontaneous hypertension. Reportedly, naofen expression is important in embryo, but seems to diminish in the neonates and infants, again elevating along aging. What factor may affect the naofen expression is still obscure.

The late professor Sagawa used to teach about the black box when discussing the systems analysis and interaction between carotid sinus and aortic baroreflexes. I could not always understand, but I now realize that especially from molecules to whole body, the mechanisms of action of intracellular compound need to be considered on a line.

1MS1A-4

Pressure–volume relationship *in silico*

Sugiura, Seiryo[1]; Washio, Takumi[1]; Okada, Jun-ichi[1]; Takahashi, Akihito[1]; Watanabe, Hiroshi[1]; Hisada, Toshiaki[1]; Yamashita, Hiroshi[1]; Yasuda, Soichiro[1]; Kariya, Taro[1]; Imai, Yasushi[1]; Nagai, Ryozo[1]; Kadooka, Yoshimasa[2]; Hosoi, Akira[2]; Watanabe, Masahiro[2]; Hirahara, Takao[2]; Yamazaki , Takashi [2]; Iwamura, Takashi[2]; Nakagawa, Machiko[2]; Hatanaka, Kohei[2]; Yoneda, Kazunori[2]; Ataka, Tadashi[2] ([1]*The University of Tokyo, Tokyo, Japan;* [2]*Fujitsu Ltd., Kawasaki, Japan*)

Physiological function of the heart is supported by the elaborate network of cellular and subcellular machineries. Although studies at the cellular and molecular levels have identified number of defects causing the abnormalities in macroscopic cardiac function characterized by the ventricular pressure-volume relation, complex crosstalk inherent in the hierarchical biological system often makes it difficult to establish the causal relations between them. Recent advancement in computational science has enabled us to develop a multi-scale, multi-physics heart simulator in which contraction and relaxation of the heart and the resultant blood flow as well can be reproduced based on the molecular functions in each myocyte. Such an integrative approach will surely promote our understanding of cardiac functions under normal or diseased conditions. In this presentation, we will introduce in silico heart,"UT-Heart". Examples of simulations relating the molecular abnormalities and macroscopic cardiac function will be presented.

1MS1A-5

The pressure–volume relationship continues to be a central framework unifying multiscale, multiphysics cardiovascular sciences

Sunagawa, Kenji (*Department of Cardiovascular Medicine, Kyushu University*)

The pressure-volume relationship of the heart was first reported more than a century ago. It was not widely accepted, however, until the mid-1970s. The pressure-volume diagram became a central framework of cardiac mechanics once it was shown to be a good representation of ventricular mechanics. Early in 1980s, the introduction of the ventricular interaction with afterload using the effective arterial elastance made it possible to translate ventricular mechanical properties represented by the pressure-volume relationship to the pumping ability of the heart. Furthermore incorporating the framework of ventricular arterial interaction into the classic Guyton's circulatory equilibrium early in 2000s enabled us to express quantitatively how the mechanical properties of the ventricles and vascular systems determine the circulatory equilibrium. This opens up vast clinical applications. This is to say that if we develop a feedback mechanism to manipulate mechanical properties of ventricle and vascular system, we can in turn feedback regulate the circulatory equilibrium, and thereby navigate hemodynamics. Recently we developed a prototype of fully automated closed-loop treatment system that stabilizes hemodynamics of decompensated left heart failure. Accelerating introduction of circulatory assist systems into the clinical settings will further inspire more intricate applications of the pressure-volume relationship. The pressure-volume relationship will remain to play a major role in bridging multiscale, multiphysics basic research and their clinical applications.