Energized by Circulation Research Over 30 Years

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Congratulations on the 50th anniversary of Circulation Research in 2003.

As a medical student of Okayama University in Japan in the early 1960s, I was very impressed by the well-designed cardiac pump function after watching and touching beating hearts in situ in canine open-chest experiments and learning about the heart in physiology classes. This definitely motivated me to learn more about cardiac function throughout my education. My dream in those days was to combine medicine and engineering as an extension of my electronics and mechanics hobbies since childhood days. I heard that the University of Tokyo had started the Institute for Medical Electronics and opened its PhD course for the first time in Japan.

After getting an MD at Okayama University in 1966, I entered the PhD course of Applied Physiology and Biomedical Engineering at the University of Tokyo instead of taking a clinical internship. As a PhD student, I decided to investigate the attractive but still mysterious cardiac function and started to measure left ventricular pressure and volume in the in situ beating canine heart. For aortic flow measurement, the electromagnetic flowmeter that had just been commercialized, but I built one from the parts I bought in radio shops, relying on my own electromechanical savvy. I even made aortic flow probes by making their coils and electrodes and putting them together with epoxy glue.

Using the homemade electromagnetic flowmeter and a commercial manometer, I succeeded in measuring aortic flow and left ventricular pressure continuously for the first time in my career. This excited me greatly and tremendously energized me to go further along the line.

In those days, world-renowned physiology and cardiology textbooks showed the Frank-Starling Law of the Heart and cardiac output curves, the Sarnoff ventricular function curves, and the Sonnenblick myocardial force-velocity curves as the cardiac output curves, the Sarnoff ventricular function curves, and the Sonnenblick myocardial force-velocity curves as the standard measures of cardiac function and contractility. Circulation Research and other international heart-related journals were publishing studies mostly on cardiac contractility using Vmax or Vcf derived from the cardiac force-velocity relation. I read these studies and tried to confirm the conventional and contemporary concepts in my own canine heart experiments. I gradually recognized cardiac function to be more mysterious than described in the literature.

One day, I transiently clamped the ascending aorta during ejection to various extents and released it after variably short lags and observed the changes in both aortic flow and left ventricular pressure. I found that aortic flow dropped and ventricular pressure rose instantaneously on clamping and both returned on releasing. The more the aorta was clamped, the more the flow dropped and the pressure rose. The force-velocity relation seemed to account for these inversely proportional changes. However, I did not know how the force-velocity relation could account for the instantaneous relations between the observed flow and pressure changes.

I continued to think about how to explain this finding by the already-known mechanisms in literature, but vainly. One day, I experienced a serendipitous insight, one of the biggest in my research career, obviously thanks to my electromechanics hobby. That is, if the heart is assumed to behave like a time-varying elastic chamber, the proportional aortic flow dip and ventricular pressure rise could be reasonably accounted for.

To test this hypothesis, I needed to obtain the instantaneous left ventricular volume simultaneously with its pressure so that I could calculate the instantaneous pressure/volume ratio, ie, elastance, through a cardiac cycle. Ventricular pressure measurement was relatively easy and accurate even with a water-filled catheter and a diaphragm-type pressure gauge; neither a micromanometer nor a catheter-tip manometer was available in those days. However, ventricular volume measurement was very difficult approximately 30 years ago. I made an impedance catheter for a saline (indicator) dilution method combined with stroke volume obtained by integrating the instantaneous aortic flow. This volumetry was not fully reliable, but no other methods were easily available for me.

In addition, since personal computers were not yet available, I had to get pressure and volume values by reading fast-run strip-chart tracing curves of many heart beats at 5- to 10-ms intervals. This visual reading of one experiment’s data took a full week. Then, I manually calculated pressure/volume ratio by dividing ventricular pressure by volume again at the same 5- to 10-ms sampling intervals using an electronic calculator. What a terrible data processing experience as I recall now, but I did not feel so in those days because no other ways were possible.

One year later, I finished about 20 successful experiments and completed all the data analyses. I consistently found that the instantaneous pressure/volume ratio or elastance increased with contraction throughout both the isovolumic and ejection phases and decreased with relaxation to the end-diastolic level. I further found that the time curves of the pressure/volume ratio of contractions at different preloads and afterloads in a stable contractile state were superimpos-

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able, and those at different contractile states and heart rates resembled each other. Taken together, I concluded that the left ventricle performed as if it were a time-varying elastic chamber stiffening during systole and softening during diastole. I also designated the peak of the elastance curve as the end-systolic maximum elastance $e_{max}$ and proposed it as a load-independent index of contractility. On these findings, I wrote three English papers in the Japanese Heart Journal in 1969 to 1970 and finally in my PhD thesis “Analysis of Left Ventricular Pumping by Its Pressure-Volume Coefficient” in Japanese, and obtained a PhD in 1970.

In those days, I rarely encountered *Circulation Research* papers written by Japanese authors and I heard that *Circulation Research* was a highly prestigious journal and rarely accepted manuscripts from Japan. In fact, I submitted a paper on my first proposal of left ventricular end-systolic elastance as a new index of contractility to *Circulation Research*, but it was in vain, largely due to my unpolished English writing. This experience disappointed me for a week or so but then gradually energized and challenged me to get my papers accepted some day in a near future by *Circulation Research*.

In 1971, as an Assistant Professor of Tokyo Medical and Dental University, I joined Dr Kiichi Sagawa first at Case Western Reserve University and a few months later at Johns Hopkins University. He advised me to change “$e_{max}$” to “Emax” and encouraged me to establish the Emax concept with more persuasive evidence using more accurate and reliable ventricular volumetry. I developed a left ventricular plethysmographic (cardiometer) volumetry combined with a right heart bypass. Then, I was able to confirm the essence of the time-varying elastic property of the contracting left ventricle and Emax as a largely load-independent index of left ventricular contractility.

One and a half years later, I submitted a paper coauthored with Drs Sagawa and Shoukas on Emax to *Circulation Research*. At this time, it was accepted after a minor revision and published in 1973. I cannot forget my excitement when I saw it printed in the issue. Dr Sagawa shook my hand and said: “Hiro, congratulations! You are now a circulationist!” This greatly energized me to challenge the field further. My next paper that further confirmed Emax with a more accurate ventricular volumetry using a newly developed water-filled balloon and cylinder system was also accepted and published in *Circulation Research* in 1974. These two papers on Emax have been cited equally well, and the number of their citations by other papers counts more than 1300 times together and is still increasing even now. These two papers were ranked as the 15th and 16th most cited papers in *Circulation Research* up to 1995.

Overall, I have published 18 *Circulation Research* papers mostly on Emax and PVA (pressure-volume area) that I later established as a new and sound measure of ventricular mechanical energy from the time-varying elastic property and the Emax concept. In addition, I have published 7 papers in *Circulation* and 60 papers in the *American Journal of Physiology: Heart*, among a total of 230 original papers in English mostly on Emax and PVA. The number of citations of these papers counts around 6000 times and is still rising. Probably most endorsed by my *Circulation Research* papers, I was honored as a 1983 Johns Hopkins University Society of Scholars Lifetime Membership Awardee, a 1990 American Physiological Society Physiological Review author, and a 1993 AHA Paul Dudley White International Lecturer, etc. The Emax and PVA concepts have also been gradually recognized internationally as key concepts in cardiac function, or more specifically, cardiac mechanoenergetics in physiology and in cardiology textbooks not only for professionals but also for students.

To promote better understanding and progress of the Emax and PVA concepts globally, I started the Emax & PVA Club (http://www5b.biglobe.ne.jp/~EMAXPVA/) 12 years ago when I was the Chair and Professor of Physiology at my alma mater and have issued a Lifetime Membership Award to about 60 young fellows who more or less collaborated with me. I also have issued an Honorary Membership Award to 25 internationally distinguished professors.

As a past Editorial Board member and a present Consulting Editor of *Circulation Research* as well as an AHA Honorary Fellow, I hope that *Circulation Research* continues to energize ambitious circulation researchers worldwide to advance their research at all different levels ranging from genome, proteome, etc, to physiome and envirome.

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