THE DEVELOPMENT OF ECHOCARDIOGRAPHY IN CHINA: THE PIONEERING ROLE OF XIN-FANG WANG

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Introduction

I cannot discuss the history of the development of echocardiography in China without describing the pioneering role of Xin-fang Wang (王新房) from Wuhan, China, who is the "father of modern echocardiography."[1] Although Inge Edler from Sweden[2-5] and Harvey Feigenbaum from the United States[6] were also oftentimes referred to as the fathers of echocardiography, both Edler[7] and Feigenbaum[8] recognized that the Chinese used cardiac ultrasonography in the very early years (Figure 1).

Development of Echocardiography in China

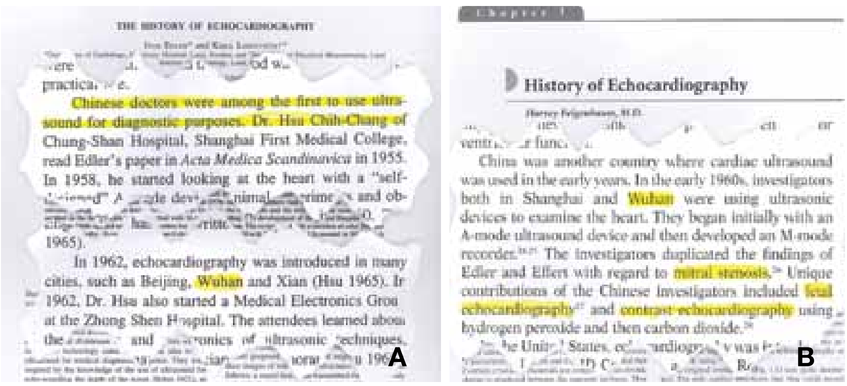
In the late 1950s, investigators in both Shanghai and Wuhan were already making and using ultrasonic devices to examine the hearts of their patients.[9] In 1958, research on ultrasound was very popular in all industries throughout China. The pioneer of using ultrasound technology to perform medical diagnosis was Shi An (安适)(Figure 2A), who was not a physician but a customs officer and later a librarian in Shanghai.[10] Working with human subjects, An successfully used a Type 1 converted ultrasound metal flaw detector of Shanghai Jiangnan Shipyard with a frequency of 2.5 megahertz (Figure 2B).[9]

It might be of some interest to point out here how Edler and Hertz developed echocardiography. The son of Gustav Hertz, the famous 1925 Nobel Prize Laureate in Physics,[4,7] C. Hellmuth Hertz was not a physician but had a deep interest in ultrasonography. He was aware of an ultrasonic reflectoscope at a shipyard in Malmö and borrowed the device during a weekend in May 1953.[3,7] When Edler and Hertz placed the transducer of the reflectoscope over the chest, they could detect moving echoes, obviously originating from the movements of the heart. Whereas Hertz knew there was no possibility of obtaining research grants for buying an ultrasonic reflectoscope, he discovered that the Siemens Corporation in Germany was building ultrasonic reflectoscopes for nondestructive material testing and flaw detection at the shipyard.[7] Since Hertz's father had been the director of Siemens & Halske AG's Research Laboratory before the end of World War II, he contacted director Wolfgang Gellinek of the Siemens medical branch in Erlangen, Germany. Hertz demonstrated the discovery using a Siemens reflectoscope in the factory laboratory. Immediately recognizing its potential for application in cardiology, Gellinek ordered one of their reflectoscopes to be sent to Lund as a loan for a year, despite the fact that some of their regular customers had to wait.[7] Due to later development, this loan was never returned. It is, indeed, fascinating to note how both Hertz's and An's discoveries about echocardiography originated from a shipyard!

In 1958, An founded the Shanghai Ultrasound Medical Research Group at the Sixth People's Hospital of Shanghai, and his team included Tao-Hsin Wang, a classmate of mine who later became a well-known neurosurgeon, and Zhi Zhang Xu, a.k.a. Chih Chang Hsu. This special research team made further studies of patients and published a preliminary report in Chinese in 1960.[11] In 1962, his team reported the results of its application in 4,618 patients, studied from December 1958 to October 1961, in the English edition of *Chinese Medical Journal*.[12] The organs they examined included the liver, stomach, uterus, breast, brain, lungs, and heart. This was a seminal publication as far as the hydatidiform mole was concerned because it had not been previously reported in the medical literature.

Role of Xin-fang Wang

Xin-fang Wang was born in Henan, China in 1934. Xin-fang in Chinese means "new house" (新房); Wang's father gave him this



THE HISTORY OF ECHOCARDIOGRAPHY

Chinese doctors were among the first to use ultrasound for diagnostic purposes. Dr. Hsu Chih-Chang of Chung-Shan Hospital, Shanghai First Medical College, read Edler's paper in *Acta Medica Scandinavica* in 1955. In 1958, he started looking at the heart with a "self-

1965).

In 1962, echocardiography was introduced in many cities, such as Beijing, Wuhan and Xian (Hsu 1965). In 1962, Dr. Hsu also started a Medical Electronics Grou at the Zhong Shen Hospital. The attendees learned abou

History of Echocardiography

China was another country where cardiac ultrasound was used in the early years. In the early 1960s, investigators both in Shanghai and Wuhan were using ultrasonic devices to examine the heart. They began initially with an A-mode ultrasound device and then developed an M-mode recorder. The investigators duplicated the findings of Edler and Effert with regard to mitral stenosis. Unique contributions of the Chinese investigators included fetal echocardiography and contrast echocardiography using hydrogen peroxide and then carbon dioxide.

Figure 1. China's early contribution to echocardiography from Shanghai and Wuhan (where Wang is) acknowledged by both (A) Edler[7] and (B) Feigenbaum.[8]

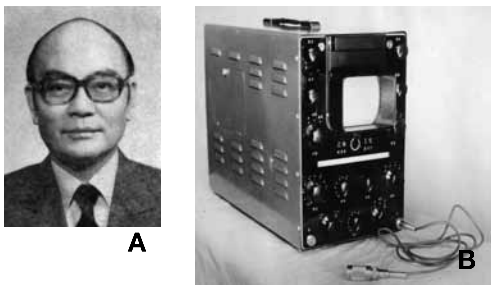


Figure 2. (A) Shih An (courtesy XF Wang) and (B) China's earliest ultrasonic diagnostic device, the A-mode scanner, made in Jiangnan Shipyard in Shanghai and used in 1958 by An for diagnosing various diseases in patients at the Shanghai Sixth People's Hospital (courtesy B Hu and XF Wang).

name because they had just moved into a new house. However, I tend to think that his father had the foresight of recognizing his son's ultimate career in echocardiography, which in essence deals with new knowledge about the heart including, among other things, the "atrial chamber" (心房), which is homophonous with "new house"(新房). Wang received his medical degree in 1958 from Tongji Medical University in Wuhan. He became associate professor of medicine and director of the echocardiographic department at Union Hospital of the Tongji Medical University in 1980. In 1986, he was promoted to professor of medicine and deputy director of the Institute of Cardiovascular Disease at the Tongji Medical University, now called the Cardiovascular Institute of Huazhong University of Science and Technology.

Wang began to study medical ultrasound technology in 1961. He found ultrasound to be very effective in examining pathological alterations of accumulated body fluid, which appears as a fluid flat segment in A-mode ultrasound image and a fluid dark area in B-mode ultrasound image. Based on these characteristics, he then classified human tissues into four categories: (1) tissues with non-ultrasound reflection, such as urine, ascites, pleural effusion, and pericardial effusion; (2) tissues with little ultrasound reflection, such as liver and spleen; (3) tissue with strong ultrasound reflection, such as the mammary glands; and (4) tissue interface with almost complete ultrasound reflection, such as the interface between soft tissue like chest and abdominal wall, and the air-filled space like lungs. Using this classification of human tissues by ultrasound reflections, he then introduced a new ultrasonic imaging method to diagnose liver abscess, pleural effusion, and pericardial effusion, each of which appears as a dark region because there is no reflection of ultrasound in liquids. Since 1963, Wang concentrated on the application of ultrasound to study the heart, realizing that the heart chambers were full of blood with little ultrasound reflection and thus depicted as dark regions, while the heart walls were solid tissues with strong ultrasound reflection resulting in a clear delineation between them on the ultrasound image.

Wang's Pioneering Work

Fetal Echocardiography

Wang in the early 1960s raised this question: If ultrasound could be used to detect fetal movement, why could it not monitor fetal heart beat in accordance with the differences of ultrasound reflection of the amniotic fluid and the fetus?[1] In1963 at a national ultrasound meeting in Wuhan, he reported echocardiographic findings of normal fetuses in pregnant women.[13] His 1964 report of the M-mode echocardiographic study of the fetal heart rate and size in 140 pregnant women was the earliest such report in the world literature (Figure 3).[14] This seminal publication appeared 8 years before such application was reported in the English literature by Winsberg in 1972.[15]

Mitral Stenosis

In the early 1960s, Wang pioneered the prototype echocardiographic equipment synchronized to electrocardiographic and phonocardiographic signals.[1] In addition to duplicating the findings of Edler with regard to mitral stenosis,[16, 17] he clarified the mechanisms of various points, peaks, and segments of the echocardiograms in mitral stenosis. He was the first in the world to show that the opening snap in mitral stenosis coincides with the E-peak of the echocardiogram (Figure 4A).[17]

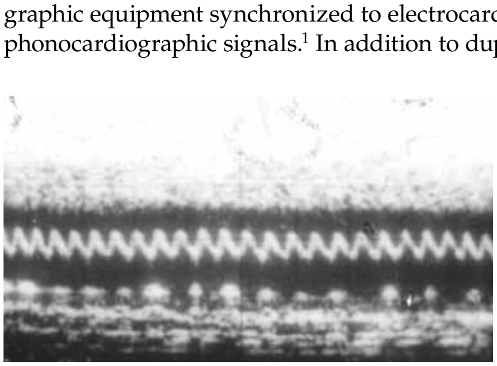


Figure 3. World's first fetal echocardiogram (courtesy XF Wang).

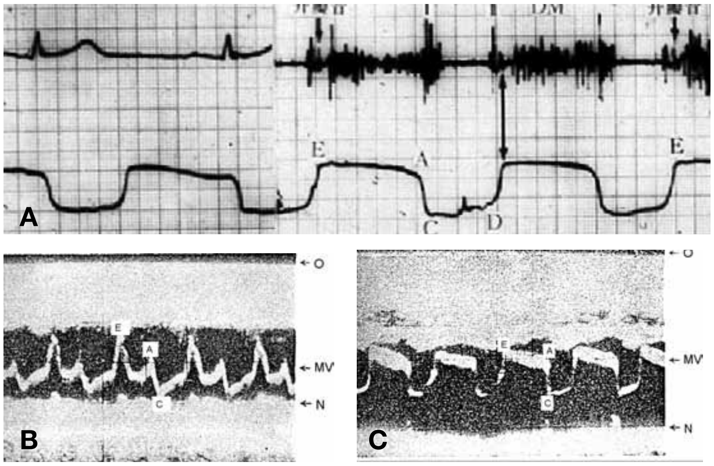


Figure 4. (A) World's first demonstration of coincidence of the E-peak (double-headed arrow) on echocardiogram with the opening snap (arrow) followed by the flat EA (now called EF) slope corresponding to a long diastolic murmur (DM) in a simultaneously recorded phonocardiogram in a patient with mitral stenosis (courtesy XF Wang). (B) Echocardiogram of a normal-sized left atrium in a normal subject. The distance from the closed mitral valve (C) to the posterior wall of the left atrium (N) is the size of the left atrium, which is 8 mm here (courtesy XF Wang). (C)The world's first echocardiographic demonstration of enlarged left atrium in mitral stenosis. The distance from C to N is widened to 22 mm in this patient. Note also the flat EA curve that is typical for mitral stenosis (courtesy XF Wang).
O: transmission pulse; MV: mitral valve curve; N: posterior wall of left atrium near atrioventricular ring.

Wang was also the first in the world in 1965 to measure the size of the left atrium by echocardiography.[17] He showed that, in contrast to a normal subject (Figure 4B), patients with mitral stenosis showed an increased left atrial size (Figure 4C). In recent years, assessment of left atrial size has gained increasing importance in clinical practice, because left atrial enlargement is an important marker of cardiovascular disease and a predictor of such adverse events as atrial fibrillation, stroke, congestive heart failure, and even mortality in a wide range of cardiovascular conditions including obesity.[18] Although volume measurement of the left atrium should be made nowadays from two-dimensional (2D) or three-dimensional (3D) echocardiograms because of asymmetric left atrial enlargement due to constraint by surrounding structure, the pioneering work of Wang in using M-mode to assess the left atrial size should not be forgotten.

Intracardiovascular Smoke-Like Echo

Intravascular smoke-like echo always appears in regions of stasis, but the exact mechanism of its production remained unclear until 1992, when Wang reported a close correlation between intravascular smoke-like echo in the left atrium and erythrocyte rouleaux formation (Figure 5).[19] This new finding has considerable significance in the interpretation of echocardiographic findings in terms of hemodynamic and cellular mechanisms, especially in patients with mitral stenosis.

Red blood cells aggregate to form rouleaux in patients with severe mitral stenosis because of blood flow stasis and decreased shear force; therefore, smoke-like echo is observed in the left atrium.[20-22] When blood flow passes through the stenotic mitral orifice into the left ventricle, flow velocity and shear force are increased, rouleaux disperse, and smoke-like echo disappears.[19] Smoke-like echo in the left atrium has also abated

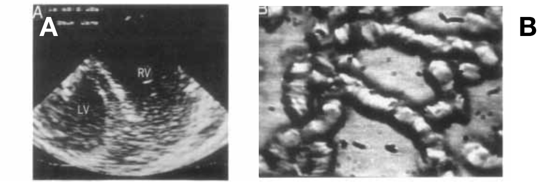


Figure 5. From a preagonal dog, (A) smoke-like echoes in both left ventricle (LV) and right ventricle (RV) as seen on the ultrasonogram, and (B) red blood cells as a dense network of rouleaux seen under a microscope (courtesy XF Wang).

after relief of mitral stenosis following percutaneous balloon mitral valvuloplasty.[23] Smoke-like echo is seldom seen in the left atrium of patients with mitral stenosis associated with mitral regurgitation because of the stirring effect on the shear forces.[19]

Contrast Echocardiography

Contrast echocardiography is now a well-established technique, useful in studying various cardiovascular disorders. However, in early days it did not enjoy widespread use due to lack of a safe and inexpensive agent that could reliably produce dense, sustained contrast effects with either M-mode or 2D echocardiography. After testing various contrast agents, Wang eventually discovered hydrogen peroxide as an ideal echocardiographic contrast agent.[24-27]

Wang's publications in 1978 and 1979 anteceded the 1983 article of Gaffney et al. by 5 years.[24-28] Xu[29] from Shanghai in 1981 and Hua[30] from Wuxi in 1982 later each reported the use of carbon dioxide as an echocardiographic contrast agent. Roelandt's group from the Netherlands published their work in 1981 as well.[31]

Pericardial Disease

Pericardial Effusion

Although Feigenbaum was generally credited with the first report of an ultrasound diagnosis of pericardial effusion in 1965,[6, 32] the use of echocardiography to diagnose pericardial effusion began in China even earlier.[33, 34] In 1961, Chih Chang Hsu, now spelled Zhi Zhang Xu (徐智章), in Shanghai reported the first use of A-mode echocardiography in diagnosing pericardial effusion.[33-36] Wang started using echocardiography in diagnosing pericardial effusion in 1961 as well and published a series of 51 patients in 1973.[37]

Wang was also the first in the world to use echocardiography in guiding pericardiocentesis in August of 1963 (Figure 6).[37] The patient was a 21-year-old male. His echocardiogram revealed pericardial fluid located 1.5–6.0 cm beneath the skin in the left sixth intercostal space at the midclavicular line with a wave pulsing with the heart beat at 6.0 cm. Wang diagnosed a large amount of pericardial effusion and recommended that pericardiocentesis be performed, with the aspirating needle inserted to a depth of 3.0–5.0 cm beneath the skin (Figure 6A). On August 21, 1963, pericardiocentesis was performed using sterile technique and under local anesthesia, with the aspirating needle inserted to a depth of 3.0 cm beneath the skin through the sixth left intercostal space midway between the midclavicular line and the anterior axillary line. A total amount of 370 ml of grass-green fluid was withdrawn. The procedure was successful and uneventful (Figure 6B).

Constrictive Pericarditis

Diagnosis of constrictive pericarditis is clinically important, therapeutically challenging, and oftentimes quite difficult. The diagnosis of constrictive pericarditis is usually based on the measurement of pericardial thickness and hemodynamic alterations. However, it is difficult to measure the pericardial thickness by echocardiography, and a few patients with constrictive pericarditis had normal pericardial thickness. Furthermore, similar symptoms and hemodynamic changes may exist in other disease states such as restrictive cardiomyopathy.

Adhesion of visceral and parietal pericardium, which is the sine qua non of constrictive pericarditis, leads to diminution of relative motion between pericardium and myocardium. Wang and associates analyzed the systolic displacement of pericardium and myocardium quantitatively using 2D echocardiography and quantitative tissue Doppler imaging.[38] They found that, in normal subjects, the motion of myocardium is stronger than that of pericardium and, although relative motion exists between them, the outer and inner layers of myocardium move identically (Figure 7A). On the other hand, in patients with constrictive pericarditis, where there is adhesion of parietal and visceral pericardium, the motion of outer-layer myocardium adjacent to visceral pericardium is limited (Figure 7B). In patients with restrictive cardiomyopathy, displacement of outer-layer myocardium is very close to that of inner-layer myocardium and higher than that of pericardium (Figure 7C). Therefore, by observing the motion of pericardium and myocardium by means of 2D echocardiography and quantitative tissue Doppler imaging, Wang and associates introduced a new and sensitive objective technique not only in the diagnosis of pericardial adhesion, which is the most important pathological change in patients with constrictive pericarditis, but also in the oftentimes difficult differential diagnosis between constrictive pericarditis and restrictive cardiomyopathy.[38]

Other Major Contributions

Transesophageal echocardiography came into clinical practice in Shanghai in 1988 and was first reported in 1989.[39] Soon thereafter, Wang conducted extensive studies with, and published numerous pacesetting articles on, monoplane, biplane, and multiplane transesophageal echocardiography, real-time 3D echocardiography, and tissue Doppler imaging, and I was privileged to collaborate with him on several publications.[19, 33, 38, 40-51]

There are more than 50 textbooks on echocardiography published in China. Wang published China's first textbook on

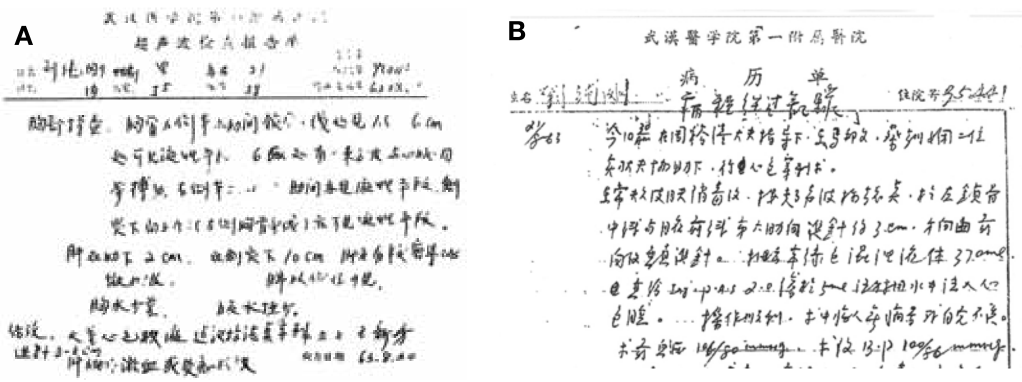


Figure 6. Original handwritten notes of world's first pericardiocentesis under echocardiographic guidance performed in Wuhan, China in August 1963. (A) Echocardiographic findings on the day before pericardiocentesis; (B) Procedure notes on the following day during and following pericardiocentesis (courtesy XF Wang). See text for detailed discussion.

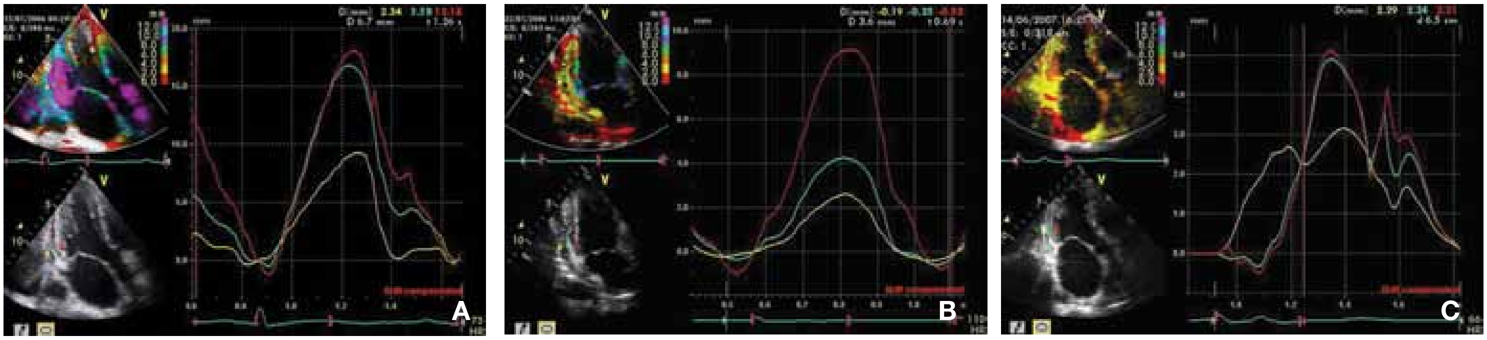


Figure 7. Quantitative tissue Doppler imaging in (A) a normal subject, (B) a patient with constrictive pericarditis, and (C) a patient with restrictive cardiomyopathy. Yellow line: parietal pericardium; blue line: outer-layer myocardium; red line: inner-layer myocardium (courtesy XF Wang). See text for discussion.

echocardiography in 1975, although his name never appeared anywhere in the book; during the period of China's Cultural Revolution, only the name of the institution, and not the author, was allowed. The first edition of his book was formally published in 1981. Its second, third, and fourth editions were published in 1985, 1999, and 2009, respectively. Wang also published China's first color Doppler textbook in 1991. His classic publication in 1995 on dynamic 3D echocardiography, also known as 4D echocardiography, was the first in China if not the first in the world.[52]

All of Wang's outstanding work and publications, which numbered over 200, received high praises both at home and abroad. Consequently, he was awarded many national and international honors, such as the "History of Medical Ultrasound Pioneer Award" by the World Federation of Ultrasound in Medicine and Biology and the American Institute of Ultrasound in Medicine (1988) — along with Yong Chiang Chou, Wang Xue Guo, Zhi Zhang Xu, and Ruo Feng — and other prestigious awards by the State Council of China (1979, 1998, 2005), the State Education Commission (1992), and the Ministry of Health (1992). His most recent honor is an Honorary Fellowship in the American Society of Echocardiography awarded in July of this year. This honor has been awarded previously to only 11 recipients from around the world, namely, Jos Roelandt from the Netherlands, Liv Hatle from Norway, Junichi Yoshikawa from Japan, Fausto Pinto from Portugal, Namsik Chung from Korea, Allessandro Distante from Ialy, Shintarro Beppu from Japan, Jorge A. Lowenstein from Argentina, Chuwa Tei from Japan, Jean G. Dumesnil from Canada, and Raimund Erbel from Germany

In short, echocardiography is continuing to advance under the very able and resourceful leadership of Wang, who certainly deserves the title of "Father of Modern Echocardiography." He may even be worthy of the title "Grandfather of Modern Echocardiography" since he has trained many well-known echocardiographers in China who in turn train younger generations of echocardiographers. But despite his "grandfather" status, Wang is not prepared to retire anytime soon: he continues to respond to my letters and e-mails within 24 hours, goes to his university library and echocardiographic laboratory every day, attends important ultrasonic meetings, and continues to publish.[49-51]

Conclusion

Echocardiography has revolutionized the practice of cardiology in the 21st century. It is the most popular and widely used cardiac imaging technique in the world and is the second most-frequently ordered cardiologic test after ECG. It is indispensable in the practice of medicine, and continues to benefit countless patients around the world. The extraordinary progress made in echocardiography in China under very limited resources is indeed a magnificent tribute to the dedication of Wang and his colleagues. All of us owe a great deal to Wang for his many pioneering contributions to echocardiography. As the Chinese saying goes, "When drinking the water, think of the man who dug the well."[1] So whenever we perform or order an echocardiogram for diagnostic, prognostic, or therapeutic purposes, always think of, and also be thankful to, Xin-fang Wang in Wuhan, China.

Epilogue

Both Edler and Wang are pioneers in echocardiography, and I had the good fortune of knowing them both. I met Edler in Atlanta during the 40th annual convocation of the American College of Cardiology in 1991, when he was awarded an Honorary Fellowship along with two other awardees — Bakken, the founder of Medtronic, and Tung, the "Paul D. White of China" (Figure 8A).[9] William Winters, the editor-in-chief of this journal and then-president of the American College of Cardiology, served as Edler's marshal while I served as Tung's marshal (Figure 8B). I sat with Edler and other dignitaries on the dais (Figure 8C), and we had a long conversation afterwards. I found Edler not only extremely knowledgeable but also very friendly and unassuming. According to Winters in his presentation speech, Edler was responsible for his own interest in echocardiography dating back to the early 1960s.

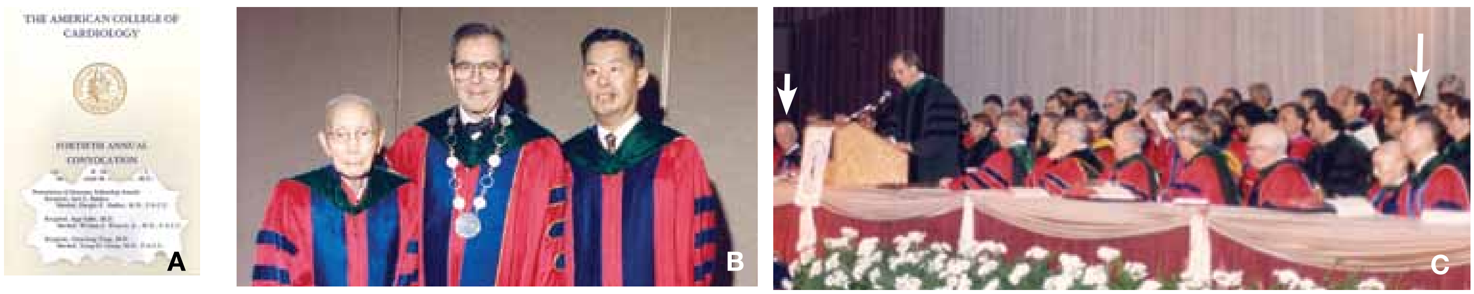


Figure 8. Fortieth annual convocation of the American College of Cardiology, during which three honorary fellowships were awarded. (A) Names of recipients and their marshals. (B) Dr. C.L. Tung, Shanghai, China (left), William Winters, Houston, Texas (center) and this author (right). (C) Seated on the dais, Edler (short arrow) and this author (long arrow) next to Tung and other dignitaries.

Figure 9. Meetings of this author with Wang in China on various occasions: (A) in 1979 with Wang (right) and his mentor Y.S. Li (left) in Li's home; (B) in 1992 in Tiananmen Square in Beijing; (C) in 1994 discussing an interesting echocardiogram in Wang's laboratory. Note the contrast of Wang's attire between A and B; Wang wore a Mao jacket in 1979 but a western suit in 1992 in front of the portrait of Chairman Mao in Tiananmen Square.

Edler, likewise, paid tribute to Winters for his contributions in the echocardiographic evaluation of mitral stenosis, post-mitral and aortic valve replacement, and pericardial effusion and atrial septal defect.[7]

I first met Wang in Wuhan, China in 1979 during the 4-week visit of the first teaching delegation of the American College of Physicians to China, which I led (Figure 9A).[9] I was instantly impressed by his intelligence, brilliance, innovativeness, diligence, earnestness, and humility. Because we share many common interests, we become very close friends and have collaborated on many publications and projects. I visited him in China often and always learned a great deal from him at each visit (Figures 9B-9C).

Wang is also adept in photography and Chinese poetry. He frequently combined both to compose beautiful and touching stanzas that he would send to me periodically. I am particularly moved by the following that he sent to me in 2010, the Year of the Tiger (Figure 10). I was born in the Year of the Tiger. It reads:

> *"Dedicated to Professor Tsung O. Cheng*
> (English translation courtesy Lü Fei, Second Secretary, Chinese Embassy, Washington, D.C.)
> *Like the tigers crouching on the summit,*
> *Marvelous is your achievement in the study of heart.*
> *With students everywhere in the world,*
> *Your accomplishment will run through the vast universe.*
> *Congratulations with respect*
> *From your student Wang Xin-fang"*

I consider myself extremely fortunate to have made my acquaintances with Wang — my best friend, my most respected confidant, and my most inspiring colleague.

Figure 10. Pictorial stanza this author received from Wang in 2010, the Year of the Tiger, which was this author's year of birth. In the Chinese calendar, every lunar year is represented by an animal, and the cycle repeats every 12 years. See text for English translation.

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