Review

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Heart failure－lessons learned and evolving concepts

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Successes and challenges in heart failure

Heart failure (HF) is the archetypal chronic cardiovascular disease, with late presentation and high mortality.[1] Much progress has been made in the treatment of patients with symptomatic systolic HF. The combinatorial neurohormonal modulatory therapy, including ACE (angiotensin converting enzyme) inhibitors (ACEi), beta blockers (bB), and aldosterone antagonists have significantly reduced mortality. However, there is still a paucity of information regarding the treatment of diastolic HF,[2] early stage intervention, stepwise pathophysiology, and novel targets for intervention leaving significant residual mortality, hospitalization, and increasing prevalence in HF, including diastolic HF.[3,4]

In the Canadian database, we can see that the outcome of patients with a preserved ejection fraction (EF) or diastolic HF in those with reduced EF are in fact quite similar to each other. The etiology may be different in diastolic HF particularly common in patients with previous hypertension, diabetes, and/or cardiac hypertrophy, whereas systolic HF is often due to previous myocardial dysfunction. Regarding systolic HF, many cases are due to interventions with pharmacological therapy. Certainly in the early days of digitalis + diuretics baseline mortality was around 13% per year, which has been reduced with ACEi by 2% and by the combination of ACEi and bB by an additional reduction of 3%. And now with the triple combination of ACEi + bB + aldosterone antagonists, mortality from systolic HF is now half that than what it was before the triple combination intervention. So this is really team work, and you can see that having the right combination, we can achieve our goal, and that this is an making impact. For example, again in the database in Canada, we can see that mortality in this age is just the mortality rate now. And that it has begun to decrease, which is really good news for the population. And that this is making an impact of saving many people from systolic HF. This is especially, a very important lesson in terms of our health care systems.

Evolving pathophysiology

HF is the long-term consequence of cardiovascular remodeling in response to stress injury, whether ischemic injury, pressure overload, or inflammation. A systematic biology approach identified the major contributors to be cytoskeletal transitions, metabolic modulations, signaling network changes, including endoplasmic reticulum stress, abnormalities in protein processing, and growth/deaths pathways.[5] The latter includes not only necrosis and apoptosis but also autophagy and necroptosis. Alterations in protein quality control, autophagy, and lysosomal degradation of proteins can lead to dramatic hypertrophy and heart failure, and improvement can reverse the abnormalities.[6] With the Homologous to the E6-AP Carboxyl Terminus (HECT) domain and ankyrin domain containing E3 ubiquitin ligase 1, which blocks the protein autophagy step, we can see that there is an accumulation of ubiquitinated proteins. Abnormal protein accumulation can then lead to the development of protein aggregates, increased protein oxidative stress, and activation of innate immunity.[7] Indeed, we realized following any type of injury that there is activation of Toll-like receptor signaling. Toll-like receptor signaling, present in all activated signaling pathways, subsequently leads to the activation of cytokine release. These can lead to the release of cell stress proteins (e.g., BNP), subtle inflammatory cytokines, and evidence of cell damage (e.g., high-sensitivity troponin [hsTn]). However, these types of approaches build on earlier seminal work in the role of the sympathetic system in HF.[8] For the survey of the contributing factors, microarray gene expression patterns are now available to actually look for a dominant signal pathway that may be responsible for HF.

We also now know that HF is a condition of cardiac remodeling in addition to the earlier concept of the human dynamics of neurohormonal activation, so now we know that under a stressful condition, either from the environment or from genetics, as we learned earlier, the

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On the other hand, the heart can also be remodeled in a detrimental direction. Now we know that for sure from experience with HF cases.

Biomarkers for prognosis and personalized therapy

To properly define prognosis and especially earlier stage patient identification for potential more personalized or precision based therapy, it would be ideal to have a panel of pathophysiologically based early stage markers. By integrating high throughput systems biology tools together with stem cell differentiation platform and human tissue samples, we have developed a platform for translational biomarker discovery and validation.[9,10] To date, we have not only confirmed the existing HF markers, but uncovered many different novel targets, using the whole cardiac proteome atlas approach.[11] These build on the existing data already generated by many investigators, including that of bilirubin,[12] BNP,[13] and IL-10[14] from Dr. Tohru Izumi's laboratory. The ability to define early and pathophysiologically relevant biomarkers will help to tailor therapeutic approaches to allow intervention on natural history.

Health systems innovation to translate discovery to benefits

A major challenge in HF, and typical of chronic diseases, is the translation of innovation to clinical practice. An approach will generally involve health system innovations, such as the development of intermediate-risk outpatient clinics to decrease hospital readmission, teaching patients to manage their own disease, and to promote community-based support systems.[15] The ability to maintain evidenced-based health care significantly improves the patients' outcomes. This has been demonstrated not only in North America, but also here in Japan.[16] The future of this major challenge is very exciting in terms of the ability to use modern investigation tools to uncover the pathophysiology of HF, novel biomarkers, and targets for therapy for all HF patients around the world.

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Appendix:
Personal congratulations letter for Professor Izumi's contributions on the occasion of his retirement from Kitasato University, Japan

Professor Tohru Izumi is a leader in cardiovascular medicine, an icon in the field of cardiomyopathy and myocarditis, an advocate for trainee excellence and a wonderful colleague and friend. It is on this auspicious occasion of his retirement as professor from the department of medicine that I offer this heart felt note of congratulations.

Professor Izumi started his career in Niigata University in Japan, which was also his alma mater. His important contributions to cardiovascular medicine started with the original descriptions of the disorganized 3-dimension ultra-structural changes in the Z-band architecture and the intramyocardial microvasculature in hypertrophied human hearts (*J Mol Cell Cardiol* 1984; 16: 449-57). This of course is a fundamental observation that led to the entirely new appreciation of the importance of ultra-structural perturbations and microvasculature in cardiomyopathies in the ensuring decades.

Then young Dr. Izumi undertook a Humboldt fellowship to study with Professor Maisch at Wurzberg University, where a lifetime interest in myocarditis and cardiomyopathy germinated, with initial clinical observations on the new approaches to analyzing cardiac biopsies [*Heart Vessels* 1985; Supp 1: 59-67).

After returning to Niigata University, Dr. Izumi started a series of ground breaking observations in myocarditis that established his international reputation in the field. This started out with a unique rat model of autoimmune myocarditis induced by myosin inoculation in the susceptible Lewis rats, with the development of giant cells that can be adoptively transferred through T-cells (*Clin Immunology* 1990; 57: 250-61, 216 citations; and *Eur Heart J* 1991; 12D: 166-8). This led to a series of observations, with his esteemed colleagues at Niigata university, including the localization of the myosin epitope to the RDCB9 and S-1 regions of the myosin rod (*Circ Res* 1995; 76: 726-33), and the characterization of T-cells and cytokine profiles in these models (*Circ Res* 1996 and *J Mol Cell Cardiol* 1997). The role of IL-12 in particular in the induction of the Th1 T cells in this model (*Circ Res* 1998; 82: 1035-42), and the unique role of iNOS in regulating cardiac hemodynamics established some of the most important fundamental understandings of myocarditis. This spurred an era of rapid advances in this entire field, and certainly has consolidated my personal research interest in the field, and formed lifelong friendship with Professor Izumi.

However, Professor Izumi's thoughts and influence have gone beyond the mechanisms of myocarditis alone, but also expanded to the utilization of these cytokines as translational biomarkers of heart failure and cardiomyopathy. This included the use of IL-18 and IL-10 in combination as a means not only to define risk in patients with heart failure, but also to infer its pathophysiology (*J Cardiac Fail* 2002; 44: 1292-7). In addition, Dr. Nishii from his team has made very important observations that IL-10 is a critical predictor of outcomes in patients with fulminant myocarditis, which is of course extremely difficult to manage (*J Am Coll Cardiol* 2004; 44: 1292-7).

In addition to inflammation and immunity, Professor Izumi has also performed seminal work that helped to define new paradigms of heart failure and refine our concepts. One example is the link between brain and the heart, specifically how brain injury can lead to heart damage and heart failure. In a unique porcine brain hemorrhage model, Dr. Izumi and his team identified that the heart can be severely injured and dysfunctional following major brain hemorrhage through activation of sympathetic system (*Stroke* 2002; 33: 1671-6, citation 85). Indeed, the amount of myocardial damage is directly related to the degree of sympathetic activation. This paved the way for the understanding of sympathetic activation in heart failure, and the role of beta blockade in protecting the heart.

Most recently, Professor Izumi has taken up a new emphasis on knowledge translation. One of the important concept is that while the evidence for treating systolic heart failure using ACE inhibitors, beta blockers and aldosterone antagonists is overwhelming, the actual clinical adoption of these guideline mandated treatments is highly variable. Indeed Dr. Izumi and colleagues have identified that patients discharged on at least 2 of the combination therapies had a dramatically better outcome than patients who were not (*Int J Cardiol* 2008; 49: 59-73). This underscores the importance of developing a health system infrastructure to ensure compliance and long term benefits.

In addition to Professor Izumi's extensive contributions, he has also been provided exemplary leadership in cardiovascular medicine in Japan and the world beyond. While at Niigata University, Professor Izumi has led an excellent cardiology team with tremendous strengths and reputation through patient care and high quality publications. This was subsequently expanded when Professor Izumi moved to Kitasato University in Yokohama. There, he has provided

exemplary role model and leadership in building one of the most envirable cardiovascular teams in Japan. He has also built the academic reputation to match its excellence in clinical care.

Professor Izumi has also participated in many major Japanese and international organizations in leadership roles, including the Japanese Circulation Society, as well as the Japanese Society of Heart Failure, where he had played a leadership role in shaping the organization and maximized its impact on the Japanese professional practice and welfare of the Japanese patients. He has also been instrumental in promoting research through orgnaizations such as the International Society of Heart Research, and the International society of Cardiomyopathy and Heart Failure, at the World Heart Federation.

Professor Izumi is also a most ardent champion of his trainees, being a great role model, and encouraging some of the best and brightest to come abroad to study and enhance their research skills and return to build their academic careers. This has led to the next generation of leaders, allowing the refreshment of academic excellence in Japan in cardiovascular medicine. I was fortunate to have worked with a number of these excellently trained fellows, including Dr. Koichi Fuse, and Dr. Mototsugu Nishii, as some of the best fellows we have had in our research laboratory accommodating research fellows from across the globe.

Finally, Professor Izumi is a wonderful friend. His personal generosity and kindness from his heart have always influenced his friends and make the world a better place. His passion and sense of humour bring magic to any social encounter, and naturally bring people together, expanding a network of like minded individuals, who enjoy collaboration despite the distance. I will always treasure his words of wisdom, his insight and admire his dedication and unwavering commitment to his young trainees.

While Professor Izumi is retiring officially, unofficially we know that his energy and vision will continue to ignite the field. Indeed from he has accomplished already, and what great person and passion that he has, that his influence and impact will be felt for years and generations to come.

Please join me amongst all of Professor Izumi's friends and colleagues our heartiest congratulations for a lifetime's journal of dedication to excellence and commitment, and the world is a better place to be because of him.

Sincerely yours,

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