Available online at www.sciencedirect.com

Integrative Medicine Research

journal homepage: www.imr-journal.com

Editorial

A step from the physiology to the physiome

1. How is the tissue volume regulated by capillary fluid exchange?

The circulatory system provides body organs with nutrients and oxygen and removes carbon dioxide and other waste materials. Most exchanges occur at the capillary bed. The capillary exchange is not fixed but regulated by several factors such as hydrostatic and oncotic pressure in the vascular and extracellular compartments.[1] Himeno et al[2] tried to predict mathematically a steady state tissue volume and protein movement at capillary bed in response to change in blood pressure. By using a capillary model, which was based on Starling's principle, they concluded that the system of the capillary is stable near equilibrium at a normal physiological capillary pressure and the time course of tissue volume change is determined by the rapid fluid exchange and protein fluxes. This article is especially invaluable in that effects of nonlinear compliance, lymphatic fluid, and protein drainage on dynamic tissue volume were systematically assessed by using an integrated computational model of capillary fluid exchange. We hope the capillary fluid exchange model is further integrated into the model of heart and circulation to explain how intake or loss of fluid, salt, and protein can develop tissue dehydration or edema.

2. Can a mathematical model of cardiovascular system predict the efficacy of a ventricular assist device for patients suffering from valvular heart diseases?

A left ventricular assist device is generally used to assist the failing heart by helping the left ventricle pump blood for patients suffering from advanced congestive heart failure.[3] Valvular heart diseases with aortic regurgitation or mitral regurgitation are believed to develop the heart failure by increasing the workload.[4] Kim et al[5] predicted the efficacy of a left ventricular assist device on varying degree of aortic or mitral regurgitation by using a mathematical model of the cardiovascular system and found that cardiac performance in mitral regurgitation was significantly improved by implementing a left ventricular assist device whereas that in aortic regurgitation was not. The mathematical model of cardiovascular system was based on circulatory physiology and reproduces blood pressures of aorta and left ventricle during each heartbeat. This model of the cardiovascular system is expected to be used as a test platform for an optimal therapeutic choice for various stage valvular heart diseases.

3. How is the scaling law of basal metabolic rate affected by radiative heat loss and insulation?

The basal metabolic rate (BMR) is variable among people and animals.[6] The BMR per body weight is higher in small individuals or animals. There is also a sex difference in that a female individual generally shows a lower BMR per body weight than a male at the same age. However, if the BMR is normalized to the body surface area, little difference is observed among people and animals.[7] Kwak et al[8] examined the Roberts, Lightfoot, and Porter model[9] and proposed a new theoretical model of metabolism by considering two additional factors: a radiative heat loss and an insulation fur layer. They numerically solved model equations based on an analytic heat balance approach. They found that although external heat transfer makes deviations in the scaling law, which is more prominent at smaller masses, a further consideration of the additional heat loss and the insulation fur layer attenuates those deviations from the scaling law. This model provides the empirical scaling law of metabolism with a reasonable explanation based on heat physics.

4. Electrophysiological properties and calcium handling of embryonic stem cell-derived cardiomyocytes

Stem cell therapy using embryonic stem cell-derived cardiomyocytes (ESC-CMs) is currently one of a rapidly expanding number of clinical applications for cardiac repair or regeneration.[10,11] Comparison of electrophysiological properties and calcium handling between ESC-CMs and sinoatrial, atrial, and ventricular myocytes in the adult heart has been carried out for proper clinical applications. Youm[12] reviewed detailed electrophysiology covering a variety of ion channels and exchangers and also the calcium handling features

of ESC-CMs during differentiation into adult cardiomyocytes. The review suggested that the source of Ca^{2+} recruitment is mostly trans-sarcolemmal Ca^{2+} influx and inositol-1,4,5-trisphosphate receptor-mediated Ca^{2+} release in the early stage of differentiation, whereas ryanodine receptor-mediated Ca^{2+} release with well-developed transverse tubular system primarily contributes to the Ca^{2+} recruitment in the terminal stage of differentiation. The review also emphasized that the role of TRPC3 in Ca^{2+} oscillations and the role of Ca^{2+}-dependent K^+ channels in diastolic depolarization should be addressed in future research. A complete understanding of physiology in ESC-CMs is possibly confirmed by a properly constructed mathematical model.

5. Perspectives of the physiome research

The term 'physiome' was for the first time presented at the International Union of Physiological Sciences (IUPS) Council in 1993 by the Commission on Bioengineering in Physiology which James B. Bassingthwaighte chaired, and the term comes from 'physio-' which means nature and '-ome' which means as a whole. The physiome is a rapidly expanding area of research to generate a whole system by integrating scattered and fragmented information. Leem[13] reviewed the historical and conceptual aspects, relations with model simulations, and potential applications of physiome. The review also emphasized that oriental medicine is now being revisited with the development of physiome research because the holistic but still systematic approach of physiome could resolve many of complex features of oriental medicine. The review clearly addresses the difference between physiome research and the other database-driven researches such as big data analysis, bioinformatics, and network biology. The role of model simulations in the development of physiome research was also well addressed.

REFERENCES

1. Scallan J, Huxley VH, Korthuis RJ. *Capillary fluid exchange: regulation, functions, and pathology*. San Rafael: Morgan & Claypool Life Sciences; 2010.
2. Himeno Y, Ikebuchi M, Maeda A, Noma A, Amano A. Mechanisms underlying the volume regulation of the interstitial fluid by capillaries: a simulation study. *Integr Med Res* 2016;5:11–21.
3. Lazar RM, Shapiro PA, Jaski BE, Parides MK, Bourge RC, Watson JT, et al. Neurological events during long-term mechanical circulatory support for heart failure: the Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) experience. *Circulation* 2004;109:2423–7.
4. Acker MA. Should moderate or greater mitral regurgitation be repaired in all patients with LVEF <30%? Mitral valve repair in patients with advanced heart failure and severe functional mitral insufficiency reverses left ventricular remodeling and improves symptoms. *Circ Heart Fail* 2008;1:281–4.
5. Kim YS, Kim E-H, Kim H-G, Shim EB, Song K-S, Lim KM. Mathematical analysis of the effects of valvular regurgitation on the pumping efficacy of continuous and pulsatile left ventricular assist devices. *Integr Med Res* 2016;5:22–9.
6. Johnstone AM, Murison SD, Duncan JS, Rance KA, Speakman JR. Factors influencing variation in basal metabolic rate include fat-free mass, fat mass, age, and circulating thyroxine but not sex, circulating leptin, or triiodothyronine. *Am J Clin Nutr* 2005;82:941–8.
7. White CR, Seymour RS. Allometric scaling of mammalian metabolism. *J Exp Biol* 2005;208:1611–9.
8. Kwak HS, Im HG, Shim EB. A model for allometric scaling of mammalian metabolism with ambient heat loss. *Integr Med Res* 2016;5:30–6.
9. Roberts MF, Lightfoot EN, Porter WP. A new model for the body size-metabolism relationship. *Physiol Biochem Zool* 2010;83:395–405.
10. Wobus AM, Wallukat G, Hescheler J. Pluripotent mouse embryonic stem cells are able to differentiate into cardiomyocytes expressing chronotropic responses to adrenergic and cholinergic agents and Ca^{2+} channel blockers. *Differentiation* 1991;48:173–82.
11. Maltsev VA, Rohwedel J, Hescheler J, Wobus AM. Embryonic stem cells differentiate in vitro into cardiomyocytes representing sinusnodal, atrial and ventricular cell types. *Mech Dev* 1993;44:41–50.
12. Youm JB. Electrophysiological properties and calcium handling of embryonic stem cell-derived cardiomyocytes. *Integr Med Res* 2016;5:3–10.
13. Leem CH. Perspectives of physiome research. *Integr Med Res* 2016;5:37–40.

Akinori Noma [a,*]
Jae Boum Youm [b]
[a] *Biosimulation Research Center, College of Life Sciences, Ritsumeikan University, Shiga, Japan*
[b] *National Research Laboratory for Mitochondrial Signaling Laboratory, Department of Physiology, College of Medicine, Cardiovascular and Metabolic Disease Center, Inje University, Busan, Korea*

* Corresponding author.
E-mail addresses: noma@sk.ritsumei.ac.jp (A. Noma), youmjb@inje.ac.kr (J.B. Youm)

http://dx.doi.org/10.1016/j.imr.2016.02.001
Available online 4 March 2016