Interview

The Reality of Aging Viewed from the Arterial Wall

An Interview with Dr. Edward Lakatta, Founder and Director of the Laboratory of Cardiovascular Science, National Institute on Aging

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Abstract

An exclusive interview conducted by Professors Jeong Bae Park and Sungha Park with Dr. Edward Lakatta in Seoul while he was visiting for the Pulse of Asia 2013 in Seoul. In this interview, Dr. Lakatta explains and describes vascular aging and aging.

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Curriculum Vitae

Dr. Lakatta is the founder and Director of the Laboratory of Cardiovascular Science, National Institute on Aging, National Institutes of Health (NIH). He also holds adjunct appointments as Professor, Department of Physiology, University of Maryland School of Medicine, and Professor, Division of Cardiology, Johns Hopkins School of Medicine.

Dr. Lakatta received his MD at Georgetown University School of Medicine. Following an internship and residency in Medicine at Strong Memorial Hospital, University of Rochester, he trained in basic research for 2 years at the NIH. Subsequently, he completed his cardiology fellowship at Georgetown and Johns

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Hopkins University Schools of Medicine. This was followed by a year of basic research training at the Department of Physiology, University College and the Cardiothoracic Institute, London, UK.

Dr. Lakatta has made a sustained 30-plus-year commitment to a broad-based research career. His studies range from molecules to humans, including translation of novel findings into the clinical realm. The overall goals of his research program are (1) to identify age-associated changes that occur within the cardiovascular system and to determine the mechanisms for these changes; (2) to determine how aging of the heart and vasculature interacts with chronic disease states to enhance the risk for cardiovascular diseases in older persons; (3) to study basic mechanisms in excitation-contraction coupling and how these are modulated by surface receptor signaling pathways in cardiac cells; (4) to elucidate mechanisms of pacemaker activity in sinoatrial nodal cells; (5) to elucidate mechanisms that govern cardiac and vascular cell survival, and (6) to establish the potentials and limitations of new therapeutic approaches such as changes in lifestyle, novel pharmacologic agents, or gene or stem cell transfer techniques in aging or disease states.

Dr. Lakatta is recognized both nationally and internationally as an expert in cardiovascular research. He has authored over 400 original publications in top peer-reviewed cardiovascular journals, written over 200 invited reviews/book chapters, and delivered over 450 invited lectures. He is a member of multiple scholarly societies and journal editorial boards. Based upon his accomplishments, Dr. Lakatta has received numerous awards, among which are the Allied Signal Achievement Award in Aging, the Novartis Prize in Gerontology, the Irving Wright Award of Distinction of the American Federation for Aging Research (AFAR) and the Distinguished Leader Award of the International Society of Heart Research (ISHR).

He has also received the Pulse of Asia Career Achievement Award for Hemodynamic Research, has been elected into the American Society for Clinical Research and the Association of American Physicians, and has been elected as a Fellow in the APS Cardiovascular Section and as a Fellow of the American Heart Association (FAHA), and is an Inaugural Fellow of the Council on Basic Cardiovascular Sciences of the American Heart Association.

Interview

J.B.P.: Vascular aging is a vague terminology. What actually is aging in the context of life?

E.L.: The question of what is vascular aging is best addressed in the context of a broader inquiry into ‘what is aging?’. Many scientists who participate in aging research have never stopped to think about asking about ‘what is aging?’, because it is a very difficult question, and one without any definitive answer. So, to understand how the artery ages, I think we have to appreciate how organisms age. To do this, we need to know all of the facets of life that change during the aging process. And the way I like to summarize that is to say that ‘aging is a shift in our reality’. I like to think of reality as a system of mutual enslavement of the DNA and its environment (fig. 1). There is the nuclear environment, the cytosolic environment, the tissues environment for cells, and then the organs go together to make up organisms. Organisms emerge from these interactions and develop cognitive and stress-coping mechanisms that differ, in part by differences in personalities, which also give rise to the development of distinct lifestyles, e.g. what and how much we eat, how much we exercise, etc. And there are other organisms in our reality. Friends, plants, bacteria, if you will. And then, we are all immersed in our society, which issues mandates, traditions, and religion, etc. And then, beyond that, we have geographical realities of climate, radiation, pollution, etc., and of course, gravity. Then, we may even have a cosmic connection, if you will (fig. 2). So, the integrated different environments that surround our DNA and DNA function, per se, comprise what

Fig. 1. Reality emerges from a mutually coupled (enslaved) system of DNA and its environment.

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Fig. 2. Reality is a system of mutually enslaved DNA and its environment (from Lakatta: Artery Res 2013;7: 73–80).

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Fig. 3. Aging is a constellation of failures in the DNA-environment system over time.

could be defined as our reality. There is a continual signaling back and forth across each of these environments, which is going on even as we sit here resting. Some types of signaling across these environments change acutely and others very slowly.

Aging can be construed as a series of failures that occur in the signaling within the DNA environmental system that occurs over time. Thus, changes nearly in all of DNA and its environment constitute the ‘reality of aging’. The signals change. Sensing of the signals, the transmission of signals, the response to signals, changes in the protein environment, the proteome all change as we change (fig. 3). Because the signaling must work properly for an organism to work properly, aging can be defined as failure of signaling of the various mechanisms mentioned. So, all of the environments that I mentioned and all of the interfaces change over time. We see people differently; they see at us differently. Our entire bodies become different. We’re not exactly the same people we were 10 years ago and 10 years before that.

J.B.P.: So, what’s arterial aging?

E.L.: Arterial aging is no exception to the discussion above. As I see it, we need to know what’s going on in so many different aspects of the arterial wall and integrate all this information, and then try to understand how arterial aging affects the rest of the organism. Many of our textbooks describe the ‘physiologic’ characteristics of how central arteries change with aging (fig. 4). Characteristically, there is diffuse intimal thickening and medial thickening, increased deposition of collagen and collagen cross-linking, making the arteries stiffer. In contrast, the elastic fibers become fragmented. Arterial aging is also characterized by increased intimal and medial calcification, and amyloid deposition in the medial layer. For example, a novel protein that is responsible for generating the substantial amyloid depo-

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Fig. 4. Risky arterial aging. VSMC = Vascular smooth muscle cell.

sition in the arterial aortic wall is called milk fat globule protein E8, MFGE8. The breakdown product of MFGE8, called Medin, is an amyloid that has characteristics similar to amyloids found in the brains that are afflicted with Alzheimer's disease. Oxidative stress and low-grade inflammation are important factors in accelerating the vascular aging process by affecting molecules that lead to cellular and matrix structural and functional changes. The aforementioned events act in concert to make the central arteries stiffer, which will result in faster pulse wave velocity and early return of the reflection wave in the systolic ejection duration. As a result, the systolic blood pressure increases, diastolic pressure decreases, and the pulse pressure increases with aging. Chronic increases in pulse pressure, transmitted to the brain and kidney, damage the atrial system of those organs, leading to stroke and chronic renal failure (fig. 4).

S.P.: How would you define healthy vascular aging compared to pathologic vascular aging?

E.L.: I think on the one hand, it's a semantic issue. We might take issue with the phrase, 'healthy arterial aging'. What if there was no such thing as healthy aging? What if healthy aging is all a myth? The most logical way to understand what is going on in the arteries with increasing ages is to measure noninvasive parameters of vascular aging in a population cohort of varying age groups. If the population is large enough, the average degree of variability around the mean for any parameter can be assessed at different ages. For example, we can determine the mean value of aortic pulse wave velocity (fig. 5a) or carotid intimal medial thickness (fig. 5b) for a 50-year-old Caucasian male (fig. 6). If someone's pulse wave velocity is higher than the mean + standard deviation, we might argue that the vascular aging process of the person in question is accelerated. Another approach would be to attempt to establish the cutoff value of pulse wave velocity that is known to adversely affect long-term cardiovascular prognosis. Using such an approach, we can try to determine the independent risk factors that are associated with accelerated vascular aging.

Fig. 5. **a** Baltimore Longitudinal Study of Aging (BLSA) aortic pulse wave velocity (from Vaitkevicius et al.: *Circulation* 1993;88:1456–1462). **b** BLSA common carotid intima media thickness (from Nagai et al.: *Circulation* 1998;98:1504–1509).

J.B.P.: Is aging a disease? Isn't it just a risk factor? If vascular aging is a disease, what is the consensus to score vascular aging?

E.L.: That is an important question. Is aging a disease? This has been debated since the time when we have written records, and it's very difficult to answer (fig. 7a). Scientists try their best to separate aging, disease, lifestyle, genetics, and environmental effects from each other to learn about each of them (fig. 7a). But in one sense, this is artificial, because reality is precisely defined by interactions of age, disease, lifestyle, genetics, and environment that define our existence at any one time. How these interactions change over time results in a difference in how our organisms age (fig. 7b). I think there are certain new types of information becoming available that may help to make it easier to answer this question. There's a big gap between what's going on in the arterial wall and what can be measured in vivo under the microscope with respect to structure or function of the large arteries. To determine whether or not arterial aging is a disease, we have to really know what's going on in the arterial wall. Although what happens structurally in the arterial wall causes functional changes in arteries with aging, these are adaptive measures that our body uses. For example, when the walls of central arteries stiffen, indexed by aortic pulse wave velocity (fig. 5) and systolic pressure, they also remodel and dilate to lessen the impact of pressure. I guess that the major limitation for us to address this issue is that we do not have a definitive diagnostic test to determine the exact degree of vascular aging. The devices that have been used to measure pulse wave velocity have not really been standardized yet. They have different normal values that are established in different populations. Thus, you see how difficult it is to answer this question clinically. One must look into the arterial wall to determine whether arterial aging is a disease.

Arterial aging is the same in humans, nonhuman primates, rabbits, and rats (fig. 6). When you think of arterial aging as an inflammatory process associated with oxidative stress, the inflammatory patterns are the same for most species. Increased activation of the renin-angiotensin-aldosterone system and the sympathetic nervous system with the subsequent activation of the downstream receptor signaling cascades (fig. 8) are ways in which our body responds to chronic and acute stress, respectively. But this signaling results in additional oxidative stress and chronic inflammation that may accelerate arterial aging.

Fig. 6. Chronic arterial inflammation and arterial remodeling with aging, hypertension, atherosclerosis, and diabetes mellitus. VSMC = Vascular smooth muscle cell.

Another question is, when does the arterial aging process start? Is it a constant run-down? Or does it begin to accelerate after a certain age? I believe the answer to this question is the latter. Evolutionary biologists have been telling us for years that we are wired to be very healthy, most of us, until after the age of childbearing because the main reason for reality they would say is to perpetually generate the next generation. After that, in the evolutionary perspective, there is no reason for us alive after that point. However, we remain alive because our environment has been protected by better hygiene, better nutrition, better healthcare that keep us alive well beyond our evolutionary life expectancy. But in outliving our paleolithic gene set, the incidence and prevalence of cardiovascular diseases or arterial types of diseases become so high (fig. 9). What do you think the lifetime likelihood for hypertension for someone aged 40 with no clinical signs or symptoms is 85%. Unbelievably, 85% of people who are aged 40 will become hypertensive in their lifetime (fig. 9). And if their age is 70 and they don't have any clinical signs or symptoms, the likelihood remains to become hypertensive. This is the inevitability of aging in the context of what I portrayed earlier. So, I think that what we've learned, then, to nail down about the question of whether aging is a disease, is that what's going on in the arterial wall with aging looks exactly like experimental diabetes, early atherosclerosis, and hypertension in animal models (fig. 6). And you know what? If we knew more about what was going on with aging in the arterial wall when these diseases got their names, we probably wouldn't have named them the way that we do. We said that these diseases are accelerated aging with exaggeration of lipid, metabolic stress, blood pressure stress, etc. Regarding your question of whether or not aging is a disease, what's really going on is that the clinical medicine is focusing on arterial

Fig. 7. Interactions between aging, disease, genetics, lifestyle, and environment define reality.

disease diagnoses and treatment that is only at the tip of an iceberg of which aging is the base for most of the quintessential cardiovascular diseases. In this context, arterial aging may be considered to be a disease (fig. 6).

J.B.P.: So you told us the definition of arterial aging or the meaning of arterial aging in our life. But still, we are very curious about how accurately it is applied in the clinic. If I have patients who have high blood pressure, but I want to say, ‘You have high blood pressure and you are in your forties, but your vascular aging is much greater than your blood pressure’. So, in the clinic, how can we apply the idea?

E.L.: I think that a change in clinical practice, in this regard, may be long overdue. But we are on the verge of integrating the information that we are acquiring from epidemiologic studies about intimal medial thickening, arterial calcification, and arterial stiffening, which has been the first step in the identification of what is the appropriate arterial profile at a given age. The second step requires application of this knowledge to real-world clinical practices by designing and implementing proof-of-concept clinical research studies. Unfortu-

Fig. 8. Proinflammatory mechanisms of age-associated arterial remodeling. VSMC = Vascular smooth muscle cell.

nately, in many countries, it's impossible to do research that way because aging would be considered as a surrogate endpoint for disease, and treatment of surrogate endpoints may not be reimbursed. For example, in some countries, increased pulse velocity wouldn't be considered a disease and won't be reimbursed by the insurance system, because even though we know it's important, high pulse velocity or arterial stiffening is not considered to be a disease. That means you can't begin to treat it. There will be no reimbursement. So you can't 'get to first base' to start treating it. It's not a diagnosis, but we must learn how to change things to move in the right direction. I believe it is very important to have clinical trials to determine whether aggressive preventive treatment of patients with increased arterial stiffness and carotid intimal thickening affects clinical endpoints. Regarding what types of drugs to use to treat arterial aging, people in the hypertension field developed an important perspective. Physicians learned that when they treat high blood pressure, the drugs are segregated into those that could lower blood pressure only and those that in addition to lower blood pressure could alter the structure and function of the arterial wall. For example, β -blockers may be inferior to calcium channel blocker and RAS inhibitors in terms of reducing central blood pressure and carotid intima media thickness. So, we've come to understand that there are different categories of drugs that can work directly on the arterial wall to lessen arterial wall changes that evolve from the interaction of aging and elevated arterial pressure. But again, it's not that simple, because we have interactions of blood pressure and what's going on in the wall.

Fig. 9. Remaining lifetime risk for cardiovascular disease and other diseases among men and women free of disease at 40 and 70 years of age.

S.P.: What are some of the possible molecule targets maybe that could be a therapeutic target for retarding vascular aging? For example, there have been published reports regarding the genetic engineered mouse models of the Hutchinson Gilford Progeria Syndrome. There's been some data that interruption of prelamin and progeria formation in the nucleus, either by administration of farnesylation inhibitor or mTOR inhibitor, is very important in terms of retarding accelerated aging. I believe there are clinical trials underway for patients with Hutchinson Progeria Syndrome. Also, there are some data which show that even in a normal aging process, not just Progeria Syndrome, the enzyme ZMPSTE-24 which transforms prelamin A to mature lamin A is defective. So are there any other possible molecule targets?

E.L.: Yes. Every molecule is a potential candidate. What I told you before is true. All aspects of molecular signaling (fig. 6) are probably changing as we age.

S.P.: Do you believe there is a common pathway?

E.L.: Well. There are some, but let me try to say it this way. There are countless, numerous pathways that become inflamed. Many of these pathways are downstream from the angiotensin (AT) II receptor. There are many factors, such as Klotho, BMP1, osteocalcin, and osteopontin, which are related to the vascular calcification process. You could target MMPs which are involved in the vascular remodeling process as are calpains. The MMP inhibitors have been tried, but serious side effects of tendinopathy have been a major roadblock. SIRT1 and reactive oxygen species (ROS) and related molecules are also very important in the aging process. SIRT1 and ROS systems are connected to IGF signaling, AMP signaling, and mTOR, which are all important products of the longevity genes (fig. 6). But there is a complex network of signaling processes that accelerate and/or retard aging. Let's say you have a real big office, Dr. Park. The entire network of the signaling processes will cover all of the walls of your office and ceilings and everything will be interconnected. It is via the complexity conferred by these redundancies that nature has made organisms so robust. So, I don't believe that there is a single common pathway that we can control to prevent arterial aging, but we can try to define critical nodes within these interconnected signaling systems and start by targeting those. The more proximal the node within the system, the better the likelihood that perturbing it will be successful. In this regard, targeting AT II or its AT receptor, or aldosterone and its receptors (fig. 8) makes perfect sense. And guess what? The drugs required for this are already at hand and approved for clinical use for exaggerated forms of arterial aging, i.e. hypertension and atherosclerosis.

S.P.: Your slide mentioning the caloric restriction is very interesting because there is a current best-selling book in Korea regarding a fad diet that is a craze in Korea now. It is written by a Japanese physician who champions eating one meal a day will increase your longevity. Although there are data regarding the beneficial effects of fasting in retarding aging in primates, do you believe this is so in humans?

E.L.: There are different types or degrees of caloric restriction. One type is every other day feeding. Another is just eating one meal a day, but having your body be hungry for a while. It's likely to be related to preconditioning the protection against a severe heart attack by short bouts of ischemia. I believe there is a benefit to mild to moderate caloric restriction. Caloric restriction is really interesting from an energy expenditure point of view. And what if you think about it in this way: that as we age, one thing that's happening is that our ability to curtail excessive ROS production becomes less efficient. Eating lots of food generates free radicals. When we are older, we can't quench all of the free radicals generated. So, we end up with oxidative stress that goes beyond normal redox signaling. So, theoretically, caloric restriction is a sound strategy to reestablish a proper balance between oxygen free radical formation and our machinery to quench the free radicals. This may be a factor in why two recent major studies performed in nonhuman primates differ with respect to the beneficial effects of caloric restriction. A study from the National Institute on Aging did not show any benefit, whereas a study from the University of Wisconsin showed caloric restrictions improved longevity. What you need to consider is that when we put animals in captivity and allow them to eat as much as they want to (which we conveniently consider the control group), their longevity becomes reduced. When they are calorically restricted, there's a shift to a longer life span, but this is really only allowing the achievement of their normal life span. This is an important issue to consider with regard to caloric restriction. With regard to extreme caloric restriction, such as that championed by the Japanese author mentioned earlier, I have no answer at this time.

Further Reading

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