Alan Daugherty: cardiovascular research takes courage to roll with the punches

Submitted Jul 24, 2018. Accepted for publication Jul 24, 2018.
doi: 10.21037/jtd.2018.07.121
View this article at: http://dx.doi.org/10.21037/jtd.2018.07.121

Editor's note

Urban dwellers are prone to a series of unhealthy lifestyles and conditions—unbalanced diet, lack of exercise, stress, smoking, high blood pressure, high cholesterol levels, diabetes and obesity, which in fact are all risk factors accelerating the abnormal condition of the blood vessels, and are likely the causes of a variety of vascular diseases—stroke, abdominal aortic aneurysm, atherosclerosis, coronary heart disease, peripheral artery disease, carotid artery disease and so on. Stroke is a leading cause of disability in the United States (1). Just abdominal aortic aneurysm alone causes over 175,000 deaths worldwide (2). Coronary heart disease is estimated to claim over 7 million lives every year (3). Vascular diseases-induced deaths could happen in every second, in every breath, and pose potential risk and danger to anyone of us.

Dr. Alan Daugherty, Associate Vice President for Research, Senior Associate Dean for Research, Director of the Saha Cardiovascular Research Center, and Chair of Physiology at the University of Kentucky, Lexington, KY, has been spending four decades of efforts examining the molecular mechanisms of vascular diseases with a more recent focus on the role of renin angiotensin system, commonly considered a hormone system regulating blood pressure and fluid balance, in vascular diseases like atherosclerosis and aortic aneurysms. In an interview with *Journal of Thoracic Disease* (*JTD*), Dr. Daugherty shared with us his insights into the renin angiotensin system in vascular diseases, the technical problems in extrapolating from animal models to human trials, the sex differences in angiotensin-induced vascular diseases, as well as some challenging and interesting aspects of his research.

Figure 1 Dr. Alan Daugherty.

Expert's introduction

Alan Daugherty, PhD, DSc, currently serves as the Associate Vice President for Research, Senior Associate Dean for Research, and Chair of Physiology at the University of Kentucky, Lexington, KY, USA (*Figure 1*). He is also the Director of Saha Cardiovascular Research Center and Gill Foundation Endowed Chair in Preventive Cardiology at the same university.

Dr. Daugherty's research is primarily focused on molecular mechanisms of human vascular diseases, specifically the role of the renin angiotensin system in atherosclerosis and aortic aneurysms and the development of reagents including conditional cell specific deficient mice, vectors using adeno-associated virus and a pharmacological approach in antisense oligonucleotides. He has been leading a number of NIH-funded research projects such as "Mechanisms of thoracic aortic aneurysms", "Adventitial-medial interactions in thoracic aortic diseases", and "Atherosclerosis mechanisms: Angiotensin II production and action", as well as an American Heart Association-funded strategically focused research network center program "Sex differences in angiotensin-induced vascular disease".

Dr. Daugherty has been actively involved in a variety of

academic activities. He has memberships in a wide range of learned societies, such as American Heart Association, American Physiological Society, American Society for Investigative Pathology, Arteriosclerosis, Thrombosis and Vascular Biology Council of the American Heart Association, British Pharmacological Society, British Society for Cardiovascular Research and International Atherosclerosis Society. Besides, he is also keen on academic publishing, such as writing a multitude of original research manuscripts, educational materials, book chapters, reviews, editorials and so on.

Interview

JTD: What is the role of renin angiotensin system in vascular diseases such as atherosclerosis and aortic aneurysms?

Dr. Daugherty: Activation of the renin angiotensin system may exert numerous adverse effects on the cardiovascular system, such as promoting atherosclerosis and aortic aneurysms. Experimentally the system has a really dramatic and consistent effect on these diseases. In terms of extrapolating from animals to humans, there have been quite a few clinical trials for atherosclerosis that are very consistent, whilst those for aortic aneurysms are not so consistent. It has been consistent that in the experimental world we will be able to antagonize the effects of the system effectively, whereas in humans the effectiveness has not been as satisfactory as we do in animals. This does not negate the importance of preclinical research. However, there are many confounding factors that need to be taken into consideration for translational research from animals to human uses. I still hope that there is a very profound effect of the system on both atherosclerosis and aortic aneurysms even in humans. In terms of mechanism, despite how consistent the system has an effect on these diseases, we still lack information on mechanisms that promote these diseases. This is an area that needs a lot more attention—if we could really define what the mechanism was, we can refine the approaches for human use instantly.

JTD: Your animal model has led to a clinical trial that determines the effects of renin inhibition on preventing the progression of coronary atherosclerosis in humans. Using this as an example, what are the points of attention when bringing an animal model to a human trial?

Dr. Daugherty: That's always a big question—it's hard to find a cutoff point where the animal model could be productive in humans. I'd say it's helpful if the effects in animals are very large and reproducible by multiple research groups and multiple animal strains. When we see effects on diseases in animal models that are statistically significant, but not that big, I think the chances of extrapolating from animals to humans is lower. We do not know if the animal models are very predictive of the human disease. One major shortcoming of animal models is that the experimental intervention is usually initiated at the same time the disease is initiated. This is very different from the clinical environment—patients will have atherosclerosis for many years before an intervention is started since the disease has no overt clinical symptoms in the early phase. They usually start getting therapy only after having clinical symptoms. In other words, for both atherosclerosis and aortic aneurysms, we treat people who have the diseases, not people who might get the diseases. Therefore, it's much more difficult to investigate in human situation. One example is what you mentioned about our renin inhibition study that prompted a clinical trial. In our initial prevention study (we gave the drug before the atherosclerosis started to form), renin inhibition prevented the development of atherosclerosis in mice (4), but this effect was not impressive as this initial study in our later regression study when we gave the drug after the disease formed and advanced in mice (5), which mimicked the human clinical situations.

JTD: What are the current status of these trials?

Dr. Daugherty: In the atherosclerosis world, it is unclear that there will be many subsequent large trials. The early trials when I first got into this 20 years ago demonstrated the inability of angiotensin-converting-enzyme (ACE) inhibitors and angiotensin-receptor blockers (ARBs) to reduce cardiovascular death. In the aneurysm research world, there have been a few limited trials throughout the world that have looked at the ability to inhibit the action of angiotensin on both abdominal and thoracic aortic aneurysms. Unfortunately, only one trial has been completed for abdominal aortic aneurysms, which failed to show any benefit (6). The trials looking at the ability to inhibit angiotensin actions in thoracic aortic aneurysms are being mixed with the biggest one in the US, showing no additional benefit over statin therapy (7). One thing that I keep emphasizing is that angiotensin receptor blockers have very different properties. The drug used most commonly in these trials is losartan, which is the first drug of angiotensin

receptor blockers. While it is an angiotensin receptor blocker, it has a short half-life and less effectiveness in antagonizing angiotensin than other drugs in this class. I think it would be better to use one of the newer drugs that has much preferable profile. One of the trials is using irbesartan that I hope will show superior benefit.

JTD: In a study that you are co-investigating, you examined the sex differences in angiotensin-induced vascular diseases. What are the reasons causing such differences?

Dr. Daugherty: This is a study led by my colleague Lisa Cassis. It came about because we accidentally noticed that in our animal model with abdominal aortic aneurysms, there was a profound sex difference. The incidence of abdominal aortic aneurysms was much lower in females than in males. This is consistent with the human disease. The mechanism of this sex difference is not clear. Lisa Cassis's lab has been exploring hormonal influences on the disease. Testosterone does not seem to be a good thing in terms of abdominal aortic aneurysms, which certainly is one of the lines of investigation. Another fact is that male and female have different chromosomes—male having XY and female having XX. X chromosomes contain many genes, and the expression could differ between males and females. Genetic differences determined by the X chromosomes could lead to the sex differences of abdominal aortic aneurysms. Lisa Cassis has been able to manipulate chromosomes and hormones so she can make a male mouse to have the chromosomes for female (8). It's a very complex experiment, but Lisa has made significant progress to demonstrate there is chromosomal involvement in the sex differences of the disease.

JTD: Would you introduce us to a recent NIH-funded research project that you are involved in?

Dr. Daugherty: My colleague, Hong Lu, and I just received a 4-year grant from NIH. The emphasis of the grant is studying the effects of the renin angiotensin system on atherosclerosis. We have consistently shown the effect of angiotensin on atherosclerosis in multiple mouse models, but we have been unable to determine where the angiotensin is synthesized and how it is acting to cause the disease. We have spent many years looking at different approaches. If we inhibit angiotensin production in the kidney, atherosclerosis is diminished. Therefore, our study is trying to determine whether kidney is the location for angiotensin to affect atherosclerosis. One of the mechanisms that we are looking at is what causes the synthesis of angiotensin in such a local area and how it transmits a signal from the kidney to the atherosclerosis-prone arteries. We do not have direct evidence now and this concept has not been widely embraced, but we have planned over the next 4 years to show that the renin angiotensin system within the kidney is indeed a very profound factor of atherosclerosis.

JTD: What do you regard as the most difficult aspects of doing research?

Dr. Daugherty: Our type of research takes a long time. For example, in the experiment that I have just mentioned, we have had to make genetically manipulated mice and that has taken a year and a half. We have to breed and crossbreed them to the sufficient number, and it may take 2 to 3 years just to get mice to start an experiment. The atherosclerosis experiment can take 3 to 6 months, in addition to a few weeks to a month for analysis. Sometimes it takes many years to come to an end result. Therefore, it's important to stay focused on what we have been doing over those many years, keep the funding going, and hope to get results that will be sufficiently exciting to continue the research.

JTD: Seeing that these researches often take a long time to get a result, how do you motivate yourself and your team to keep moving forward?

Dr. Daugherty: I really like being in research. I like reading and writing papers and I like giving presentations. One interesting aspect of research is that it takes stages and thus you will be continuously producing new data and interacting with people that brings new research.

JTD: What would be your advice to young researchers who would like to be successful?

Dr. Daugherty: A lot of young people are a little dispirited because they think doing research is a tough life. I usually tell them that I've been doing this since starting my PhD in 21. Now—40 years later—I'm still doing research and I still really enjoy what I'm doing. One exciting part of scientific research is that you can enjoy it for a life time and you can still work and write when you are really old. I'd say 61 is actually not that old for science since I've still got a long time to do research. It might be

pretty tough at the beginning as you struggle to establish yourself and make sure people know your identity as a researcher. At certain point, you will manage to establish yourself—it doesn't mean you can just rest and do nothing, but it does make it a lot easier to keep going. One of the most important issues about getting on in research is being persistent. You are going to get a lot of knocks—just roll with the punches, and when people criticize you, take that positive mode and move up.

Acknowledgements

We would like to express our sincerest gratitude to Dr. Alan Daugherty for sharing his insights and opinions with us. Alan Daugherty's research work is supported by NIH grants (HL133723 and HL139748) and by the American Heart Association Strategically Focus Network Grant in Vascular Disease.

Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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Cite this article as: Li B. Alan Daugherty: cardiovascular research takes courage to roll with the punches. J Thorac Dis 2018;10(8):E646-E649. doi: 10.21037/jtd.2018.07.121