From the Swimming Pool to Precision Cardiovascular Physical Therapy: What a Journey!

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Good afternoon. I would like to start by thanking the American Physical Therapy Association's Academy of Cardiovascular and Pulmonary Physical Therapy, its awards committee, and those who nominated me to receive this prestigious award. I did not have the chance to meet Dr. Linda Crane. According to previous awardees of this award, she was a trailblazer, a great clinician, and a very kind person.[1-7] Receiving this award with her name and reading from other trailblazers, great clinicians, and kind persons is humbling to the core.

For those who know me, I always say that I am not from this planet, especially when dealing with topics from the American culture. This lecture is a story on how I have found my tribe here in the United States, and how, I hope, the tribe will learn something from my planet. I always like to start my talks with this quote from Albert Einstein, "imagination is more important than knowledge" because I think that creativity and thinking outside the box is always something that we need to encourage our students and colleagues.

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As some of you know, I am originally from Chile and a former swimmer. Someone once said that Chileans are the British of South America. Not because of a kingdom or really good manners, but because of the sense of isolation. We are way down South, behind the Andes Mountains, beside the driest desert on earth, and bathing in the Pacific Ocean. Back in the old days, nobody wanted to visit because it was hard to get there. People from Europe always ended their journeys either in Brazil or in Argentina, and this is why Brazil and Argentina have much richer cultures and exchanges with the rest of the world. Swimming was my way to escape this sense of isolation. Not that I started swimming my way out in the ocean but by having the chance to travel and see other places. Competing for team Chile, I was able to see the world.

I was lucky. I grew up in a stable middle-class family. My dad was an entrepreneur, I knew at least 6 different businesses that he tried and succeeded in and many others where he didn't succeed, and retired as a department store supervisor. He taught me that nothing comes easy and that hard work always pays off. My mom was a high school biology teacher. She taught me about the power of education and science. She was always grading papers and learning new things from different certificates, diplomas, and professional development courses. She still teaches. In fact, my students have learned from her as she has had several health conditions related to PT and cardiovascular pathophysiology that make her the perfect case study. Her last lesson was a perfect cardiopulmonary case when she survived Takotsubo syndrome 9 months ago.

This culture of hard work and science ignited a need to learn how things worked. I lost count of how many wristwatches and portable transistor radios I took apart in the 80s. In high school, I thought that engineering was my

path as I wanted to create stuff, until we had a biology laboratory where we dissected a rat. It blew my mind away. I wanted to know how the human body worked. It changed the way I would apply for college. As a high-performance swimmer, I always loved physical activity. Therefore, the natural path was … being a swimming coach. I did not want to be a surgeon, which was the second option. I did not know what physical therapy was, as I never got injured and I was never exposed to rehabilitation. But luck struck again. I got accepted to the only Kinesiology school in Chile at that time.

Before I move on, I need to disclose some differences between the United States and the Chilean educational systems and show you that the same words can mean different things, especially in different worlds. First, there is not an undergraduate education in Chile. You go from high school to professional school; PT is a five-year degree. The first 2 years you take several general and foundational courses, what would be considered "prerequisite" here in the United States, but these courses are connected to your next 3 years: Two years of PT didactics and 1 years of clinical rotations. It is similar to the United States, but it is straight from high school, which has pros and cons. The pros are that you can get your degree in 5 years instead of 7. The downside is that most of the people are not ready to accomplish high-level learning when they are just 18 years old. There are multiple people who I know, in their third year of PT school are getting into the real PT school content, leave because they discover it is not for them. And when they move to another profession such as medicine, dentistry, law school, etc., they need to start from zero. Some people can think that this five-year model is better, but I think that the undergraduate education here in the United States allows for greater maturity for students to understand what they really want to be. Second, early PT in Chile was influenced by Europe, especially Belgium, where PT is called "Kinésitherapie", or in Spanish "Kinesioterapia". Translated that means Kinesiotherapy or therapy through movement. During the late 80s and early 90s, there was only 1 school of Kinesiology or "Kinesiología," which in Chile means "clinical movement sciences". This is the school that I went to. It has a focus in 3 applied sciences, critical thinking, and evidence-based practice (EBP). These 3 applied sciences were applied anatomy or biomechanics, applied physiology or exercise physiology, and applied neurology or neurorehabilitation. The other 3 schools that we had in Chile at the time were called "Kinesiterapia". These schools were more technical schools with less EBP and applied sciences. The professional degree is "Kinesiólogo" or Kinesiologist. That is what PTs are called in Chile. In early 2000, all the schools became kinesiology schools. All the schools that were called "kinesiterapia" saw the value of centering more on applied sciences and EBP than just the technical aspect. Finally, and because of the aforementioned factors, PT practice in Chile looks different than that in the United States. There is no exercise science because we do not have an undergraduate education and people do not have the option to have a bachelor's degree in exercise science, so they go into physical education. It is a professional school because we need teachers in the schools or coaches in the athletic environment. In addition, we do not have athletic trainers. Moreover, we do not have respiratory therapy or chiropractors as professional paths. Chilean PTs do all the above: athletic rehabilitation, respiratory therapy, and spinal manipulation. I like to think about my Chilean colleagues as Swiss Army knives. However, we do not have direct access, except for respiratory therapy during wintertime, where Chilean PTs can diagnose and treat upper respiratory illnesses to prevent hospitalizations and deaths in children and the elderly.

My early professional years were full of several interesting activities. First, and as soon as I finished PT school, I did a post-professional diploma in exercise science. I went to Argentina to the Biosystem Institute to work with Dr. Juan Carlos Mazza, who was trained by Dr. David Costill at Ball State University in Indiana, where I learned about the use of lactate metabolism as a marker for exercise intensity. In addition, I got introduced to the American College of Sport Medicine and its annual meeting, which I attended for the first time in 1998. Then I worked as a clinician for 15 years in cardiovascular rehabilitation, sports rehabilitation, and sports performance. My background gave me the tools to be able to combine these 3 things and most of my patients in cardiovascular rehabilitation were training using the same principles as high-performance athletes.[8] In 1998, I got an adjunct position in the School of Kinesiology (i.e. Physical therapy) at the Pontificia Universidad Católica de Valparaíso, where I moved up the ladder from a young adjunct professor to tenured faculty.

So, what do you do after 15 years in the profession, you have your own clinic with many patients, and athletes that follow you? In fact, I had 2 clinics. I was tenured in a PT school. I was doing research. I was teaching. I was doing service. I was living in a nice place by the beach. So, what would you do? Well, you go back to school. I moved thousands of miles north to the University of Florida to pursue my PhD. I wanted to have a PhD in exercise physiology, something that is not very common right now. During my gator years, I first went to the College of Health and Human Performance in the Department of Applied Physiology and Kinesiology. Dr. Randy Braith accepted me in his laboratory as a research assistant. It was an amazing experience where I learned many noninvasive cardiovascular assessment tools, as well as some invasive techniques such as endothelial cell biopsies. I'll be forever grateful to Randy for taking me into his laboratory. Then, when I finished my PhD, I went to the School of Medicine at the University of Florida Department of Physiology and Functional Genomics to do my postdoc. Instead of having 1 mentor, I had 3 mentors: Dr. Judy Delp who taught me a lot of in situ techniques in vascular biology, Dr. Chris Baylis who was the director of the Hypertension Center at the University of Florida and taught me about vascular

regulation in the kidney, and Dr. Debbie Scheuer who taught me about cardiovascular control in the central nervous system.

In 2011, it was time to make a decision: to stay or not to stay in the United States? On the one hand, I had my job in Chile, my whole family in Chile except for my wife who was with me, and I found things a little complicated here in the United States. Why are there so many different people working in the same field but do not work together? For example, a clinical exercise physiologist, who has a bachelor's or a master's degree in kinesiology (kinesiologist) with an ACSM certification and working with patients. Well, is not that a PT? Why do we need clinical exercise physiologists if we have PTs? Or a biomechanist with the same bachelor's or master's degree in kinesiology working in biomechanics? I was educated like a PT. We deal with biomechanics every time you treat a patient. Why are they so siloed here? Why things are so different? On the other hand, and even though I was in a kinesiology department, I learned more about the PT world in the United States. I had a spy at the Department of Physical Therapy at University of Florida: My wife Carolina. My wife was pursuing her PhD in Rehabilitation Sciences at the same time as me, under the mentorship of Dr. Steve George who most of you know and is the new editor-in-chief of the PT Journal.

So, Carolina introduced me to this PT environment with Steve, Krista Vandenborne, Carolyn Pattern, Mark Bishop, and others, and I was able to understand the differences in clinical practice a little better. However, I really was at the edge of a neuropsychiatric disorder wondering "Who am I"? What can I do with everything I've learned? I was like Jean Valjean from Les Misérables asking "Who am I"?[9] I had 3 options: (1) I could have gone to a Kinesiology department as I had a really good network and I was in one of the best departments of the nation; (2) I could have gone to a medical school's physiology department like many of my peers and I had another great network in physiology through experimental biology; or (3) I could go to a PT school where my network was very limited, but I knew that they were looking for PT faculty with terminal academic degrees. As Jean Valjean, I was not able to deny my roots—I'm a physical therapist. Therefore, I applied to 24 DPT programs in the United States. There were at least 10 programs that did not even send me an email after my application. I qualified for 8 phone interviews. I might have done pretty well on the phone interviews because I qualified for 6 campus interviews, but I received only 1.5 offers. When negotiating with the dean or chair, I said that my wife also needed a job and she was finishing her PhD with Steve George, so it was a "two for one" situation. One program said no and the other 1 said yes; therefore 1.5 offers.

We moved to Indiana State University (ISU) in Terre Haute, Indiana, in the middle of the Midwest. Terre Haute, Indiana, at the crossroads of America, was a good place. We were an hour from Indianapolis, 3 hours from Chicago, and 2-and-a-half hours from St. Louis. The truth is that we learned a lot. First lesson: ask harder questions during your job interview. We arrived in January 2012, and in March 2012, Indiana State decided to rebuild their DPT program. The chair of the department called us to a meeting and said "please don't come tomorrow because we're going to let everybody in the program go except you two. We need to do this DPT program from scratch". Second lesson: use your time wisely. As I was not teaching the first semester at Indiana State, I studied to take the NPTE, which I passed in the first attempt in October 2012, and shortly after I received my PT license. Third lesson: CAPTE accreditation is not that hard, just read the manual. In Fall 2014, almost 2 years later, we accepted our first DPT cohort. It was a great experience. Building the program from the ground up teaches you how to build a good PT program. Final lessons: there are other amazing health care professions, and academia in the United States is not easy: As the DPT program did not start until 2 years later, I taught in the physician assistant and occupational therapy programs. There, I learned that some programs are more rigorous than others. In addition, I was able to learn that faculty members are not protected from the department administration drama (a.k.a. departmental politics), and nobody teaches that in the PhD programs. In Spring 2017, I applied for the DPT program director position at The University of Texas at El Paso (UTEP) and we moved to El Paso that summer. UTEP is not BY the border, it is ON the border and the experience is unique. We have the best students that you can imagine. It is a fantastic group of diverse people that bring so much to the table. In Fall 2023, I was promoted to full professor and chair of the new Department of Physical Therapy and Movement Science. I will always be thankful of Dr. Loretta Dillon who picked me up at the airport during my interview and showed me around. Although the first impression was not the best, the institutional environment and culture were amazing, and the city had so much to offer—It is the best place ever.

Once I decided to pursue an academic career in the PT field, I knew that I had to be intentional in my APTA engagement. First, and in the middle of my psychosis trying to figure out who I was, I went to my first CSM. I immediately felt that I belonged here. It was like Percy Jackson going to the Half-Blood Camp.[10] All these conflicts with multiple professional personalities (e.g., clinical exercise physiologists and biomechanists) that did not make a lot of sense in my head, went away when I was able to be around physical therapists, especially when I saw Todd Davenport's talk about chronic fatigue syndrome in 2013. Then, I went to the cardiovascular and pulmonary section business meeting and I was able to learn who Ethel Frese, Ellen Hillegass, Dianne Jewell, and Dan Malone were. I do have a special memory about Ellen Hillegas: It was my first CSM, my first section business meeting and Ellen oversees the coding and reimbursement committee. I wanted to create a cardiovascular rehabilitation program at ISU, and I approached her to ask her questions about how I could bill and which codes I was able to use. She gave me some great ideas to make it happen. Unfortunately, and although I had Ellen's full support, the DPT program

director did not support the idea, and the project died. Despite the negative outcome, a few months later, a colleague from ISU, Kelly Hannigan, met Ellen at an NPTE item writing session for the FSBPT. When Kelle came back, she said "Al, Ellen Hillegass, said hi." I was like, what? Wait? Why? How does she remember that I exist? I'm nobody. And that completely blew my mind. So, Ellen thank you very much for remembering me and supporting new members the way you do. In 2014, I went to my second CSM in Las Vegas. I had a really bad cold and I barely remembered some of the lecturers. However, there was 1 that I remember well: Larry Cahalin's talk about predicting the future and how prognosis can change practice. This lecture also made me figure out that I was in the right place, a place with a common language. This is what I was looking for—how we can change practice, how we can do things better than anybody else, and move the profession forward. I heard Larry's stories about cycling and moving to California to learn new things to be a better clinician and academician. That is when I learned that I was not alone in this pursuit of new knowledge and that I was not the only one moving across country to enhance clinical outcomes. In that year, Chris Wells invited me to review grants for the section. I will be always grateful for Chris' friendship and the chance she gave me to meet phenomenal people like Amy Pastva, Kristin Lefebvre, Bobby Belarmino, and many others at these sessions. And I started feeling that I belonged somewhere.

In 2015, I started reviewing for Cardiopulmonary Physical Therapy Journal (CPTJ). I submitted one of my first articles to CPTJ, and it was published in 2013.[8] Shortly after, Sean Collins invited me to review my first manuscript. I might have done a good job as he asked me to be a guest editor with Rich Severin for a special issue on applied physiology.[11] It was a great experience, and I was able to find another good colleague, with a common language, with whom I could talk and brainstorm about future collaborations. In 2019, Sean asked me to associate editor of the Journal, and I immediately accepted. In 2021, Sean stepped down from the journal, and he proposed that I continue as an interim editor-in-chief. In 2022, I became the permanent editor-in-chief with an amazing team to support the CPTJ. Thank you, Todd Davenport, Kristin Lefebvre, Suh-Jen Lin, John Lohmann, Darlene Reid, Rich Severin, Mike Shoemaker, Jennifer Alison, Larry Cahalin, Joseph Norman, and Chris Wells. This is a team; it is not a one-person band. I try to keep the boat afloat, but the brilliant minds that we have here are the ones that really make the difference in the Journal. And last year, I jumped into something new for me: the Heart Failure Clinical Practice Guideline Group. Now I am working with Ashley Poole, Mike Shoemaker, Konrad Diaz, Morgan Johansson, John Heick, and Kristin Lefebvre, and it has been absolutely unbelievable. I have learned so much from these amazing people. That is why the Academy of Cardiovascular and Pulmonary PT is my home. I feel blessed to be part of this amazing organization. I am so thankful for finding my tribe. And I feel like finally I belong somewhere. I found my world. I found my tribe. For all that matters, thank you all very much. Now, let's show the tribe what I think is precision PT in cardiovascular rehabilitation.

At CSM 2019, Dr. Eric Green, director of the National Human Genome Research Institute at the NIH, and Dr. Richard Shields, chair of the Department of Physical Therapy and Rehabilitation Science at the University of Iowa, presented "Personalized PT." It was an amazing and inspiring presentation. Dr. Green showed the history and background behind the Human Genome Project and how the cost to run a full human genome analysis has dropped from $100 million to $1000 in less than 2 decades. Faster and more accessible sequencing technology will allow for the effect of any clinical intervention to be able to be monitored by changes in gene expression in the near future, including PT. Dr. Shields' presentation focused on the current studies led by physical therapists in this field. For example, Dr. Shields' group has shown how movement/exercise can affect the epigenome of the musculoskeletal system.[12] Every time we move, every time we have muscles contracting and tendons pulling over levers, we have genes being activated or deactivated. From the PT perspective, especially in orthopedics, exercise prescription will have a direct effect on gene expression. Is there a direct effect of exercise in cardiovascular-related genes? Catherine Curtis et al.[13] showed several examples where PTs can be involved in genomics. In the cardiovascular system, for example, there are a set of genes (e.g. SNP@9p21) that explain 10.6% of the coronary artery disease (CAD) heritability. However, the impact is considered modest, and there is not enough evidence to see if these genes would change with environmental changes, including physical activity. Are there other genes that PTs could impact with their exercise prescription from the cardiovascular perspective?

According to the CDC, heart disease and stroke are responsible for 26.4% of all deaths in 2022.[14] If we consider that 90% of all heart diseases and stroke are associated with atherosclerosis,[15-18] we could estimate that 23.8% of all deaths are associated with atherosclerosis, being by far the number 1 cause of death in the United States. Therefore, if we want to prevent all of these deaths, we need to understand atherosclerosis pathophysiology, and, maybe, we can find some genes we can modify with our interventions. Atherosclerotic plaque formation—or atherogenesis—is the pathophysiologic event responsible for either a chronic decrease in arterial lumen size or an acute thrombus formation, which produces an acute ischemic event.[15,19,20] The first pathophysiological step toward atherosclerosis is endothelial dysfunction (ED) and is related to a decrease in nitric oxide (NO) bioavailability and an increase in endothelial oxidative stress. According to current medical theory, ED is the primary cause/the primary event of atherogenesis.[15,19-21] The endothelial cell monolayer helps to regulate homeostasis of the vascular system by producing antithrombotic, anti-inflammatory, and antiadhesion molecules, with NO being the most

important.[21-23] Decreased NO bioavailability, which is associated with an increase in endothelial oxidative stress, produces a cascade of events including oxidation of LDL cholesterol, activation of adhesion molecules, leukocyte recruitment, and foam cell formation, which becomes a vicious cycle and the basis of atherosclerotic plaque formation.[15,19,21,22] The transition from normal endothelium to a vulnerable plaque is 10 and 20 years in the making, depending on your family history (also known aa genes) and environmental factors.[15,19,20] Therefore, when you have a heart attack in your 40s, it means that you started having ED when you were in your 20s. There are multiple diseases that are directly associated with atherosclerosis. Besides CAD and stroke, peripheral artery disease, renal artery disease, and aneurysms are also associated with the same pathophysiology.[15] Currently, all cardiovascular risk factors, such as smoking or dyslipidemia, have been linked to either increased endothelial oxidative stress or decreases NO bioavailability. Nitric oxide has been shown to be an excellent antioxidant, which decreases the chance of LDL oxidation therefore decreasing the expression of adhesion molecules, monocyte adhesion, and foam cells formation.[15,20,24,25] In summary, increased NO bioavailability enhances endothelial health and prevents atherosclerosis.

There are 2 physiological pathways to produce NO: an acetylcholine-mediated biochemical pathway and a hemodynamic-mediated mechanical pathway.[26] Interestingly, the mechanical pathway is more physiological, as it depends on arterial exposure to regular blood flow–derived shear stress, allowing for a more natural endothelial cell homeostasis.[27-30] Then, blood flow will produce sheer stress on the endothelium and will activate the glycocalyx, which is a flow (mechanical) receptor on the free endothelial cell membrane facing the lumen of the artery. The work from Davies et al.,[28] with their decentralized model of endothelial mechanotransduction by shear stress, and Thi et al.,[31] with their electronic microscopy images of the glycocalyx, were fundamental in understanding how the endothelial cell layer works. The activation of the glycocalyx will start 2 cascades of events mediated by mechanotransduction (Fig. 1). On the one hand, the activation of the glycocalyx will open transmembrane calcium channels and activate a G-protein receptor, which are key elements in the activation of the endothelial NO oxidase (endothelial nitric oxide synthase (eNOS)) enzyme and NO production (Fig. 2). On the other hand, an intracellular mechanotransduction system formed by intracellular actine and stress fibers will mechanically activate the cell nucleus to elicit different gene expressions (e.g., eNOS, actin, and stress fibers). In addition, 4 weeks of endurance exercise training can increase eNOS expression and decrease endothelial oxidative stress (Fig. 2).[32] When I learned these different pathways during my PhD and postdoc, it blew my mind. This was exactly what I was

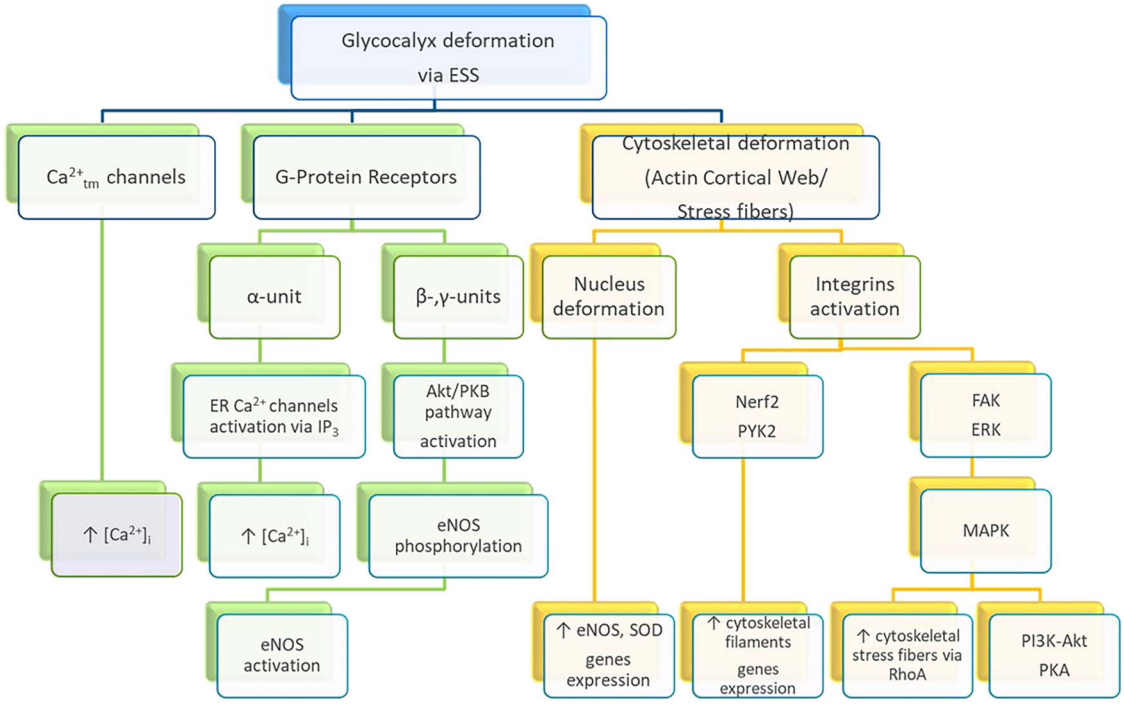

Fig. 1. Schematic representation of the biochemical (left-hand side in green) and mechanotransduction (right-hand side in yellow) cascades of events that happen when the endothelial glycocalyx is activated through increased ESS. On the left-hand side in green: Akt/PKB, protein kinase B; eNOS, endothelial nitric oxide synthase; ER, endoplasmic reticulum; i, intracellular; IP3, Inositol trisphosphate; tm, transmembrane. On the right-hand side in yellow: Akt/PKA, protein kinase A; ERK, extracellular signal-regulated kinase; FAK, focal adhesion kinase; MAPK, mitogen-activated protein kinase; Nerf2, transcription factor; PI3K, phosphatidylinositol 3-kinases; PYK2, protein tyrosine kinase 2-beta; RhoA, Ras homolog family member A; SOD, superoxide dismutase.

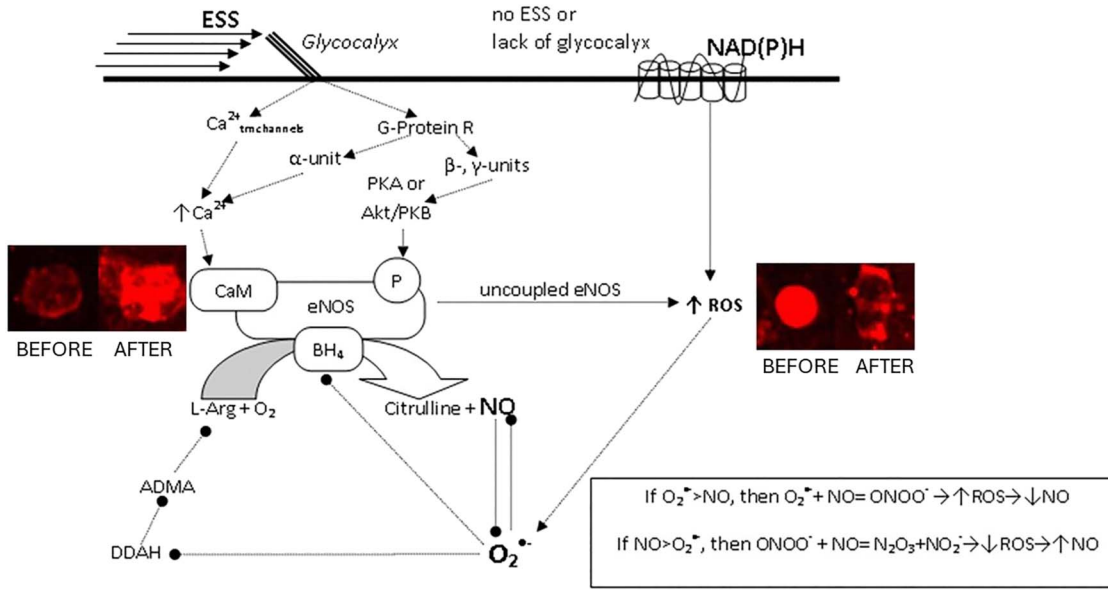

Fig. 2. Schematic representation of endothelial sheer stress (ESS)–mediated activation of the glycocalyx, and the tide balance between NO bioavailability and oxidative stress. In normal physiological conditions, ESS produces a mechanical activation of calcium (Ca) channels and G protein receptors which, on one hand, will increase intracellular Ca binding to calmodulin (CaM) to activate eNOS on its reductase domain, and, on the other hand, beta and gamma subunits will activate phosphor kinase A and B (PKA and Akt/PKB) pathways to phosphorylate (P) eNOS. Once activated, eNOS will synthesize NO from L-arginine and oxygen with the help of tetrahydrobiopterin (BH_4) as an important cofactor. When ESS is decreased or flow receptors are downregulated, there is an increase in reactive oxygen species (ROS) production through NADPH oxidase. This increase in superoxide ion ($O_2^{\bullet-}$) will inhibit BH_4, uncoupling eNOS and producing a further increase in ROS production. Moreover, $O_2^{\bullet-}$ will inhibit dimethylaminohydrolase (DDAH), which normally inhibits ADMA, increasing this eNOS competitive inhibitor, and further decreasing NO production. Vascular endothelial cell redox balance is highly dependent on NO as the major antioxidant. Therefore, if $O_2^{\bullet-}$ production is larger than NO production, peroxynitrite ($ONOO^-$) is form, which will further increase the oxidative status of the cell. However, if NO production is larger than $O_2^{\bullet-}$ production, $ONOO^-$ binds to another NO molecule forming nitrogen trioxide (N_2O_3) and nitrite ion (NO_2^-), decreasing oxidative stress and increasing NO bioavailability. Finally, the immunohistochemistry pictures show the increase in eNOS expression (left picture) and the decrease in oxidative stress (right picture) after 4 weeks of endurance exercise training.[32]

looking for, the merge of biomechanics (intracellular mechanical levers) and physiology and how we can modulate them with exercise (and more specific, with different exercise intensities)—the essence of PT intervention. In summary, during resting conditions normal heart rate and blood pressure do not generate enough shear stress to activate the glycocalyx; however, during exercise, heart rate and blood pressure produce an increase in shear stress, which will activate the glycocalyx triggering the cascades of events to improve endothelial function and gene transcription.

The next step is to define endothelial shear stress (ESS). Endothelial shear stress is the tangential force, or friction, that blood produces on the endothelial surface.[27] Depending where in the arterial tree it happens, ESS can be steady, pulsatile, or oscillatory.[27-29] The larger the artery (e.g., aorta), the more pulsatile and oscillatory (bidirectional) than smaller arteries (e.g., arterioles) where ESS is steady. In addition, ESS depends on blood flow, which can be laminar or turbulent. As it relates to ESS, the effect of blood flow pattern may depend on the location in the arterial tree.[27-29] Turbulent flow is observed in larger arteries (e.g., brachial artery) and at bifurcations of conduit arteries (e.g., coronary arteries), whereas laminar flow will be observed in smaller arteries (e.g., arterioles). There is a direct relationship between turbulent blood flow at the bifurcations and atherosclerotic plaque.[28] However, and although turbulent flow has been historically blamed on plaque formation, the decreased ESS that happens around turbulent flow in the bifurcation during resting conditions is the reason for ED and plaque formation. During exercise, blood flow will produce an even larger turbulent flow in the bifurcation; however, ESS would also increase at the bifurcation, enhancing endothelial function.[33-35] Therefore, turbulent flow is not necessarily the bad guy; it is the lack of ESS that resting turbulent blood flow produces at the bifurcations. The impact in cardiovascular rehabilitation is evident: exercise intensity becomes a paramount variable to enhance endothelial function.

For some time now, we have questioned whether we are using the right exercise intensities when treating our cardiovascular patients.[36] And recently, there has been some evidence against standardized training models and that tailored programs can prevent "nonresponders".[37] As shown in my first published article in CPTJ,[8] exercise training programs for cardiovascular patients should follow basic principles of exercise training, which include individuality (i.e., tailored), progressive overload,

specificity, and variation/periodization. In addition, Weatherwax et al.[37] showed that individualized workloads based on ventilatory threshold and some principles in exercise training (i.e., individualization and progression) can avoid nonresponders. In fact, and very fascinating at the same time, the traditional model using 40%–65% of heart rate reserve resulted in almost 50% of the sample as nonresponders, as reliable as flipping a coin. Furthermore, my group also showed that traditional clinical markers of exercise intensity were reliable only at low exercise intensities when compared with more physiological markers, such as blood lactate.[38] Therefore, the main problem with cardiovascular rehabilitation is that (1) we do not normally follow basic exercise training principles (i.e., sound exercise prescription) and (2) we do not have a clear purpose for the exercise prescription. At least in my patients, the purpose is to enhance endothelial function and endothelial gene transcription.

In the past few years, I have been trying to bring all of these principles together to enhance our PT services. On the one hand, atherosclerosis pathophysiology, endothelial function, and gene transcription. On the other hand, better markers for exercise intensity to enhance our exercise prescription. First, we found a model to study blood flow patterns in both the brachial artery, which is a model for the coronary arteries and carotid artery.[34,39,40] Using that model, we have consistently showed that (1) ESS is exercise intensity dependent in both endurance and resistance exercises, (2) endurance exercises produce larger ESS than resistance exercise, (3) endurance exercise can produce ESS from 40 to 90 dynes/cm^2, (4) blood flows bidirectionally and unidirectionally in the brachial and carotid arteries, respectively, and (5) most of the blood flow is turbulent during exercise. In addition, our preliminary data show no major differences in ESS and blood flow patterns between young healthy and healthy older adults; however, there is a trend of lower ESS in patients with CAD. Second, we have developed an *in vitro* model to study the molecular and genetic changes of endothelial cells under exercise-induced ESS levels.[41] Previous *in vitro* studies[42] used 10 to 20 dynes/cm^2 as "high" sheer stress, which is not even baseline ESS and is so far from exercise-induced ESS (i.e., 40–90 dynes/cm^2). In our laboratory, we use a closed-circuit pneumatic pump system (Ibidi GmbH, Germany) that generates ESS from 35 to 80 dynes/cm^2 continuously for 1 to 6 hours.[43] Using this model, we have published results showing an increase in eNOS with the highest ESS after the bifurcation and an increase in endothelial cell actin expression at the bifurcation, which is intensity dependent.[41] These results have shown, for the first time, that high levels of ESS, regardless of the turbulence, can improve the function and resiliency of the endothelial cell. In addition, some preliminary results using the same model have shown promising results on

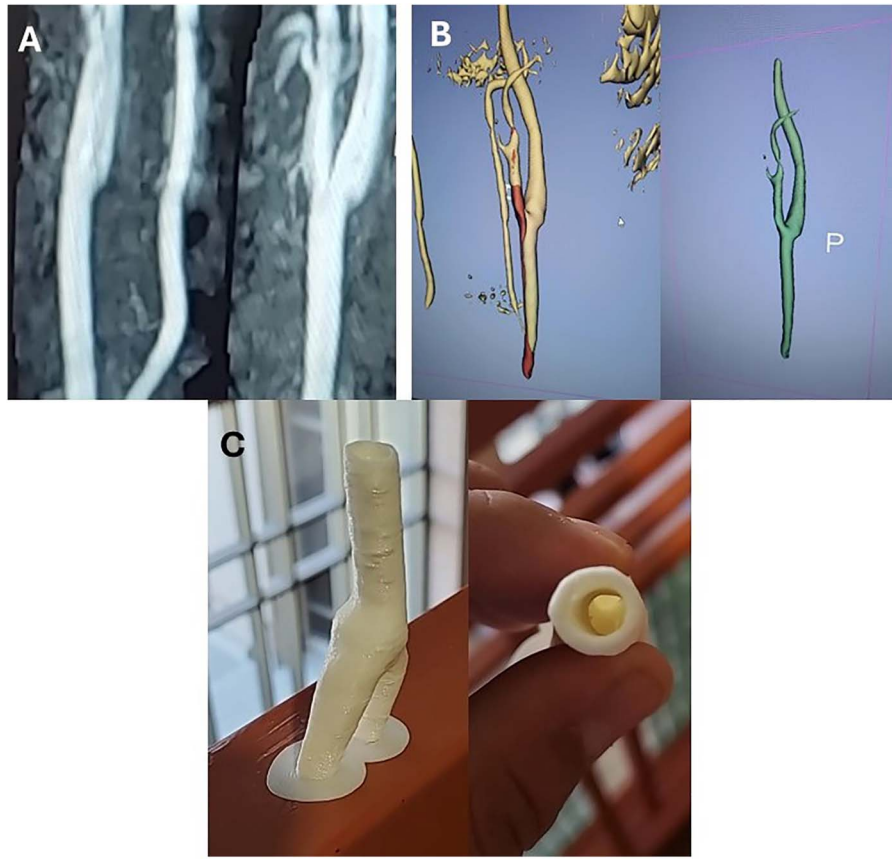

Fig. 3. Carotid artery 3D printing process. A, Noncontrast MRI of a human carotid artery; B) images are transferred to imaging processing software (P = posterior); C) carotid artery printed in polylactic acid (PLA) from a traditional 3D printer.

eNOS expression and different antiatherogenic gene expressions. Third, and thanks to an NIH SCORE-2 grant, we are developing a synthetic 3D bioprinted model of the carotid artery (Fig. 3). This model will allow for *in vitro* experiments in 3D considering not only ESS but also arterial compliance. Finally, my postdoc Dr. Daniel Conde has been working on some experiments looking into gene expression, measured through DNA sequencing, of endothelial cells cultured in different lactate concentrations associated with different exercise intensities. The preliminary results are puzzling: higher lactate concentrations do not appear to have any effect in atherosclerotic-related genes; however, exposure time (>6 hours) appears to increase gene expression of adhesion molecules. These results could be associated to higher coronary calcium scores in ultramarathoners.[44,45]

In summary, the Clinical Applied Physiology (CAPh) Lab, my laboratory, uses a "Reverse Translational" model to study the association between exercise intensity/modality and cellular and genetic responses. First, we measure exercise-induced blood flow patterns at different exercise intensities *in vivo* (in humans). We have performed this in different demographic groups, and our findings show an exercise intensity dependency of ESS and turbulent flow. Then, we have replicated these findings *in vitro*, first with the Ibadi pump system and soon in our own 3D bioprinted model, to determine the molecular and genetic changes of endothelial cells. Finally, once we know the best cellular results, we will return to our *in vivo* studies to determine the best exercise modality/intensity to elicit the best cellular outcomes in our patients. And that is Precision Physical Therapy: designing the exercise prescription that will produce 100% responders and cellular changes to improve the health of our patients.

Thank you very much again to the Academy of Cardiovascular and Pulmonary PT for this amazing honor of writing the Linda Crane Lecture. I hope I have represented Dr. Crane's vision and memory in the way in which she would have been proud.

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