AN INTERVIEW WITH…

Caroline Caradu, MD, PhD

Dr. Caradu discusses the role of Hedgehog signaling in CLTI pathology, the potential for biological substitutes in aortic care, capabilities and downsides to artificial intelligence, and why physicians should not give up their hobbies.

A unique component to your work is a focus on the biology of vascular diseases. How do your efforts in this area inform your clinical work?

During the past 50 years, researchers have learned that cardiovascular system disorders are caused by complex molecular mechanisms related to endothelial dysfunction leading to structural and functional alterations of blood vessels and the development of atherosclerosis. We have already witnessed major transformations in the diagnosis and treatment of peripheral artery disease (PAD). However, chronic limb-threatening ischemia (CLTI) remains a major burden on the health care system, with patients described as "no-option" CLTI patients when their angiograms show a "desert foot." Interestingly, if you are very aggressive in revascularizing those patients endovascularly, you will see that some of those vessels will light up again. As we gain an understanding of the mechanisms regulating capillary functionality, we are holding a promise for the development of novel therapies such as small molecules, protein, gene, or cell-based therapies. The thought of implementing genetic or molecular technologies within endovascular devices is a particularly exciting area.

For your PhD thesis, you considered the role of endothelial cell dysfunction in CLTI pathology, specifically the role of Hedgehog (Hh) signaling. Can you briefly summarize where we are today regarding research in this area? What are the big unknowns?

The role of Hh signaling in vascular biology was first highlighted in embryos in 1998. We know from observations during the formation of the aorta that Hh signaling is essential for vasculogenesis. It is also involved in angiogenesis, especially under pathological conditions including cancer and ischemia, and participates in vascular maturation, including arterial differentiation and capillary muscularization. Finally, it promotes vascular integrity by maintaining endothelial intercellular junctions both at the blood–brain barrier and in peripheral tissues. Inserm U1034–Biology of Cardiovascular Diseases—with which we are affiliated—has demonstrated that Hh signaling agonists may be beneficial in the setting of diseases in which endothelium integrity is compromised, including cardiovascular diseases (eg, diabetic microangiopathies).[1] Moreover, the proangiogenic potential of the Hh signaling agonists is of growing interest in the treatment of PAD. However, it is a prerequisite to fully understand the mechanisms underlying Hh pathways because of the potential carcinogenic effect of sonic Hh. This is why it is necessary to design therapies targeting specific signaling molecules that would promote the revascularization of ischemic tissue but not carcinogenesis.[1]

With a presentation last year at the European Society for Biomaterials annual conference on biomaterials in vascular surgery and endovascular repair and a recent paper on primary and secondary aortic infections,[2] aortic graft infection is a key component of your research. What does the future hold for biological substitutes in the vascular realm, and what are some tips for managing infection now?

In 2020, the European Society for Vascular Surgery published new guidelines regarding the management of vascular graft and endograft infections.[3] Currently, the gold standard is the surgical removal of the infected material with complete debulking, followed by in-situ reconstruction using autologous superficial femoral veins or heterologous arterial or venous allografts, omental flap coverage, and targeted antibiotic therapy.

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I believe that the key remains a multidisciplinary team approach to provide the best care possible for those very complex cases.

Importantly, the use of autologous substitutes has proven difficult in daily practice. Vascular grafts with antimicrobial properties have been a big part of our recent work under the leadership of Prof. Berard. A knitted polyester graft coated with silver acetate and triclosan (Intergard Synergy, Getinge) has been used quite successfully in our center.[2]

Another very interesting area is tissue engineering, and we are lucky enough to currently collaborate on a project with the Laboratory for the Bioengineering of Tissues (BioTis U1026) using cell-assembled extracellular matrix produced by normal human fibroblasts in vitro for the development of a new generation of small-diameter (≤ 5 mm) vascular grafts assembled with a textile-inspired method.[4] Who knows, with time, maybe these methods could be expanded to larger vessels and provide off-the-shelf biological substitutes for aortic reconstructions.

You and colleagues also provided a review of inflammatory aortic aneurysms.[5] With that insight, can you share your best practices for approaching this pathology?

I think the first challenge is to recognize inflammatory aortic aneurysms because they are characterized by nonspecific symptoms. Once that is done, corticosteroids should probably be considered a basic treatment that all patients receive initially. At the moment, I do not think that there are enough data in the literature to determine which treatment strategy is best between an open or endovascular approach. Hence, the treatment should be tailored to each patient, depending on presentation, comorbidities, and the center's experience with the technique.

From what we could gather, the early advantage that endovascular aneurysm repair could offer over open repair on 30-day mortality and iatrogenic injuries (duodenum, veins, ureters, pancreas) is counterbalanced by a higher incidence of persistent perianeurysmal fibrosis and its associated complications during follow-up. I think another important point is to follow those patients up very closely; positron emission tomography–CTs, which our team is used to implementing in follow-up schemes when managing aortic infections, seem very promising in this setting as well.

Artificial intelligence (AI) and machine learning are popular topics of conversation in the vascular world, and you've specifically focused on their role in aortic care. What are the capabilities of AI for aortic management in the next decade? Are there any current or predicted downsides to AI?

The number of publications on AI has increased exponentially over the past decades. AI is now part of our everyday life, with applications in a wide range of fields. AI has offered new tools to develop diagnostic supports, improve risk prediction and stratification, discover new therapeutic targets, facilitate imaging analysis, or optimize the organization of health information systems and care.

Our preliminary work with Nurea's PRAEVAorta suggests that, beyond assisting in the prediction of abdominal aortic aneurysm (AAA) growth and rupture risk, the use of AI could also assist physicians in determining the indications and optimal surgical treatment strategy for AAA patients by discerning which treatment strategy has the lowest risk of complication and reintervention based on a combination of clinical, biological, and imaging criteria. It might also be able to assist in planning for tailored postoperative monitoring, leading to potential economic benefits.

However, challenges remain. The interpretability of the AI algorithms is extremely difficult to establish, and the techniques developed are highly dependent on the training data sets that are used. Therefore, the generalizability of the tools developed and their applicability in different populations need to be thoroughly investigated. Moreover, AI applications raise major ethical issues regarding patients' privacy, data protection, and security.

DR. CARADU'S TRAINING ESSENTIALS

01 Open and endovascular complex aortic surgery training

02 Multilevel chronic total occlusion endovascular revascularization training

03 Simulation training (Simbionix, silicon models, anatomic and animal models)

You've discussed your love for horse riding and show jumping as well as playing piano and violin. What do you enjoy about these hobbies? Why is it important to have these interests outside of work?

I learned to ride a horse at age 4, and I could not imagine my life without horseback riding. I believe that it teaches a sense of responsibility. On top of helping you stay in shape, you will need strong reflexes, a sense of balance and coordination, and to think quickly in the saddle to remain safe and in control. If you think about it, this resembles a lot of what you need in an operating theater. Also, being able to communicate and interact with horses has been shown to have therapeutic effects on people and help develop confidence and self-esteem. I think it is the same with music. It helps you relax, gives you a moment of peace, and helps in regaining your thoughts. I would advise my fellow physicians to pick at least one hobby and engage themselves in something that they can enjoy outside of work to stay balanced.

What are the overarching goals for your career? Are there any specific milestones you hope to achieve?

The older I get, the less career oriented I become. I think I am where I am supposed to be at the moment, and I mainly want to focus on things that would make me happy. I have the chance to work in a great city with an amazing team directed by Prof. Ducasse, work on what interests me the most, and spend time with my family and friends—what more could I ask for? ■

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Disclosures: None.