Interview

From pacemaker in a donkey to valve disease research in humans

Philippe Pibarot speaks to Caroline Telfer, Assistant Commissioning Editor

Philippe Pibarot

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Philippe Pibarot was born in Toulon, France in 1964. He obtained a doctorate in veterinary medicine in 1987 at the University Claude Bernard (Lyon, France). He obtained his PhD degree in biomedical sciences from the University of Montreal (Montreal, Canada) in April 1995. He is now a professor at the Department of Medicine of Laval University and he holds the Canada Research Chair in Valvular Heart Disease at the Québec Heart & Lung Institute (Québec, Canada). The objective of his research program is to develop and validate novel approaches to improve the diagnosis, prevention and treatment of valvular heart disease. He is currently the principal investigator of three multicenter studies funded by Canadian Institutes of Health Research and the Heart and Stroke Foundation of Québec. He has published more than 250 articles in the course of his career. He recently received the Annual Achievement Award of the Canadian Society of Echocardiography (2010), the Research Achievement Award, Canadian Cardiovascular Society (2010) and the Feigenbaum Lecture Award, American Society of Echocardiography (2012).

■ **Can you tell us a little bit about your background & how you got into the field of interventional cardiology?**

My background is in veterinary medicine, so I had an atypical career pathway. I'd been interested in cardiology very early in my veterinary training and career; I find the cardiovascular system fascinating as it is a remarkably well-designed system and has a very complex efficient anatomy, structure and function. To address the challenges posed by this complex cardiovascular system, you need insight from multiple disciplines and multiple expertise including biology, physiology, fluid mechanics, genetics, imaging and intervention. This is the aspect I like the most, this multidisciplinary aspect. My first paper was a case report of the implantation of a pacemaker in a donkey. The donkey was the mascot of a day care system and it had a third-degree atrioventricular block and had syncope three- to four-times a day so it became dangerous for children. We fixed that by implanting a pacemaker and the donkey went back to its mascot work. While I was at the veterinary school I started working with a group led by Louis-Gilles Durand at the Clinical Research Institute of Montreal (Montreal, Canada), and this group was using a large animal model of a valve replacement to test bioprosthetic valves and needed expertise in veterinary cardiology and anesthesiology; therefore, I jumped into this project and worked with them and got really hooked by this fascinating field of valvular heart disease. I decided to do a Masters and then a PhD with this team. I worked on the hemodynamics of prosthetic valves, fluid hemodynamics concepts and imaging, Doppler echocardiographic evaluation of prosthetic valves and also the concept of prosthesis–patient mismatch, which was in its infancy at the time.

The focus of my PhD was on prosthesis–patient mismatch. This problem occurs when the prosthesis implanted in the patient is too small for the size of the patient and, thus, for his/her cardiac output requirement. It would be similar to implanting a mouse's valve in an elephant; even if the valve is functioning normally, it is still too small to accommodate the cardiac output requirement of the patient; a harmony is needed between the size and the efficiency of the valve and the patient's needs in terms of cardiac output. After completing my PhD, I established my laboratoy and research program at the Quebec Heart and Lung Institute (Quebec, Canada), which is affiliated with Laval University (Quebec, Canada), since this was a place where there was a tradition with valvular heart disease. I arrived in Quebec in 1998 and since then I became the Canadian research chair in

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valvular heart disease; a chair supported by the Canadian Institutes of Health Research. This is how I got into the field, and then from year to year, we established a research group. We recruited noninvasive cardiologists, cellular molecular biologists, geneticists and so on and now we have a multidisciplinary team of great people and students. More specifically, I have always been interested in valve replacement and in trying to find the optimal way to replace the valve. However, if we take the field of interventional cardiology senso strict by catheter, what really got me into the field was transcatheter aortic valve replacement (TAVR). I was interested in the hemodynamics of surgical prostheses, but in the mid-1990s when I started my career, I could never imagine that, one day, we could implant a prosthetic valve that has a diameter of 20–29 mm, and moreover, through a catheter without opening the chest of the patient. It is amazing how fast this has developed and how successful it is. Personally, this is a revolution, not only in the field of interventional cardiology, but in the field of medicine in general. This has been successful owing to the multidisciplinary approach, bringing together engineers, interventional cardiologists, medical imagers and cardiac surgeons. This is one of the aspects I like with this research program; working in tight collaboration with many different people and learning from them every day. You need state-of-the-art core laboratories to properly assess these transcatheter devices, the function is even more difficult to assess compared with surgical valves, there are some pitfalls and challenges that need addressing; therefore, we established an echocardiography core laboratory in our institution to be able to centrally analyze the data from the TAVRs that are performed with the Edwards SAPIEN (Edwards Lifesciences, CA, USA) valve in several centers across Canada. When you bring together investigators with complementary expertise and vision. You advance the field much more than if you are alone in your laboratory, as was often the case 50 years ago.

■ **Which of your achievements, to date, are you most proud of?**

When you're a medical investigator, your objective and your dream is that your discovery and contribution will move into clinical practice. You want an impact on clinical practice and to improve the care of the patient. Some outstanding investigators have discovered great things, but in their lifetime, they have not seen the impact. In our case, we have been successful as we have already seen an impact of what we have done and the work that we carried out in the mid-1990s on prosthesis–patient mismatch. With my colleague and friend Jean Dumesnil, and other great collaborators, we published over 30 papers on the topic, first looking at the impact of this problem on hemodynamics and the recovery of left ventricular (LV) function and then looked at the impact on mortality and quality of life. At first, it was difficult since it was not a priority in the field. The priority for the prosthesis manufacturers was more the durability and thrombogenicity of the valve, which is very important, but hemodynamic performance was a lower priority. At that time, the surgeons had few options and these valves were not necessarily optimal and the patient was feeling better, but not that much better. Our main goal was to increase the awareness of prosthesis–patient mismatch, and the prosthesis manufacturers responded well by producing valves with better hemodynamic performance. The surgeons are now aware of mismatch and try to implant the valve that provides the best hemodynamic performance. This is still a work in progress because, with the introduction of TAVR, we have another tool to avoid mismatch since one of the limitations with surgery was that when patients have a small aortic annulus, you cannot find a prosthesis that will provide a good hemodynamic performance or that will be large enough to avoid any residual stenosis. However, now with TAVR, we have another solution because TAVR performs very well in these small aortic annuli and there is a lesser incidence of mismatch compared with surgical aortic valve replacement. In the randomized trials, TAVR is associated with reduced incidence of mismatch. Thus, now the physicians have another alternative to optimize the operation in terms of hemodynamics as when you have a severe stenosis, you want to bring the patient to zero stenosis, not mild or moderate; you don't want to do half of the job.

We also discovered a new entity of aortic stenosis (AS) called paradoxical low-flow low-gradient AS. It was known for a long time that patients with a low LV ejection fraction (LVEF), could have reduced flow across the valve and, thus, a low transvalvular gradient despite the presence of a severe stenosis. The problem in these patients with low LVEF, is that it is difficult to know if it is a severe stenosis or not, so you need additional tests to determine its severity. Now we have TAVR that may provide an interesting alternative for these patients. And with my colleague JosepRodés-Cabau (Québec Heart & Lung Institute), we are now starting a multicenter registry of these patients with low LVEF, low-flow, low-gradient undergoing TAVR.

The discovery that we made in 2007, published in *Circulation*, was that patients with normal LVEF may also have a low flow and a low gradient despite severe stenosis and this is why we call it paradoxical low flow. These patients have a pronounced concentric hypertrophy in response to the AS and they have a small LV cavity. Therefore, even if they have a normal LVEF, what goes out from the ventricle – that is, the stroke volume and, thus, the transvalvular flow is markedly reduced. This entity was really under-recognized and the stenosis severity was underestimated and, therefore, valve replacement is underused and the patients may have worse outcomes. We published several papers on this, and this has been something that became a hot topic at the present time. In the recent European Society of Cardiology's guidelines, the committee mentioned that paradoxical low-flow, low-gradient AS is an important entity that requires special attention and more data and they included a class IIa recommendation for valve replacement in these patients after careful confirmation of disease severity. This was very rewarding for our group as we described this for the first time in 2007, and in 2012 it was in the guidelines so there was a fast translation into practice.

Finally, what I'm most proud of is my students. I have been very lucky in the course of my career, having superb, great and smart students and I'm very proud of what they have become. They are all now professors and brilliant investigators in different institutions across the world. It's a bit similar to if they're your children; you educate them, you act as a mentor, as a support, and then, when they have a successful career, you are very proud. I am very proud of them.

■ **You have mentioned a lot about TAVR. What do you think are the most significant advances that have been made in the field?**

I wrote a paper for *Nature Reviews Cardiology*, 'Evolution and revolution in valvular heart disease', and the word revolution was for TAVR. I think it's one of the most significant and outstanding advances that has been made in the field, and I think many people would agree. Transcatheter valve therapy, in general, is really exploding and this is just the start. TAVR has had the greatest impact on practice so far, but there is also intervention on the mitral valves and we will see it on the other valves, and probably intervention for heart failure as well. I think if we can do major procedures less invasively with the same efficacy and durability, this is the way forward.

■ **You are the principle investigator in the TOPAS study. Can you tell us a little about the aims of this study?**

The TOPAS is a prospective observational cohort study recruiting patients with the classical low-flow low-gradient AS with reduced LVEF. We also recruit the new category of patient that we previously identified, these patients with paradoxical low-flow low-gradient AS and preserved LVEF. Therefore, the mechanisms for the low flow are different in both groups, but the challenges are similar. We need to differentiate a true severe stenosis that will benefit from valve replacement from a pseudo-severe stenosis that will need aggressive heart failure therapy. Therefore, the diagnosis is very important as it has an impact on therapeutic management: valve replacement versus medical therapy. The problem is that it is very challenging to make this distinction. One of the main objectives is to develop and validate new noninvasive parameters, essentially based on imaging, Doppler echocardiographic imaging, multislice computed tomography imaging, to improve the distinction between true-severe versus pseudo-severe AS. The other challenge is to assess the state of the LV function since this is important for risk stratification and again

imaging is critical for this. Phase I of this study was started in 2002, and we are now Phase III, we have just got the renewal for funding from Canadian Institutes of Health Research. It started with three centers in 2002, and we are now up to 24 centers. It is a multicountry trial with a fantastic group of investigators and centers.

■ What has come out of this study so far?

We proposed a new parameter that is called the projected valve area at normal flow rate that really improves the accuracy of diagnosis of the distinction between true-severe versus pseudo-severe AS and also better predicts outcomes. Now the guidelines have included this parameter as a tool that may improve the assessment of these patients. We also demonstrated the usefulness of Six-Minute Walk Test for the risk stratification of these patients. This is important because these patients may have high operatic risk, sometimes up to 30%. If this is the case, then a decision must be made whether to treat them medically or refer them to TAVR, so it's important to improve risk stratification. The other important thing that came out of this study is the discovery of the paradoxical low-flow, low-gradient AS. There is always the concern that these patients with low flow, low gradient may not benefit from valve replacement therapy as they are too sick. However, we have recent data showing that valve replacement improved the outcome of both patient groups. We obtained recent data from the PARTNER study, which I am also involved with, where these patients with paradoxical low flow and low gradient, may do better with TAVR compared with surgical aortic valve replacement as these are patients with small ventricles, a small aortic annulus and these patients have a high operative risk with surgery and are at high risk of having a prosthesis–patient mismatch, whereas with TAVR there is less risk of procedural risk and less mismatch. We need more evidence to validate this concept though.

■ You are also principle investigator of the PROGRESSA & PROGRAM studies. Can you tell us a little about these?

The TOPAS study targets the patients at the high risk part the spectrum. With the PROGRESSA study, and we are now in Phase II, it is the patients with asymptomatic AS, who have mild, moderate or severe stenosis and we follow them prospectively. We have a similar study in patients with asymptomatic mitral regurgitation. Both studies are observational cohort studies and we do multimodality imaging. One of the issues, both in asymptomatic AS and asymptomatic mitral regurgitation at the present time is: should we consider a watchful waiting strategy, so wait for the onset of symptoms and/or LV dysfunction to have aortic valve replacement; or should we consider an early prophylactic surgery. This is a big debate and a case of controversy, and I think we should individualize the strategy. This is why we do these studies. The purpose is to develop parameters based on imaging and on the metabolic profile to identify patients who may have a rapid progression of the disease and who may be at higher risk of events in the short term so we can triage these patients and refer them to early prophylactic surgery versus the other patients who are at lower risk and then you can reasonably do a watchful waiting follow on. In both the PROGRESSA and PROGRAM studies, we have also been very interested in the link between obesity/metabolic syndrome and the risk of developing valvular heart disease. It is well established that there is a link between obesity, coronary artery disease and hypertension, but not for valvular disease. We demonstrated, for the first time, that visceral obesity is associated with faster progression of AS. This is an important message because when you have a patient with valvular heart disease, a lifestyle modification program is also needed.

■ Your most recent publication focuses on the imaging of valvular heart disease. In your opinion, what is the most useful imaging modality in these conditions & why?

I think it is Doppler echocardiography. That is the cornerstone of the evaluation of valvular heart disease as it is versatile. There are many things that we can measure, not only in terms of assessing the valve function, but also the consequences of valvular disease on the other cardiac chambers and on pulmonary circulation, so we can have a comprehensive evaluation

of the valvular dysfunction and its impact on the cardiovascular system at large. It is noninvasive, relatively low cost, relatively fast and it can be carried out in the operating room or in the catheterization laboratory. Therfore, it really is the main tool that we use to assess the valvular disease. Having said that, there is an important role for multimodality imaging, for example, multislice computed tomography. Especially for the assessment of valve calcification and for the sizing of the aortic annulus and the selection of the prosthesis size, which is critical to minimize the paravalvular leak following TAVR. MRI is also emerging as an important modality for the assessment of valve morphology and function, but more importantly, to assess the ventricular dysfunction and the extent of myocardial fibrosis. These modalities, combined with stress testing, provide incremental information. What we need now is well-designed randomized trials to validate the incremental prognostic value of the different imaging modalities and the different tests that we use. This is important to determine which imaging test should be used in which patient and when. This is key to optimizing the management of the patient and, at the same time, minimizing the cost for the healthcare system.

■ To go back to prosthetic valves, which of the recently developed prosthetic valves do you think is the most effective?

There is no medical therapy for valvular disease, but there is active research in this. We know that statins failed in AS, but there are other directions being studied. I would guess that in the next 5–10 years we will see a drug that could significantly slow the progression of valvular disease, in particular AS. For now, the only option is to replace the valve and until now, surgical replacement is still the gold standard. The operative mortality is now very low. The newer generation prosthetic valves have an excellent durability, a low thrombogenicity, good hemodynamics and much less prosthesis–patient mismatch. I could not identify one specific valve that is better than the others but I think that newer-generation bioprosthetic valves are being used more and more. Of course, we still have the issue in younger patients as the durability is much more limited so we use mechanical valves, and again newer-generation mechanical valves have good hemodynamics and thrombogenicity with anticoagulation.

In terms of TAVR, the performance of the transcatheter valves is amazing, in terms of gradients and prevention of prosthesis–patient mismatch. The drawback is that they are more prone to paravalvular regurgitation, which is associated with increased mortality. Newer generations of valves have a better sealing system with a cuff and so this should reduce or eliminate regurgitation. Regarding durability, for now we don't know. You need a follow-up of 10 years or more, but here we have a maximum of 5 years. Therefore, it is still too early to conclude. So far so good, but we need more time and more data.

■ You have highlighted a lot of the recent advancements, but where do you see the field of interventional cardiology in the next 5 years?

I see an exponential growth of TAVR. I think this will be huge and I think potentially, 50% or more of the total number of aortic valve replacements will be performed by catheter. I think it will grow very fast. There are some limitations and pitfalls, but we already have potential solutions to most of these problems. The engineers, the interventional cardiologists and the cardiac surgeons are bright people, and a new model of a valve comes out almost every month and so it progresses very rapidly. There will be problems and barriers, but as Churchill said, "Success is going from failure to failure without loss of enthusiasm," and I see a lot of enthusiasm and a lot of positive results, and I am sure that TAVR is here to stay and that within 5–10 years it will cover the vast majority of aortic valve replacement. There are still some cases that will not be manageable by TAVR and these challenging cases will need to be addressed by highly skilled cardiac surgeons. For transcatheter mitral valve procedures, I think the rise will be slower. For now the solution that we have, the MitraClip (Abbot Vascular, IL, USA) procedure, for example, reduces the mitral regurgitation, but it does not correct it completely so it's not a perfect repair as the surgeons generally do. Transcatheter valve procedures should replace surgery, as long

as it is as efficient and durable. I think there will be a niche for transcatheter mitral valve procedures, but they will be more limited than for aortic procedures and the progression will be slower because this is a much more challenging field. I could be wrong, but if I would put my money on something I would put it on TAVR.

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