Prof. Randall Starling: left ventricular assist device therapy for advanced heart failure

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Prof. Randall Starling, MD, MPH (*Figure 1*), is Head of the Section of Heart Failure and Cardiac Transplant Medicine, the Medical Director of the Kaufman Center for Heart Failure and a Staff Cardiologist in the Robert and Suzanne Tomsich Department of Cardiovascular Medicine. He also serves as Vice Chairman of Cardiovascular Medicine, Operations. His expertise has been focusing on congestive heart failure, cardiac transplantation, cardiomyopathy and mechanical circulatory support devices.

Prof. Starling has been a main investigator on numerous clinical trials, including National Institutes of Health (NIH) grant-funded trials and numerous industry-sponsored trials. He has published over 300 articles scientific and professional journals and authored numerous chapters in related medical textbooks.

During April 10th-12th, 2015, the 17th South China International Congress of Cardiology was held in Guangzhou Baiyun International Convention Center, China. Prof. Starling was invited to present a lecture on "Left Ventricular Assist Device Therapy for Advanced Heart Failure". I was honored to meet Prof. Starling after his speech and invited him to share his expertise regarding left ventricular assist device (LVAD) as treatment for advanced heart failure.

Figure 1 Professor Randall Starling.

CDT: Mechanical circulatory support is now a well-known therapy for patients with advanced heart failure and cardiogenic shock. What is the impact of mechanical circulatory support devices?

Prof. Starling: Mechanical circulatory support has been used for over 20 years. There are two categories. The first one is temporary mechanical circulatory support, which is used when a patient is in the hospital and cannot be discharged. The second one is permanent mechanical circulatory support.

Temporary mechanical circulatory support can be placed percutaneously by a catheter. A catheter-based system can deliver 2-5 L of flow, used in the setting of acute myocardial infarction or cardiogenic shock. It is also applied to complex ventricular tachycardia ablation in heart failure patients and complex percutaneous coronary interventions. The duration is typically from hours to at most 5-7 days. In addition, temporary mechanical support can also be used in patients in cardiogenic shock with chronic heart failure. Because these patients are very ill the goal is to stabilize them; improving renal and hepatic function prior to taking the patients to operating room for durable mechanical support is an important strategy.

For longer term mechanical circulatory support an approved LVAD is implanted by a cardiac surgeon via sternotomy. Such devices used today have percutaneous drivelines. They are very durable and could last for easily 5 years with an external power supply. Normally, patients could be discharged from the hospital in 10-14 days after the operation. Permanent mechanical circulatory support can be also used in patients waiting for heart transplant for months or years, or be offered as a definitive therapy for patients with severe chronic heart failure.

CDT: Could you make a brief introduction about the development of the mechanical circulatory support devices?

Prof. Starling: The first generation LVAD was a large pump. It can deliver up to 10 liters of flow and it has a

stroke volume of about 80 cc. The limitations of the first generation pump are stroke, and infection. In addition, the durability of the devices was very poor. The most commonly used device in the United States and Europe was known as the HeartMate XVE pump. But it would last for 18-24 months and then it had to be replaced.

So 10 years ago the HeartMate II, an axial flow pump, was developed. It has an axial rotar that operates at speeds of 8-10,000 rpms. It is silent, light and very durable. However, all pumps with bearings are subject to developing thrombosis within it. To reduce the risk of thrombosis heparin immediately after the implant, as well as chronic treatment with aspirin and warfarin with therapeutic INR of two to three is required. Even when these conditions are met, pump thrombosis may occur and if a patient encounters hemorrhagic stroke or gastrointestinal bleeding that requires stopping or reducing anticoagulation, then the risk may increase.

The pumps we use today are excellent and have saved many lives, but they are not perfect. The newest pumps are developed without bearings and has a system known as magnetic levitation or a hydrodynamic interface eliminating a traditional bearing. Magnets reside in the pump housing itself and suspend the rotar to receive the blood, as well as to generate the force and the flow. It has been used in clinical trials throughout the world. The newest pump would have magnetic levitation and no bearings, which is a significant advance in the field with less complications anticipated. The other area under development that remains unclear is the importance of the continuous flow pump and pulsatility. Continuous flow pumps with reduced pulsatility are suspected to have additional complications related to continuous flow, including gastrointestinal bleeding. Heart failure resolution depends on how well the left ventricle is unloaded and if there is shifting of the interventricular symptom into the left ventricle due to suction from the LVAD. If a continuous flow pump is completely unloading the left ventricle, the aortic valve will never open. Patients can develop fusion of aortic valve leaflets and aortic insufficiency. The newest pumps will have software algorithms to generate pulsatility to maintain the opening of the aortic valve as well as magnetic levitation to eliminate bearings and hopefully pump thrombosis.

CDT: LVADs are more and more used as a bridge to transplantation or as a destination therapy in advanced heart failure patients. Comparing to the optimal medical therapy, what are the advantages and disadvantages of LVAD?

Prof. Starling: The chronic mechanical circulatory support devices are frequently used in the US and Europe. The impact of heart transplantation on patients with heart failure is very small, which is estimated to be about 2-5% of patient in the USA with advanced heart failure. We estimate that 100,000-250,000 adults in the USA have advanced heart failure and less than 2,500 heart transplants are performed yearly. Of those patients waiting for heart transplantation in the United States, over 50% spend time on LVAD before they get a transplant because the waiting time is so long. In many countries in Europe, patients with advanced heart failure receive LVAD and will get transplant if they develop a complication on the LVAD. But if they do well on the LVAD, they will have that therapy indefinitely. Destination therapy has originally been offered in the US, always to patients who are not eligible for a heart transplant. Eligibility for a heart transplant in the US varies from hospital to hospital. Some hospitals base the decision on the age of patients. However, the majority base the decision on the age and overall health of the patient, as far as known diseases, such as diabetes and profound vascular diseases. Such hospitals try to recommend transplant to patients who have the fewer risk factors, expecting to have the best outcome with transplant. So in the US, most of patients who receive destination LVAD are the patients with more comorbidity and less optimal renal function. However, these patients have very few options because chronic inotropic therapy is offered to some advanced patients who have extremely high mortality which is approximately 90% at 1 year and 50% 6 months. Thanks to the LVAD, the survival rate now is 80-90% at 1 year and the quality of life has been improved.

So I think the future of LVAD is extremely bright and encouraging. The further growth and proliferation of LVAD may be related to two major issues. Firstly, it is the reduction in cost, which is now significant. It takes 200,000 dollars for hospitalization and implantation of the device. Secondly, some complications after LVAD that result in hospitalization must be improved with the development of technology. In addition to bearingless pumps, completely implantable system long life batteries and everything inside the body will reduce infection. I believe as long as the cost is down, LVAD will be a major form of therapy throughout the world for patients with advanced heart failure because there is no good medical therapy or device therapy other than inotropic therapy which is applied to a small subset of patients as palliative treatment. Medical therapy and inotropic therapy potentially improve the quality of life but they have a very high mortality rate.

CDT: Considering the limitations of LVADs, who you think is suitable to use LVADs as destination therapy? And when could they benefit from this therapy?

Prof. Starling: The patients with advanced heart failure, who fall into Class IV listed in New York Heart Association (NYHA) Functional Classification, could consider the LVAD. Because, first of all, they have been hospitalized for at least once or twice within the last 6 months for exacerbation of heart failure. Secondly, most of these patients become so ill that they no longer tolerate typical medications including beta-blocker and ACE inhibitor therapy. Finally, some of these patients will develop compromised cognitive and exercise function. Some patients will be asked "can you walk one block?" or "can you walk one flight of stairs?" If the answer is no, they will be told that they have poor quality of life and should be considered for an LVAD. The European Society of Cardiology defines advanced heart failure as the inability to walk 300 m on a 6-minute walk test (6MWT). So the 6MWT is generally used as a screening test. If the duration is less than 300 m LVAD could be an option. The other test commonly to be used is the cardiopulmonary exercise testing, in which we will measure the peak oxygen consumption. If the age and gender stratified peak oxygen consumption is 50% or less than the predicted one, then these patients are considered as having significant functional impairment. Therefore, who is suitable for LVAD is not merely based upon a low ejection fraction, but it is very much based upon a functional limitation which will lead to hospitalization and inability to tolerate standard medical therapy.

It is learned that the highest mortality is seen when patients are medically unstable. For example, if a patient is on mechanical ventilation on an intra-aortic balloon pump, or a temporary percutaneous form or mechanical circulatory support, he/she could have a 30-day perioperative mortality rate of 15-30%. On the other hand, more stable patients who do not meet any of these conditions, typically have a 30-day operative mortality rate at 5%. There is definitely a relationship between the instability of the patient and the time of the operation. So what we like to do is to stabilize and optimize the patients. But we avoid offering the operation to patients with renal and hepatic failure who are critically ill because the mortality rate is high in the surgery.

CDT: Heart failure is a global problem with an estimated prevalence of about 38 million patients worldwide. Although there are some progresses, the prognosis of heart failure is worse than that of most cancers. What could be done to improve the prognosis of heart failure?

Prof. Starling: Prevention through better treatment of coronary artery diseases, hypertension and diabetes would reduce the development of heart failure. I think the most exciting information about heart failure in 2014 is the new medication called LCZ696 that was studied in 8,000 patients with chronic heart failure and the article was published in the *New England Journal of Medicine* on last September. This trial involved patients worldwide with chronic heart failure with low ejection fraction under 40%. Patients had already received standard medical therapy with beta-blocker, ACE inhibitor and so on. They were randomized to receive enalapril or the new drug LCZ696, a combination of valsartan plus a neprilysin inhibitor.

It is a major breakthrough that this new drug reduces the mortality rate compared to enalapril by approximately 20% and it also reduces the need for hospitalization in these patients by about 20%. So this new drug, which is not yet available in the US but will be in later 2015, could make a big impact on the treatment of heart failure. One of the full stop will be moved out latter. In the US, there are many financial constrictions and limitations related to healthcare. I hope that the insurance company and the government will provide resources for this new medication. Other than prevention, I think that this new medication is the most positive and exciting clinical trial in heart failure in over a decade since the beta-blockers and cardiac resynchronization therapy have made their positive impact.

Plus, we must remember that about half of the patients with heart failure globally have preserved ejection fraction. We know very little now about the impact of medical therapy to be used in patients with preserved ejection fraction. At this point, we have limited experience with the LVAD in patients with some diseases, such as hypertrophic cardiomyopathy and restrictive cardiomyopathy. With respect to LVAD, it has been used in patients with systolic heart failure and for reducing ejection fraction.

CDT: Heart transplantation is said to be a "gold standard" therapy of refractory heart failure, while LVADs have proven to be effective in improving survival and qualities of life. What challenges the multidisciplinary teams are encountering in dealing with advanced heart failure?

Prof. Starling: For LVAD therapy, it does require a significant infrastructure and team to take care of these patients. In the Cleveland Clinic, we implant about 65 to 90 cases of LVAD per year. We have a whole team of physicians and nurses who are trained to perform the LVAD therapy. We have to provide availability of emergency,

telephone contact and admissions to the hospital. So the infrastructure and a team of healthcare professionals are very similar in complexity to that of heart transplantation. We also have social workers, pharmacists, dieticians as well as psychologists.

CDT: At first, LVADs were used as bridge in patients who are waiting for heart transplantation, but now they have been used as destination therapy for patients with advanced heart failure. The decision-making process of LVADs has become a challenge both in ethic and clinic. Could you share with us your opinions about the ethical challenges of deactivation of cardiac devices in advanced heart failure?

Prof. Starling: In the US, the requirement of the government and the recommendation for a hospital to implant LVAD is to have a bioethicist as a member of the team. When we identify a patient for destination therapy for LVAD, our bioethicist meets with each patient. The responsibility of the bioethicist is to make sure that the patients have a good understanding of the complexity of the therapy that they agree to. And the bioethicist also tells patients that if the machine or device goes wrong, they may have no further options. So before the operations, patients are encouraged to give consideration, which means many patients will sign a document about whether they want kidney dialysis or mechanical ventilation—the complications after the LVAD. These important documents are referred to as advanced directives.

The other area that we have worked on extensively in conjunction with our palliative medicine team at the Cleveland Clinic is the process of the withdrawal of care. We have done this both with ICD as well as LVAD. For example, if a patient has advanced heart failure with an ICD, the team will have a discussion with cardiologists. And the bioethicist will often see the patient before the electrophysiologist turn off the ICD. They look for proper documentation to make sure the patient understands all decisions. Likewise, for LVAD as far as palliative medicine and bioethics, we request and expect a family meeting with the patient's families and all the doctors involved in the care to make a decision about turning off the LVAD in patients with complications, when everyone agree that the continued use of LVAD is futile and no further options exist.

I think this definitely creates a lot of ethical complexity. Another ethical complexity is whom the devices are offered to. For example, if we see a patient who is extremely elderly such as 85 or 90 years old, the doctors might decide LVAD is not indicated. We will often bring the bioethicist in to have a discussion on it. If a patient has medical complication, there will be disagreement between the doctors, the family and the patient about offering the LVAD to the patient because of the risk involved. In addition, we spend a lot of time trying to analyze the compliance of the patient. We really work hard to make sure that the patient is compliant and motivated and will be involved in his or her medical care. We also want to make sure that he will understand LVAD and be able to look at the controls and alarms. We test patients to see if they know how to disconnect the power and how to change the battery. We have to train the family so they know all of these. In other words, a patient is requested to have a family member or another individual in his house at all time because if a patient becomes unconscious of low battery, he could die unless somebody else could come quickly and change the battery. Lastly, in the US, some of the patients have tobacco use and substance abuse, and they are not eligible for transplant, so they may ask for the LVAD. We typically will not accept patients that are active substance abusers and will request them to go through rehabilitation. All these things create very complex ethical issues.

CDT: Thank you for the interview!

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Footnote

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

(Science Editor: Silvia Zhou, CDT, editor@thecdt.org)

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