Working to Improve Understanding of the Mechanisms Underlying Microvascular Dysfunction in Allograft Failure, Systemic Inflammatory Diseases, Endocrine Diseases, and Cardiomyopathies

Francesco Tona, MD, PhD, FAHA, FESC, assistant professor of cardiology, Department of Cardiologic, Thoracic, and Vascular Sciences, University of Padua, Padua, Italy, talks to Mark Nicholls.

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 Professor Tona with Dr Osto on the day she received her doctorate. She is now working in Zurich but continues to collaborate with Professor Tona and his group. Photo courtesy of Professor Tona.

Francesco Tona, MD, PhD, FAHA, FESC, assistant professor of cardiology, Department of Cardiologic, Thoracic, and Vascular Sciences, University of Padua, Padua, Italy, is the last author of a recent article in Circulation titled, “Coronary Microvascular Dysfunction Induced by Primary Hyperparathyroidism Is Restored after Parathyroidectomy.”1 He explains that the article results from the observation that many patients with endocrine diseases have a high cardiovascular risk and a variety of cardiovascular disorders. He says, “These patients are often not recognised by cardiologists. We believe that microvascular damage may be what binds the endocrine disorder with an increased risk of cardiovascular disease.” The article concludes that coronary microvascular dysfunction in patients with primary hyperparathyroidism is completely restored after parathyroidectomy.

Parathyroid hormone independently correlates with the coronary microvascular impairment, suggesting that it has a crucial role in explaining the increased cardiovascular risk in primary hyperparathyroidism. Professor Tona comments, “This work opens new perspectives in the clinical evaluation of these patients and it is also useful in understanding some of the mechanisms underlying the cardiovascular alterations in endocrine diseases.” His group continues to study the cellular and molecular mechanisms of such microvascular dysfunction in collaboration with Elena Osto, MD, PhD (see http://circ.ahajournals.org/content/126/19/f109), University of Zurich, Zurich, Switzerland.

Awards: Heineken Young Scientist Award 2012 for Dutch Postdoctoral Researchers Recipient of this award, Linda W. van Laake, MD, PhD, assistant professor and resident in cardiology, Utrecht, the Netherlands, describes the award and her research. 

Funding: Swiss Heart Foundation Giuseppe Vassalli, MD, professor of cardiology, research group leader, and consultant cardiologist, Cardiocentro Ticino Foundation, Lugano, and Department of Cardiology, University Hospital, Lausanne, Switzerland.
“Using Doppler Transthoracic Echocardiography, We Were Able to Measure Coronary Flow in the Left Anterior Descending Coronary Artery”

Professor Tona’s key achievements include research on the development of new noninvasive diagnostic tools for evaluating cardiac allograft function in heart transplantation, with particular interests in allograft vasculopathy and coronary microvascular injury; new diagnostic tools (echocardiography and cardiac magnetic resonance) to identify microvascular dysfunction in cardiomyopathies and heart failure; the aetiology of cardiac allograft vasculopathy; the aetiopathogenesis of cardiomyopathies and myocarditis; determination of new prognostic indexes in heart failure (biomarkers and imaging); the development of new diagnostic and prognostic tools in pulmonary hypertension and embolism; and cardiac involvement in systemic inflammatory diseases and endocrine diseases.

Professor Tona was inspired to develop diagnostic tools to measure coronary flow reserve after transplantation early in his career, when he carried out research in Padua with Professor Sabino Iliceto, MD, and some of his co-workers, including Roberta Montisci, MD, and Massimo Ruscazio, MD. Professor Tona’s role was to help develop an echocardiographic technique to measure coronary flow reserve. He says, “Using Doppler transthoracic echocardiography, we were able to measure coronary flow in the left anterior descending coronary artery (first detectable only in the cath lab) in conditions of rest and during hyperaemia induced by the infusion of intravenous adenosine. The ratio between the 2 velocities corresponds to the coronary flow reserve.”

Professor Tona says that his most important article so far, is titled “Coronary Flow Velocity Pattern and Coronary Flow Reserve by Contrast-Enhanced Transthoracic Echocardiography Predict Long-Term Outcome in Heart Transplantation,” published in Circulation in 2006.2 “This work introduced, for the first time, echocardiographic noninvasive evaluation of coronary flow reserve in heart transplantation for prognostic stratification,” he says.

Throughout his studies on cardiomyopathies, heart failure, and heart transplantation, Professor Tona has focused on the pathophysiology and diagnosis of cardiac allograft vasculopathy. “This form of ‘chronic rejection’ involves both the epicardial vessels and coronary microcirculation,” says Professor Tona. “For this reason, I saw the real possibility of applying noninvasive measurement of coronary flow reserve after transplantation.”

In recent years, Professor Tona’s group has developed further diagnostics in this area, and his studies have shown that the coronary flow reserve can be used to identify cardiac allograft vasculopathy defined by angiographic criteria and coronary intravascular ultrasonography criteria. He explains, “We showed how coronary microvascular injury in terms of abnormal coronary flow reserve by transthoracic echocardiography can identify transplant patients with allograft vasculopathy.3–5 We also demonstrated how the measurement of microvascular function enabled stratification of the risk of major cardiovascular events in patients with heart transplantation. Recently, the measurement of the coronary flow reserve has been introduced in the guidelines for the follow-up of patients after heart transplantation.”
“Inflammation Seems to Be a Common Pathway Linking Some Diseases to an Increased Cardiovascular Risk”

Professor Tona was born in Venice in 1969 and developed an early enthusiasm for medical studies while still in high school. He trained at the University of Padua Medical School and completed a cardiology fellowship in 2001 under the guidance of the chair of cardiology, Professor Sergio Dalla Volta, MD, PhD. He says, “I thought cardiology was a branch of medicine that best lent itself to translational studies.” Professor Tona then completed a PhD in cardiovascular sciences in 2004 supervised by Professor Gaetano Thiene, MD (see http://circ.ahajournals.org/content/118/19/f109).

As assistant professor of cardiology in the Department of Cardiologic, Thoracic, and Vascular Sciences since 2007, Professor Tona is involved in the organisation of outpatient clinics, clinical assistance, research, administration, and teaching fellow and PhD students. He maintains a strong interest in the entire process of research, from data acquisition to statistical analysis, but like many cardiologists, he finds it challenging to combine clinical care with research.

He says, “My current focus is on the role of microvascular injury in acute allograft failure and the mechanisms mediating transplant coronary artery disease and the role of microvascular dysfunction in systemic inflammatory diseases, endocrine diseases, and cardiomyopathies. Diseases such as psoriasis have an increased cardiovascular risk, yet are often overlooked in cardiology. Several attractive and intricate pathophysiological links exist between diseases, and inflammation seems to be a common pathway linking some diseases to an increased cardiovascular risk. I think noninvasive imaging may improve our knowledge in this field and move it from bench to bedside.”

Professor Tona would advise people wanting to follow a career in medicine to make a considered choice about the direction of their career. He says, “You cannot possibly do it all at the same time, but you can do most of the things that you want to do over time. You have to make choices.”

Looking to the future, Professor Tona believes that noninvasive methods such as echocardiography and magnetic resonance imaging will bring further basic knowledge to the bedside. A key part of his future plans is to play a role in improving understanding of the mechanisms underlying microvascular dysfunction in many diseases.

References

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Mark Nicholls is a freelance medical journalist.
Awards: Heineken Young Scientist Award 2012 for Dutch Postdoctoral Researchers

Recognising Promising Young Scientists Whose Outstanding Research Sets an Example for Other Young Scientists

Linda W. van Laake, MD, PhD, assistant professor and resident in cardiology, University Medical Center Utrecht and Hubrecht Institute, Utrecht, the Netherlands, winner of the 2012 Heineken Young Scientists Award for Medicine, describes the award and her research to Jennifer Taylor, BSc, MSc, MPhil.

Candidates in the various disciplines can be nominated by the deans of Dutch universities, the general director of the Netherlands Organisation for Scientific Research, and the Royal Netherlands Academy of Art and Sciences director of research. Researchers who have received their PhD <5 years previously or who will receive it within 3 months of the presentation of the award are eligible. They should have conducted outstanding research and have promising careers ahead of them. The awards recognise promising young scientists whose outstanding research means that they set an example for other young scientists, and the winners are selected by the Royal Netherlands Academy of Arts and Sciences.

The award money is intended for personal use, to give extra encouragement to talented young scientists and scholars. “Just like the Nobel prizes, it can be spent on anything,” says Dr van Laake. “So far, I have used it for a study visit to the United States and bought a new lightweight laptop so I can work efficiently when I am travelling.”

Dr van Laake received the award for medicine for her research on regeneration of the heart with embryonic stem cells.1,2 The jury praised her as 1 of the few young medical specialists who succeeds in combining clinical work with basic scientific research, referring also to her perseverance and creativity.
focus on the understanding of fundamental cardiac developmental and repair processes will promote the recapitulation of cardiac differentiation in vitro. Currently, the team is investigating the influence of circadian or “day-night” rhythms on cardiac development and regeneration. Dr van Laake says, “Combining a variety of novel approaches together with a greater understanding of how heart development and repair work, we strive to create better personalised heart failure therapies.”

References

Jennifer Taylor is a freelance medical journalist.
Funding: Swiss Heart Foundation Grants

“Essential for Establishing My Independent Career in Cardiovascular Research”

Giuseppe Vassalli, MD, professor of cardiology, research group leader, and consultant cardiologist, Cardiocentro Ticino Foundation, Lugano, Switzerland, and Department of Cardiology, University Hospital, Lausanne, Switzerland, talks to Jennifer Taylor, BSc, MSc, MPhil, about his Swiss Heart Foundation funding.

Giuseppe Vassalli, MD, professor of cardiology, research group leader, and consultant cardiologist, Cardiocentro Ticino Foundation, Lugano, Switzerland, and Department of Cardiology, University Hospital, Lausanne, Switzerland, received funding from the Swiss Heart Foundation for 2 projects in 2011 and 2012. All researchers working in Switzerland are eligible to apply for funding of up to CHF 100'000 for 1 year and, in exceptional cases, CHF 200'000 for 2 years.

Professor Vassalli has been working on cardiovascular gene transfer since 1995, when he started using adenoviral vectors for gene transfer to blood vessels during a 3-year research fellowship funded by the Swiss National Science Foundation under the supervision of Professor David A. Dichek, MD, FAHA, Gladstone Institute of Cardiovascular Disease, University of California, San Francisco. In 1998, he returned to Switzerland and developed a cardiovascular research lab at the University Hospital of Lausanne. In 2000, he was awarded a 6-year professorship from the Swiss National Science Foundation, which allowed him to develop several projects on gene therapy for heart transplantation.

Over the past 5 years, Professor Vassalli has become interested in progenitor cells in the adult heart that may contribute to cardiac repair. One article in 2011 paved the way for receiving the Swiss Heart Foundation project funding. It shows that a small number of cells in the adult heart retain a DNA label for an extended period of time,1 a distinctive characteristic of tissue-resident stem cells that divide rarely.

Professor Vassalli says, “The funding has been essential for establishing my independent cardiovascular research career. During the past 2 years, we have explored the functional characteristics of progenitor cells isolated from the adult heart on the basis of high aldehyde dehydrogenase (ALDH) activity, which has been proposed as 1 of a small set of common characteristics shared by stem cells in many tissues, as well as by cancer stem cells in numerous types of cancer.” The group showed that these cardiac-derived cells are endowed with superior survival and growth characteristics compared with their ALDH-low counterparts.2 Professor Vassalli is currently analysing the ALDH isozymes responsible for high ALDH activity in cell populations obtained from atrial samples from patients who undergo heart surgery, and the molecular mechanisms that link this enzymatic activity to cell survival. This project is being conducted at the University Hospital of Lausanne with Albert Spicher, PhD, and Giuseppina Milano, PhD.

The second project exploring the regenerative potential of exosomes secreted by adult human cardiac progenitor cells is being conducted at the Cardiocentro Ticino Foundation with Lucio Barile, PhD, and Professor Tiziano Mocetti, MD, PhD, in collaboration with Mihaela Gherghiceanu, MD, PhD, and Professor Laurentiu M. Popescu, MD, PhD, Victor Babeș’ National Institute of Pathology, Bucharest, Romania, for electron microscopy. They have shown that exosomes are released by human cardiac-derived progenitor cells and cardiospheres,3 and that they exert protective paracrine effects on cardiovascular cells in vitro. “Exosomes secreted by adult human cardiac-derived progenitor cells are an attractive tool for regenerative approaches in patients with heart disease,” says Professor Vassalli. “Exosomes have been shown to mediate the beneficial paracrine effects of CD34+ bone marrow cells as well as embryonic mesenchymal stem cells in several models of cardiovascular disease. It is conceivable that exosomes derived directly from cardiac progenitor cells may promote cardiac differentiation and cardiac cell survival more efficiently than exosomes derived from other sources. From a practical point of view, exosomes could be stored as ‘off-the-shelf’ therapeutic products ready for use at any time.”

References


Jennifer Taylor is a freelance medical journalist.

Photo courtesy of Professor Vassalli.