Programme

Thursday, January 17

Morning Scientific Session 7:30–13:30

7:30 – 7:40 AM
Introduction and Overview of the Symposium
Jeremy Ruskin, MD

7:40 – 10:00 AM
Fibrosis and Atrial Fibrillation: From Cell to Bedside
Moderator:
Hans Kottkamp, MD
(All talks 20 minutes unless otherwise specified)

Fibrotic Atrial Cardiomyopathy Syndrome - Definition, Pathophysiology and Clinical Implications (30 min)
Hans Kottkamp, MD

Fibroblast Ion Channels and Atrial Remodeling in AF
Stanley Nattel, MD

Targeting the Cardiac Myofibroblast to Prevent Persistent AF
Jose Jalife, MD

The Role of Fibrosis and Scar Imaging in Clinical AF
Nassir Marrouche, MD

Techniques and Clinical Perspective on MRI Imaging

Continued on page 4

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Best Basic Science Papers on AF for 2012 Thursday 17 January **1:00 PM**

A stand-out year in basic science

A rundown of 2012's 'best' basic science papers in the field of atrial fibrillation will be delivered to delegates this afternoon at the symposium. By no means an easy task, the responsibility has been bestowed upon José Jalife, Professor of Molecular and Integrative Physiology and Co-Director of the Center for Arrhythmia Research, University of Michigan, Ann Arbor, USA.

"Saying that they are the best articles is a little bit biased on my part; these are things I selected based on what I read in the literature and what I find attractive and interesting," Dr Jalife told *Boston AF Symposium News*.

The first paper that Dr Jalife will discuss is a functional study looking at the stretch of atrial myocytes, and the role that inflammation plays in the eventual development of arrhythmias.[1] Dr Jalife stressed that the in vitro study, published in the *Journal of Pharmacological Sciences*, was chosen for its interesting exploration of the critical role of atrial inflammation in AF initiation and progression: "The idea is that although left atrial dilatation is a risk factor for fibrillation, the mechanisms causing atrial dilatation and inflammation are not very clear," he said.

"Inflammation is something that has been around for some time, not only in atrial fibrillation but in other diseases such as myocardial infarction and heart failure. So the objective of this study was to determine the mechanisms underlying infiltration by macrophages and how those macrophages alter atrial physiology. The methods they used are very clever: murine macrophages co-cultured with a line of atrial myocyte-derived cells from the mouse, with this co-culture located in a chamber known as a 'Boyden' chamber."

In brief, this Boyden chamber represented a system in which macrophages could be cultured on top of a rigid but permeable membrane separated from an underlying culture of myocyte-derived cells maintained on a stretchable silicon substrate. In this way, stretch could be applied to the myocytes only, while allowing any myocyte-secreted substances to diffuse through the membrane and reach the macrophages.

Crucially, the investigators found that macrophage proliferation was indeed influenced by the myocyte stretching process, as Dr Jalife explained: "They demonstrated that ATP actually is mediating the proliferation and the migration of these macrophages. And you can see that indeed the longer the time the myocytes are being stretched in the presence of the macrophages the more macrophages you will see in the chamber."


José Jalife

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> *José Jalife (Co-Director of the Center for Arrhythmia Research, University of Michigan, Ann Arbor, USA)*

In a clinical setting, these data suggest a mechanistic relationship between the stretch of the myocytes and the onset of an inflammatory response (and subsequent formation of fibrosis in the atrium). "To test this idea they looked at the infiltration of macrophages in the atria of mice in which they had produced a transverse aortic constriction," continued Dr Jalife.

"By chronically constricting the aorta they were able to produce hypertrophy in the ventricles, which also produced dilatation of the atria, followed by infiltration of macrophages. The mechanistic basis being the release of ATP through gap junctions, enabling

Continued on page 4

Continued from page 2

of Atrial Fibrosis Prior to and Following AF Ablation
Saman Nazarian, MD, PhD
Panel & Audience Discussion All Faculty (30 minutes)

10:00 – 10:20 AM
Brugada Syndrome and Atrial Fibrillation: Do They Share A Common Mechanism?
Carlo Pappone, MD, PhD

10:25 – 10:55 AM
Break and exhibits

10:55 – 12:55 PM
Difficult Cases in AF Management - Antiarrhythmic Drugs, Anticoagulation, and Clinical Decision Making: Panel and Audience Discussion (10 minutes each)
Moderator:
Eric Prystowsky, MD
Panel: John Camm, MD, Hans Kottkamp, MD, Peter Kowey, MD, and Claudio Tondo, MD, PhD

1:00 – 1:30 PM
Best Basic Science Papers on AF for 2012
Jose Jalife, MD

1:30 – 3:00 PM
Break and exhibits

Afternoon Scientific Session
3:00 PM – 6:30 PM

3:00 – 3:30 PM
Best Clinical Science Papers on AF for 2012
John Camm, MD

3:30 – 6:30 PM
Satellite Case Presentations:

Massachusetts General Hospital, Boston, MA

Moderator: Jeremy Ruskin, MD
Faculty: Moussa Mansour, MD, Kevin Heist, MD, PhD and Conor Barrett, MD

Pre-Recorded Case Presentations:

Korea University Medical Center
Young-Hoon Kim, MD, PhD

University of Pennsylvania
Francis Marchlinski, MD

Texas Cardiac Arrhythmia Institute
Andrea Natale, MD

Mayo Clinic
Douglas Packer, MD

Mount Sinai Medical Center
Vivek Reddy, MD

Loyola University Medical Center
David Wilber, MD

6:30 Reception on exhibit floor
Adjourn

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Continued from page 2

the macrophages to migrate through the atria."

For his second cherry-picked paper of 2012, Dr Jalife has chosen a study focusing on genes identified to increase the propensity of certain families to having AF.[2] In the study, the authors identified a Q76E variant within the coding sequence of the bone morphogenetic protein (BMP) antagonist gremlin-2 (GREM2) that increases its inhibitory activity. "This BMP protein is associated with another gene which is called PITX2 which has been demonstrated by genome-wide associated studies to be highly relevant for atrial fibrillation, but nobody knew the connection between the gene, the locus of that gene, and the atrial fibrillation," said Dr Jalife.

Importantly, the GREM2 variant blocks BMP signaling and acts upstream to PITX2, thus it may have implications in AF. Specifically, embryonic development of the pulmonary veins depends on PITX2, thus disruption of this transcription factor is a crucial consideration.[2]

"If there are alterations or mutations in these genes the heart does not develop correctly, and the left atrium does not form well: it's a very significant problem in embryogenesis," said Dr Jalife. "In the development of mice, PITX2 expression is regulated by these BMP signals, which is regulated itself by the GREM2 gene."

To analyze the consequences of the mutation, the authors used a zebrafish model: "Zebrafish are a great model to study mutations because the fish develop very rapidly, they are transparent (you can see the heart), and you can produce mutations with relative ease – much easier than mice. They are small in size, they breathe readily, the eggs are externally fertilized and the embryos develop very quickly. In addition, they can be genetically manipulated, and they have close homology to humans.

"They looked at the functional modeling in the zebrafish and they showed that, through regulation of the BMP signaling, GREM2 is absolutely required for the lateralization of the heart and atrial differentiation during development. They have some really spectacular pictures in which they show that after 48 hours of fertilization the heart in the wild type fish is already lateralizing and you see the formation of the atrium very nicely. In contrast, in the absence of the GREM2, the heart is just a long tube with a very small atrium. They provide very neat demonstration of the importance of this GREM2 in lateralization. "

In addition, the author's work with mouse models also demonstrated that GREM2 over-activity causes an induction of other AF candidate genes (L-type calcium channel, connexin-40, sarcolipin and atrial natriuretic peptide). "So it's really a very nice demonstration of how a genetic modification can lead to atrial fibrillation," said Dr Jalife. "Obviously this is a model, and you cannot directly extrapolate from this zebrafish to the human, but it gives you very interesting ideas of how this mutation affects the expression of channels or proteins or genes that may be involved in atrial fibrillation."

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> *José Jalife (Co-Director of the Center for Arrhythmia Research, University of Michigan, Ann Arbor, USA)*

For his final paper, Dr Jalife has chosen a study examining the effects of progressive weight gain on the substrate of AF.[3] "As we know, obesity is associated with atrial fibrillation. The more obese a person is, the more likely that person will develop atrial fibrillation," said Dr Jalife.

30 sheep were studied at baseline, and at four-month and eight-month intervals following a high-calorie diet. "They sampled some of the sheep at each point for cardiac MRI and hemodynamic studies, and also used high-density multisite biatrial epicardial mapping to quantify the refractory period, conduction velocity and some electrophysiological parameters that may be associated with atrial fibrillation inducibility," said Dr Jalife.

"They also did histology for fibrosis, inflammation and intramyocardial lipidosis, followed by a molecular analysis for various genes including endothelin-A and –B receptors and platelet-derived growth factors."

In short, the study demonstrated that as animals progressively gained weight, i.e. from baseline to overweight to obese, a progressive increase could be seen in a number of factors: left and right atrial volume; myocardial mass; pericardial fat; left and right ventricular end-diastolic volume; mean atrial pressure and left atrial pressure (indicating atrial dilation).

In addition, there was progressive adiposity associated with reduced atrial conduction velocity ($P < 0.001$), increase in conduction heterogeneity index ($P < 0.001$) and increase in inducible ($P = 0.001$) and spontaneous ($P = 0.001$) AF.

"They also demonstrated that there is indeed more fibrosis, that the atrial fibrillation is much more easily inducible, and that there is a greater propensity for spontaneous atrial fibrillation in obese animals," said Dr Jalife.

He continued: "In general the fibrosis, adiposis and inflammation seem to be the most relevant parameters associated with the development of atrial fibrillation. And so their conclusion is that obesity is associated with atrial electro-structural remodeling, and with progressive obesity there were changes in atrial size, conduction parameters, histology and expression of profibrotic mediators. These changes were associated with spontaneous and more persistent atrial fibrillation."

References

1) Oishi S et al. Stretch of Atrial Myocytes Stimulates Recruitment of Macrophages via ATP Released Through Gap-Junction Channels. J Pharmacol Sci (2012); 120: 296 – 304
2) Müller I et al. Functional modeling in zebrafish demonstrates that the atrial-fibrillation-associated gene GREM2 regulates cardiac laterality, cardiomyocyte differentiation and atrial rhythm. Disease Models & Mechanisms (2013); 6
3) Abed H et al. Obesity results in progressive atrial structural and electrical remodeling: Implications for atrial fibrillation. Heart Rhythm (2013); 10: 90–100