News & Views in ...

Interventional Cardiology

Cardiac monolayers produced from human stem cells for arrhythmia research

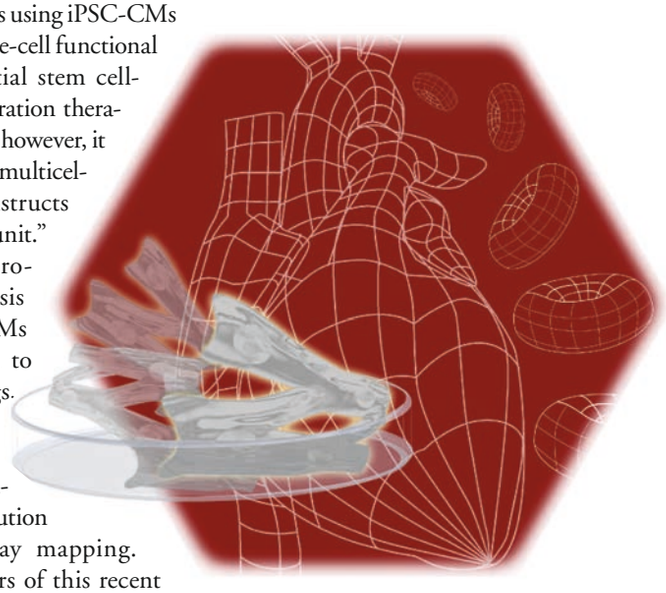
Human stem cell-derived cardiac monolayers that demonstrate a beating velocity comparable to rodent models have been developed alongside a new imaging platform for monitoring their activity.

Human induced pluripotent stem cell-derived cardiomyocyte (iPSC-CM) cardiac monolayers displaying similar activity to those seen in resting hearts have recently been developed by a team led by the University of Michigan Center for Arrhythmia Research (MI, USA). In the same study, the team also developed an imaging platform capable of multiparameter electrophysiological mapping of cardiac preparations. The study was recently published in *Circulation Research*.

These recent developments could have important implications for both research purposes and future potential cell-based cardiac regeneration therapies for arrhythmia patients, as senor author Todd Herron, an assistant research professor in the Departments of Internal Medicine and Molecular and Integrative Physiology at the University of Michigan, explained: "To date, the majority of studies using iPSC-CMs have focused on single-cell functional analysis. For potential stem cell-based cardiac regeneration therapies for heart disease, however, it is critical to develop multicellular tissue-like constructs that beat as a single unit."

Previously, electrophysiological analysis of human iPSC-CMs has been restricted to single-cell recordings. while small cardiomyocyte aggregates could only be analyzed using low-resolution microelectrode array mapping. However, the authors of this recent study addressed this shortcoming by developing a fluorescence imaging platform based on electronically controlled light-emitting diode illumination, along with a multiband emission filter and single-camera sensor. This imaging platform allows simultaneous monitoring of action potentials and intracellular calcium wave propagation in the stem cell-derived cardiac monolayer preparations. "Action potential and calcium wave impulse propagation trigger each normal heart beat, so it is imperative to record each parameter in bioengineered human cardiac patches," reported Herron.

In order to create human iPSC-CM cardiac monolayers, this recent study subsequently used a bioengineering approach utilizing stem cells generated from skin biopsies in order to create large (≥1 cm diameter) electrically coupled human cardiac monolayers.



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The monolayers reportedly generated action potentials and calcium waves at speeds closer to those of an actual human heart than previous preparations – 60 beats per min, which is 10-times faster than the majority of previously published results. This velocity is comparable to that seen in rodent systems and the authors suggest this as a reason why their human iPSC-CM cardiac monolayers are advantageous over their commonly used rodent counterparts for use in arrhythmia mechanism research; however, they acknowledge that this is still behind the velocity seen in healthy adult hearts.

Sources: University of Michigan News Release: www.uofmhealth.org/news/cardiac-patches-0619; Lee P, Klos M, Bollensdorff C et al. *Simultaneous voltage and calcium mapping of genetically purified human induced pluripotent stem cell-derived cardiac myocyte monolayers.* Circ. Res. *110(12), 1556–1563 (2012).*

New development set to sharpen up cardiac 4D PET images

Newly developed 4D PET image reconstruction could mean that the blurring seen in diagnostic cardiac imaging caused by heart movements might become a thing of the past.

A novel development in molecular imaging, 4D PET image reconstruction, has recently been unveiled at the Society of Nuclear Medicine's 59th Annual Meeting (Miami, FL, USA) which took place in June 2012. The method compensates for the blurring caused by rhythmic movements of the heart and lungs commonly seen in currently used diagnostic cardiac imaging, providing a sharper image.

Although a long way from clinical implementation, the Chinese researchers behind the development are hopeful that their work will improve heart viability studies: "This research provides an opportunity to further improve the diagnostic accuracy of cardiac PET imaging, which can be exchanged to some degree for faster scanning and lower dose," explained Si Chen, lead author of the study and research scientist for the Department of Engineering Physics at Tsinghua University (Beijing, China).

"People have previously worked on compensating for either cardiac or respiratory motion in image reconstruction in the past, but our research is the first viable reconstruction of a PET image with compensation for both cardiac and respiratory motion using all the PET data," Chen continued.

The 4D PET image reconstruction uses quantitative image data and a specially developed algorithm to transform the blurred image into a clearer version. Using PET data from multiple cardiac stress tests the researchers found that the new method significantly improved imaging contrast between the myocardium and heart chambers by 15% and that it reduced image noise by 60% compared with conventional methods of image reconstruction with cardiac gating.

It is estimated that 2–3 years of further investigation are required before the 4D PET image reconstruction is suitable for clinical implementation; however, once the multiple phases of clinical evaluation are complete, its use could reduce patient exposure and the time taken to perform diagnostic cardiac imaging.

Source: Society of Nuclear Medicine Press Release: http://interactive.snm.org/index.cfm?PageID=11718

Subclavian transcatheter aortic valve implantation is a safe, feasible alternative to transfemoral access

Recent results from a 2-year Italian study suggest that transcatheter aortic valve implantation (TAVI) via the subclavian route is an acceptable alternative to performing the procedure via the transfemoral option. This is reportedly the first study to provide medium-term data on subclavian TAVI and it was recently published online, ahead of print in the *Journal of the American College of Cardiology*.

In the recent Italian study, the procedural success and 2-year results of subclavian TAVI using the CoreValve prosthesis (Medtronic, Inc., MN, USA) were studied using propensity-matched analysis. Both subclavian and transfemoral TAVI groups consisted of 141 patients matched for baseline clinical characteristics. The only reported difference between the two groups was the higher prevalence of peripheral artery disease in the subclavian group, explained by the blocked or impeded femoral routes in patients for

whom the transfemoral route is impossible or difficult.

Similar procedural success was observed in both the subclavian and transfemoral groups (97.9 and 96.5%, respectively; p = 0.26) and there were no major differences in the combined safety end points or the prevalence of major vascular complications or life-threatening bleeding events between the two groups. Access site-related bleeding events were significantly lower in the subclavian group, indicating the safety of this option. At 2-year follow-up, similar numbers of the subclavian and transfemoral patients had survived (72 and 73.7%, respectively; p = 0.84).

The study authors conclude that "these results suggest that subclavian access represents a valid alternative not only when the femoral access is contraindicated, but also when it appears difficult, albeit feasible."

Source: Petronio AS, De Carlo M, Bedogni F et al. *2-year results of CoreValve implantation through the subclavian access: a propensity-matched comparison with the femoral access.* J. Am. Coll. Cardiol. *doi:10.1016/j.jacc.2012.04.014 (2012) (Epub ahead of print).*

Neoatherosclerosis is initially worse with drug-eluting stents

A recent study led by researchers at Massachusetts General Hospital (MA, USA) has demonstrated that lipid-rich neoatherosclerosis develops more rapidly following stent implantation using drug-eluting stents (DESs) compared with bare-metal stents (BMSs). However, lipid-laden plaques were found in both stent types after 48 months and many questions remain surrounding post-stent implantation neoatherosclerosis. The study has been published online ahead of print in the *American Journal of Cardiology*.

Following reports of neoatherosclerosis inside stents and subsequent acute coronary syndrome owing to a disrupted neointimal hyperplasia, this recent study sought to compare the characteristics and time-course of neointimal hyperplasia in patients with implanted DESs or BMSs using optical coherence tomography (OCT).

A total of 134 stents from 124 patients enrolled in the international Massachusetts General Hospital OCT registry were studied and divided into three groups determined by follow-up time: early phase (<9 months; 25 BMSs and 27 DESs), intermediate phase (≥9 to <48 months; 18 BMSs and 43 DESs) and delayed phase (≥48 months; 13 BMSs and 12 DESs). OCT was used to analyze the presence of lipid-laden intima, percentage of lipid-rich plaque and signal attenuation.

A greater incidence of lipid-laden plaque was found in the early- and intermediate-phase DES patients compared with their BMS counterparts. There was a higher proportion of lipid observed in the neointima in these phases in DES patients. Also in the intermediate phase, OCT signal attenuation in the DES group was greater than in the BMS group, perhaps indicating early changes in the neointimal hyperplasia properties of these patients.

However, in the delayed-phase groups, a similar amount of DESs and BMSs exhibited lipid-laden plaques (75 and 77%, respectively). In addition, the BMS group exhibited a greater percentage of lipid-rich plaque compared with the DES group, and OCT signal attenuation was greater in BMSs.

This study also compared OCT findings with symptom status (symptomatic [n = 35] vs asymptomatic [n = 103]). It was found that the incidence and percentage of lipid-laden plaque was greater in those with symptomatic restenosis, leading the authors to suggest that a more vulnerable plaque component could have contributed to the symptomatic presentation, in addition to stenosis severity. Neoatherosclerosis has previously been linked to very late stent complications.

The authors suggest that the more prevalent development of neoatherosclerosis in early- and intermediate-phase DESs could be caused by hypersensitivity and inflammatory changes following DES implantation, leading to an exaggerated macrophage infiltration into the neointima and subsequent tissue changes.

Further studies are required to clarify the clinical and pathological significance of neovascularization.

Source: Yonetsu T, Kim JS, Kato K et al. *Comparison of incidence and time course of neoatherosclerosis between bare metal stents and drug-eluting stents using optical coherence tomography.* Am. J. Cardiol. *doi:10.1016/j.amjcard.2012.05.027 (2012) (Epub ahead of print).*

– All stories written by Sarah Miller

About the News and Views

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