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Using the human trabeculae muscle work loop assay for assessing cardiac contractility effects of test compound

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Adverse drug response is a significant risk to human health and is costly to the pharmaceutical industry when compounds are withdrawn from market. *In vitro* cardiac safety testing is generally conducted using predominantly animal tissue or cells or stem cell derived cardiac myocytes. Although side effects of drugs can be caused by many things, one area of great concern is the effects of drugs on the force that heart muscle can produce during its role in pumping blood around the body. Development of a human heart contractility assay would greatly improve the understanding of the human relevance of non-clinical findings; a chemical might cause a change in cardiac contractility in animals but not humans and vice versa. The pharmaceutical, biotechnology, cosmetic, agrochemical, food industries and regulators require an improved assessment of cardiovascular liability associated with drug/chemical-induced changes in cardiac contractility that is more predictive than existing assays. We have demonstrated that the work loop cardiac contractility assay is 93% predictive of human findings than existing assays when using animal tissue. We have expanded this investigation to determine whether the human cardiac work loop assay had the potential to provide a more predictive model of heart muscle dynamics to assess inotropic effects. To validate this assay, a range of positive and negative inotropic agents were tested and effective concentrations compared with those tested in the clinic. The human cardiac muscle work loop assay predicted inotropic effects at clinically relevant concentrations. The human cardiac work loop assay is a new approach to the detection of drug effects on cardiac contractility, providing a superior predictivity of inotropy assessment and importantly identifying inotropy risk at clinically relevant concentrations. The use of human tissue has the potential to replace the use of animals and provide greater concordance with man.

Biography

Mayel Gharanei has completed his PhD on the investigation of the cardiotoxicity of Doxorubicin and strategies for adjunctive cardioprotection. During his PhD, he worked on the optimization of the cardiac work loop technique for safety assessment of pharmaceutical compounds. During his Post-doctoral research, he undertook dedicated studies on the development and validation of the cardiac rat papillary muscle and human trabeculae muscle work loop technique. He is working as the Lead Research Scientist at InoCardia where he supervises research staff and projects associated with testing pharmaceutical compounds on rat papillary and human trabeculae muscle mechanics. As a Research Fellow at Coventry University, he is supervising PhD and Masters by Research students in the field of cardiotoxicity, myocardial ischemia reperfusion injury, cardioprotection, obesity, aging and development and validation of novel clinically relevant cardiovascular non-clinical assays.

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