[redacted] Echocardiographic variables	Satistic analysis	Time to onset of ART
Right atrial area (cm2)	r di Pearson	-0,411
	p-value	**0,022**
iRAV (ml/m2)	r di Pearson	-0,463
	p-value	**0,009**
VRT/VTI_{RVOT}	r di Pearson	-0,102
	p-value	0,587

Legend: iRAV, indexed right atrial volume; TRV, tricuspid regurgitation velocity; VTI, velocity time integral; RVOT, right ventricle outflow; ART, antiretroviral therapy

Keywords: Exercise-induced pulmonary hypertension, HIV, Stress echocardiopgraphy

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107027

Atrial-like cardiomyocytes derived from human pluripotent stem cells: In vitro modeling of atrial cardiomyopathies

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Human induced pluripotent stem cell (hiPSC)-derived cardiomyocytes (CMs) are an attractive source for disease modeling and pre-clinical drug testing. However, standard cardiac differentiation protocols lead to a mixed population of ventricular-, atrial- and nodal-like cells, limiting the reliability for studying mechanisms of atrial fibrillation. We applied retinoic acid (RA), known to induce atrial phenotype. We aim to develop a hiPSC-based in vitro platform, for modeling human atrial-specific cardiomyopathies.

iPSCs-CMs were differentiated toward atrial-like phenotype by applying 1 μM RA, in parallel with conventional protocol (Ctrl). Contraction profiles recorded by Muscle Motion algorithm, yielded a higher beating frequency with duration, time to peak, and relaxation time shorter in RA than in Ctrl. Consistently, extracellular field potentials (FP) recorded by Multi Electrode Array (MEA) were shorter in RA-treated CMs than in Ctrl one. Patch-clamp was useful to identify atrial vs ventricular action potential parameters by injecting an appropriate IK1 computational model. RT-qPCR and IC confirmed higher percentage of atrial-like CMs in RA by an overexpression of atrial markers, and downregulation of ventricular ones.

Our human in vitro model can be a reliable platform to study the mechanism underlying inherited or induced atrial arrhythmia in human CMs, suitable to screen anti-arrhythmic agents in a translational approach.

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Istaroxime metabolite PST3093 selectively stimulates SERCA2a and reverses disease-induced changes in cardiac function

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Heart failure (HF) therapeutic toolkit would strongly benefit from the availability of ino-lusitropic agents with a favourable pharmacodynamics and safety profile. PST3093 is the main metabolite of istaroxime, an agent combining Na^+/K^+ pump inhibition and SERCA2a stimulation, shown by phase 2 trials to be promising in the acute setting. PST3093 half-life is substantially longer than that of istaroxime; therefore, if it retained the effects of the parent compound, it would allow to exploit istaroxime pharmacodynamics in chronictreatment.

We studied PST3093 for its effects on SERCA2a and Na^+/K^+ ATPase activities, Ca^{2+} dynamics in isolated myocytes and hemodynamic effects in an in-vivo rat model of diabetic (streptozotocin (STZ)-induced) cardiomyopathy. At variance with its parent compound, PST3093 is a "selective" (i.e. devoid of Na^+/K^+ pump inhibition) SERCA2a activator. In in- vivo echocardiographic assessment, PST3093 improved overall cardiac performance (e.g. stroke volume) without decreasing heart rate, and reversed most STZ-induced abnormalities. Modulation of both systolic and diastolic indexes contributed to the improvement. For i.v. administration, PST3093 toxicity was considerably lower than that of istaroxime and its evaluation against 50 targets commonly involved in cardiac and extracardiac side-effects, failed to reveal significant interactions.

PST3093 is a "selective" SERCA2a activator, the prototype of a novel pharmacodynamic category with a potential in the ino-lusitropic approach to HF, particularly with prevailing diastolic dysfunction. While PST3093 may actually contribute to the proven clinical efficacy of istaroxime, its pharmacodynamics are peculiar and its pharmacokinetics are suitable for chronic administration.

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