Online supplement:

Rate correction of action potential duration

In this study a rate correction formula was applied to the action potential repolarization phase to compensate for drug-induced changes in spontaneous rate. The correction was applied to both baseline signals and signals recorded in the presence of a drug to allow detailed comparison of repolarization timings at a standard cycle length (1s). This approach assumes that the drug effects on repolarization were not strongly rate dependent. Another way of using the rate correction is to calculate the baseline action potential duration at cycle lengths achieved in the presence of the drug. This alternative approach makes no assumption on rate dependence of the drug action but reports the relative effect of a range of drug concentrations at the different cycle lengths achieved at each concentration. This approach makes interpretation of dose-response relationships difficult. An alternative approach is to use external fixed stimulation to provide a constant cycle length across all the conditions. However, this method cannot be simply applied to iPS-CMCs that are spontaneously active. In blinded studies, the possibility exists that the drug will induce an increase in spontaneous rate to a higher value than the pacing rate. This issue can be circumvented by pacing at short cycle lengths (eg, 0.5s) to overcome most of the possible rate changes. In doing so, the effects of drugs will be recorded at physiologically high rates (~180bpm), which limits the value of the study. In summary, all methods of rate correction have issues; in this study, an APD correction was applied to both baseline and drug-based AP signals with the simplifying assumption that the drug did not affect rate dependence of APD.

Table of parameters

Parameter	iCell		Cor4U	
	Mean	SD	Mean	SD
Cycle length (s)	1.5	0.5	0.99	0.14
APD90 (ms)	427	49	229	15
Diastolic Interval (s)	1.07	0.44	0.76	0.14
Rise time (ms)	5.7	1.3	6.4	2.2
APD90 corrected to 1s (ms)	370	30	229	13