to activating $\mathrm{Ca}^{2+}$ in a site-dependent manner. The calculated CICR activity strongly correlated with the ER $\mathrm{Ca}^{2+}$ level, an index of $\mathrm{Ca}^{2+}$ leak. Importantly, the accelerated sensitivity to activating $\mathrm{Ca}^{2+}$ was linked to pathogenesis of CCD. Overall, the effects were similar to those of the amino-terminal mutations. The underlying molecular mechanism will be discussed.

1364-Pos Board B315
Characterization of Dual Mutant RyR1D-S100A1KO Mice with Disrupted CaM and S100A1 Binding to CaMBD2 and Lacking S100A1 Expression

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We recently demonstrated that age-dependent declines in intrinsic and maximal heart rates are associated with slower action potential (AP) firing rate and a hyperpolarizing shift in the midpoint activation voltage ($V_{1/2}$) of the funny current ($I_f$) in isolated sinoatrial myocytes (SAMs). Given recent studies have characterized cardiac ionic currents in cardiocytes derived from human induced pluripotent stem cells. However, direct comparison with human ventricular myocytes is hampered by differences in experimental conditions. Similarly, stem cell derived cardiocytes are different and potentially more variable than native myocytes. We examined commercially prepared cells (iCells) and scale production cells (hiPSC-CMs) using electronic expression of IK1 to distinguish ventricular cells, compared with myocytes (VM) from biopsy samples.

APs were recorded in VM, iCells and hiPSC-CMs. iCells and hiPSC-CMs had depolarized membrane potentials, slower upstroke velocities, and prolonged APD20 relative to VM. These differences were greater for electronic expression of IK1. Capacitances were larger in VM (298.97 ± 27.5 pF (4 hearts, n=44)) than in iCells (73.21 ± 5.4 (n=32), p<0.05) and hiPSC-CMs (64.25 ± 4.94 (n=75), p<0.05). At -120 mV, a large IK1 was observed in VM ($-14.3 ± 1.36 \mu\text{A/pF}$ (4 hearts, n=44)); iIK1 was much smaller in iCells ($-1.73 ± 0.92$ (n=19), p<0.01) and hiPSC-CMs ($-2.54 ± 0.49$ (n=29), p<0.01). VM had larger peak outward (Ito) currents at $+50 \text{ mV}$ ($6.2 ± 0.7 \mu\text{A/pF}$ (n=44, four hearts)) than iCells ($2.6 ± 0.2$ (n=19, p<0.01)) and hiPSC-CMs ($2.9 ± 0.3$ (n=29, p<0.01)) but all had similar variability relative to current density. Large sodium currents were recorded at 0 mV in VM ($-23.7 ± 3.4 \mu\text{pA/pF}$ (4 hearts, 32 myocytes)) as well as in iCells ($-26.1 ± 3.2$ (n=14)) and in hiPSC-CMs ($-17.0 ± 4.1$ (n=16)) with high degrees of variability for all cell types. In conclusion, there are functional differences between VM and stem cell derived cell types, but minimal differences between stem cell derived cardiocytes based on source. Similarly, cell to cell variability was similar regardless of source.

Cardiac Smooth and Skeletal Muscle Electrophysiology II

1366-Pos Board B317
A Comparison of Acutely Isolated Human Ventricular Myocytes with Stem Cell Derived Cardiocytes

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Recent studies have characterized cardiac ionic currents in cardiocytes derived from human induced pluripotent stem cells. However, direct comparison with human ventricular myocytes is hampered by differences in experimental conditions. Similarly, stem cell derived cardiocytes are different and potentially more variable than native myocytes. We examined commercially prepared cells (iCells) and scale production cells (hiPSC-CMs) using electronic expression of IK1 to distinguish ventricular cells, compared with myocytes (VM) from biopsy samples.

APs were recorded in VM, iCells and hiPSC-CMs. iCells and hiPSC-CMs had depolarized membrane potentials, slower upstroke velocities, and prolonged APD20 relative to VM. These differences were greater for electronic expression of IK1. Capacitances were larger in VM (298.97 ± 27.5 pF (4 hearts, n=44)) than in iCells (73.21 ± 5.4 (n=32), p<0.05) and hiPSC-CMs (64.25 ± 4.94 (n=75), p<0.05). At -120 mV, a large IK1 was observed in VM ($-14.3 ± 1.36 \mu\text{A/pF}$ (4 hearts, n=44)); iIK1 was much smaller in iCells ($-1.73 ± 0.92$ (n=19), p<0.01) and hiPSC-CMs ($-2.54 ± 0.49$ (n=29), p<0.01). VM had larger peak outward (Ito) currents at $+50 \text{ mV}$ ($6.2 ± 0.7 \mu\text{A/pF}$ (n=44, four hearts)) than iCells ($2.6 ± 0.2$ (n=19, p<0.01)) and hiPSC-CMs ($2.9 ± 0.3$ (n=29, p<0.01)) but all had similar variability relative to current density. Large sodium currents were recorded at 0 mV in VM ($-23.7 ± 3.4 \mu\text{pA/pF}$ (4 hearts, 32 myocytes)) as well as in iCells ($-26.1 ± 3.2$ (n=14)) and in hiPSC-CMs ($-17.0 ± 4.1$ (n=16)) with high degrees of variability for all cell types. In conclusion, there are functional differences between VM and stem cell derived cell types, but minimal differences between stem cell derived cardiocytes based on source. Similarly, cell to cell variability was similar regardless of source.

1367-Pos Board B318
Aging Alters cAMP Signaling and Membrane-Delimited Regulation of if in Sinoatrial Myocytes

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We recently demonstrated that age-dependent declines in intrinsic and maximum heart rates are associated with slower action potential (AP) firing rate and a hyperpolarizing shift in the midpoint activation voltage ($V_{1/2}$) of the funny current ($I_f$) in isolated sinoatrial myocytes (SAMs). Given that cAMP is an important intracellular modulator in SAMs, we hypothesized that reduced cAMP concentration may contribute to the slower APs and shifted $I_f$ in aged SAMs. To test this hypothesis, we applied a saturating concentration of cAMP via the patch pipette in whole cell voltage-clamp and current clamp experiments in acutely isolated SAMs from young and old mice. Here, we show that this exogenous cAMP completely reversed the age-dependent changes in both AP firing rate and $I_f$ in SAMs. In contrast, maximal stimulation of endogenous cAMP production, via co-application of the PDE inhibitor, IBMX and the adenylyl cyclase activator, forskolin, did not rescue either AP firing rate or $I_f$ in aged SAMs. These data indicate that a deficit in cAMP production and/or responsiveness may contribute to the age-dependent changes in both AP firing rate and $I_f$ in aged SAMs. We further determine how cAMP regulates $I_f$ in aged versus young SAMs, we compared $I_f$ activation in excised inside-out membrane patches from SAMs from young and old mice. Surprisingly, we found that the age-dependent hyperpolarized shift in the $V_{1/2}$ of $I_f$ persisted in the cell-free patches, indicating that soluble cAMP alone cannot account for the shifted $I_f$ in aged SAMs. Rather, aging appears to alter an additional, membrane-associated factor that regulates $I_f$ in SAMs. We are currently developing underlying mechanism(s) responsible for the age-dependent shift in the $V_{1/2}$ of $I_f$ and its relationship to AP generation in SAMs.