CA2+ entry through the ryanodine receptor (RyR1) channel is critical for activation of the sarcoplasmic reticulum (SR) Ca2+ release channel (RyR2). And this interaction appears to be disrupted during congestive heart failure (CHF). As a model of CHF, we studied cardiomyocytes (RyR2) derived from embryonic stem cells (ESC) and investigated the consequences of reduced Ca2+ buffering and Ca2+ release in ESC-derived cardiomyocytes (ESC-CMs). Using a functional knockout of Ryanodine receptor (RyR), and this interaction appears to be disrupted during congestive heart failure (CHF). In wild type (RyR+) and ryanodine receptor knockout (RyR−) ESC-R1 cardiomyocytes (CMs), rare spontaneous DADs were observed. DADs could be induced by hypercalcemia in wild type cells and by l-thyronine in RyR− CMs. Figure 4. Delayed afterdepolarizations (DADs) in ESC-derived cardiomyocytes. (A) RyR+ CMs derived from wild type (RyR+) ESCs in hanging drops (n=11). (B) RyR− CMs derived from ryanodine receptor knockout (RyR−) ESCs in hanging drops (n=7). **P<0.01. In wild type cells, spontaneous DADs could be observed at 20 mM [TEA+]o and 1 µM Bay K 8644, a Ca2+ channel agonist. The effect was lost upon washout of these agents. (C) RyR+ CMs: In wild type cells, spontaneous DADs could be observed at 20 mM [TEA+]o and 1 µM Bay K 8644, a Ca2+ channel agonist. The effect was lost upon washout of these agents.

**CONCLUSIONS**

SR Ca2+ release contributes to action potential shortening. DADs do not require RyR2-mediated SR Ca2+ release. Reduced SR Ca2+ release can be arrhythmogenic. In the absence of proper SR Ca2+ handling, an alternative thapsigargin-independent, ryanodine-dependent source of Ca2+ buffering may occur (possible mitochondria). This experiment suggests that contractile dysfunction and arrhythmogenesis are linked.