SUPPLEMENTAL MATERIAL

SUPPORTING METHODS

Model equations

The full equations for APD restitution and Ca cycling are given below, originally from Qu et al. [39], except for the APD restitution function, which comprise the full model including the equations provided in the main text. Parameter values are given in Table S1. Plots of key equation relationships are shown in Fig. S1.

The APD restitution function is given by

$$f(DI_n) = \begin{cases} a_0\,[1-\exp(-(DI_n+d_0)/\tau_0)\,], & \text{if } DI_n \geq d_{min} \\ 0, & \text{otherwise} \end{cases} \tag{S1}$$

The SR Ca release function that describes the restitution properties is given by

$$q(DI_n) = 1-\sigma_q \exp(-DI_n/\tau_q), \tag{S2}$$

and the function that describes the SR Ca load-dependence is given by

$$g([Ca_{SR}]_n) = [Ca_{SR}]_n \left[1-\frac{1-\alpha}{1+\exp(([Ca_{SR}]_n-l_c)/\beta)}\right]. \tag{S3}$$

The SR Ca uptake function that describe the dependence on the stimulus period is given by

$$u(t_{n+1}) = 1-\rho \exp(-t_{n+1}/\tau_u), \tag{S4}$$

and the function that describes the dependence on peak intracellular Ca is given by

$$h([Ca_i^p]_{n+1}) = [Ca_i^p]_{n+1} \left[1-\frac{1}{1+\exp(([Ca_i^p]_{n+1}-c_0)/\theta)}\right]. \tag{S5}$$

The steady-state total Ca concentration is given by

$$c(t_{n+1}) = c_0[1+\varepsilon \exp(-t_{n+1}/\tau_c)]. \tag{S6}$$

Cost Function

The cost function for parameter optimization reflects criteria (i)-(x) listed in the Methods and is given by:

$$cost = \begin{cases} w, & \text{if } Tonset_{NSR} \text{ or } Tonset_{CHF} = \nexists \\ -z(\Delta APD_{diff}) - z(\Delta[Ca_i^p]_{diff}) - z(\Delta APD_{NSR,comp}) & \text{otherwise} \\ \quad + w\left(F_{Ca_{SR}} + F_{J_{rel}} + F_{J_{up}} + F_{Ca^p} + F_{APD}\right) & \\ \quad + (Tonset_{CHF} - Tonset_{NSR} - \Delta Tonset_{fit})^2 & \\ \quad + (Tonset_{NSR} - Tonset_{NSR,fit})^2, & \end{cases} \tag{S7}$$

where $Tonset_x$ is the pacing period where APD alternans form ($|APD_{n+1} - APD_n| > .01$ ms) (where x is either CHF or NSR), ΔY_{diff} is the difference between the maximum CHF and NSR alternans amplitude (where Y is either APD or $[Ca_i^p]$), $Tonset_{NSR,fit} = 300$ ms is the fit pacing rate of APD alternans onset in NSR, $\Delta Tonset_{fit} = 140$ ms is the fit difference in APD alternans onset between CHF and NSR, and $\Delta APD_{NSR,comp}$ is the difference between the simulated maximum NSR APD alternans amplitude and specific criteria value (4 ms). The term F_x is a binary flag representing criteria (iii)-(vii) where a value of 1 indicates that the condition is not met, and w is a weighting variable defined as 10^9. Note that function $z(x) = sign(x)(x^2)$ is used to define differences in the cost function with the proper sign relative to the fit criteria.

SUPPORTING TABLE

Parameter	Definition	Units	NSR Value	CHF Value
a_0	APD restitution parameter	ms	275.9279	372.3244
d_0	APD restitution parameter	ms	437.7602	535.1088
τ_0	APD restitution parameter	ms	474.0194	803.6337
d_{min}	APD restitution parameter	ms	10	10
σ_q	SR Ca release parameter	-	0.5	0.5
τ_q	SR Ca release parameter	ms	160*	160*
α	SR Ca release parameter	-	0.036	0.036
l_c	SR Ca release parameter	μM	93.5	93.5
β	SR Ca release parameter	μM	14.6463	13.4016
ν	SR Ca uptake parameter	-	0.4787	0.4948
ρ	SR Ca uptake parameter	-	0.15	0.15
τ_u	SR Ca uptake parameter	ms	400*	400*
c_0	SR Ca uptake parameter	μM	28	28
θ	SR Ca uptake parameter	μM	20	20
γ	Ca-to-APD coupling parameter	μM^{-1}	10^{-3}	10^{-3}
ε	Ca accumulation parameter	-	2	2
τ_c	Ca accumulation parameter	ms	600*	600*
κ	Ca accumulation parameter	-	0.1	0.1
η	APD-to-Ca coupling parameter	μM/ms	0.1	0.1
λ	SR Ca release parameter	-	2.9864	3.0413
δ	SR Ca leak parameter	-	0	0.5464

Table S1. Model parameters. All parameters pertaining to the APD and Ca dynamics for NSR and CHF. * denotes parameters scaled by a factor of 2 to account for differences in heart rates between humans and small mammals.

SUPPORTING FIGURES

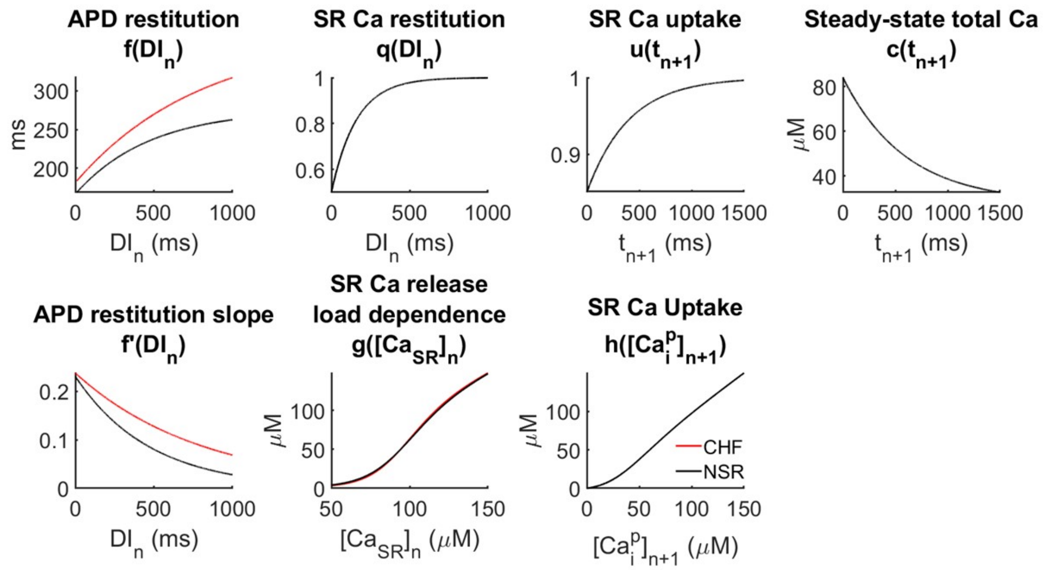

Figure S1. Discrete-time map model functions. Plots of the discrete-time map model functions and the APD restitution curve for NSR (black) and CHF (red).

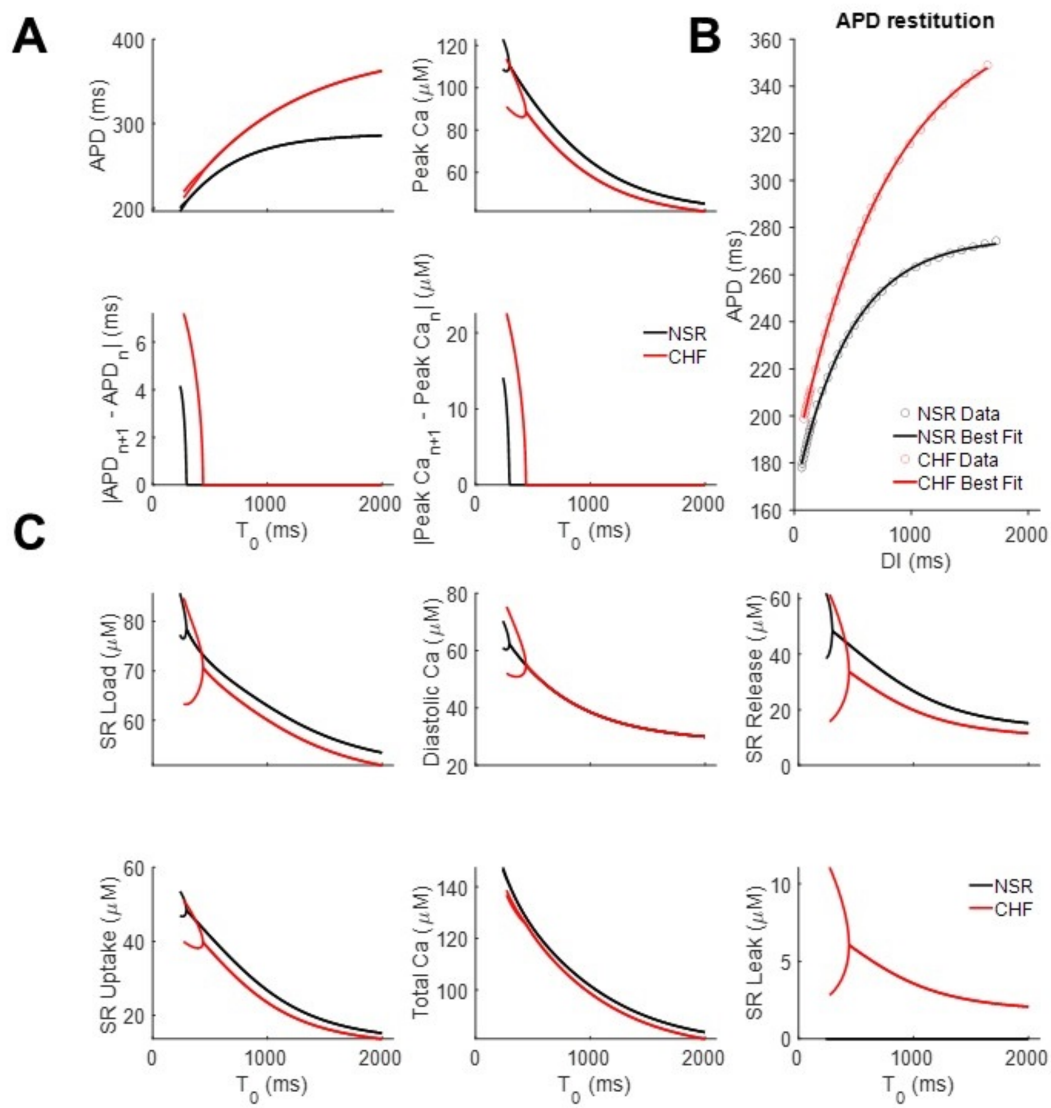

Figure S2. APD and Ca dynamics in response to constant pacing rate. (A, C) The values of each state variable are shown for the last 2 beats of simulations using a range of constant pacing periods (T_0) for the NSR (black) and CHF (red) model parameters. (B) Ionic model simulation APD restitution data (circles) and best fit (lines) are shown for both model phenotypes.

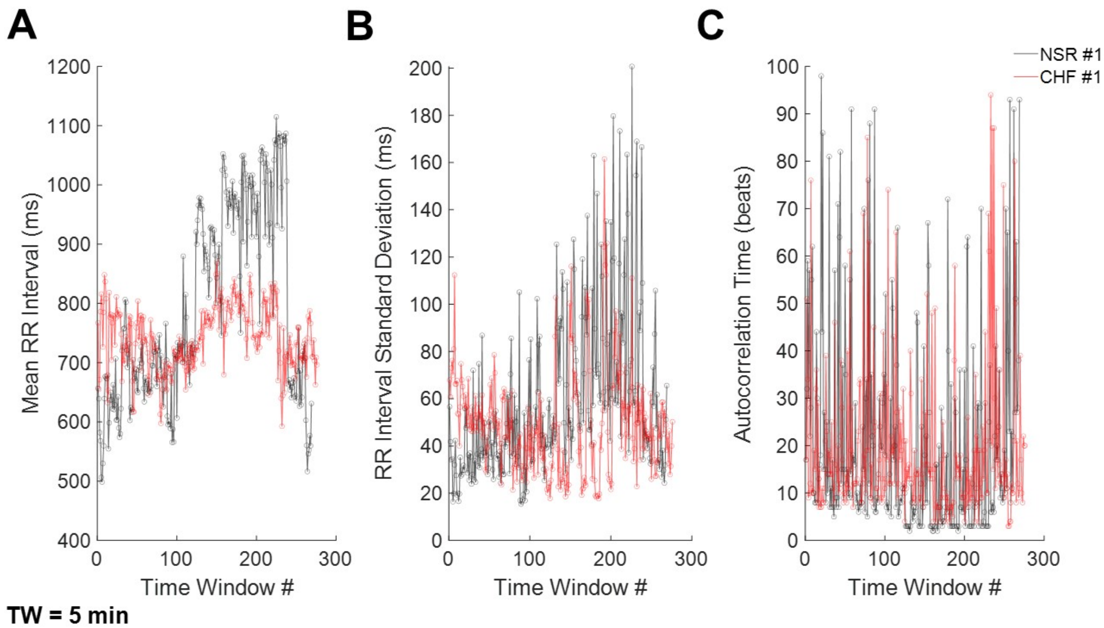

Figure S3. The mean RR interval (μ), RR interval standard deviation (σ), and autocorrelation time (τ) calculated from each 5 minute time window (TW) of the 24 hour sequences displayed in Fig. 1 are plotted as a function of time window number.

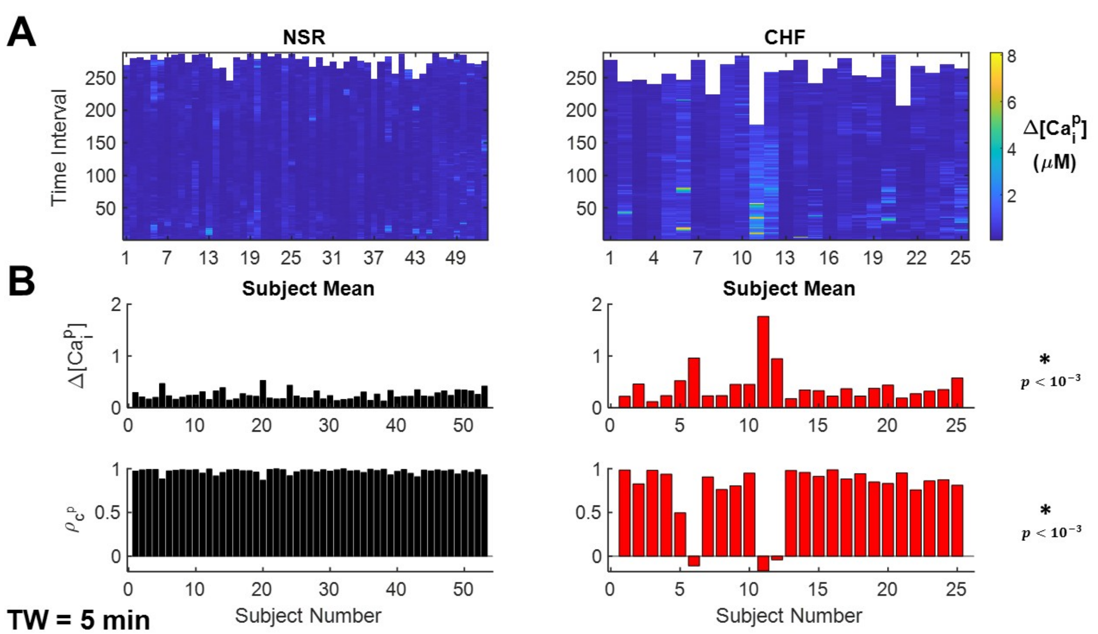

Figure S4. Peak Ca alternans formation is more prevalent in CHF. (A) $\Delta[Ca_i^p]$ is shown for each 5 minute segment of every 24 hour RR sequence in both populations. (B) The temporal mean of $\Delta[Ca_i^p]$ and ρ_{c^p} are depicted for each subject in the NSR (black) and CHF (red) populations. The populations have a significantly different temporal mean for $\Delta[Ca_i^p]$ and ρ_{c^p} ($*p < 10^{-3}$, unpaired t-test). Time window (TW) = 5 minutes. $\Delta[Ca_i^p]$: Mean magnitude of the beat-to-beat difference in peak Ca. ρ_{c^p}: Correlation coefficient between successive beats of peak Ca.

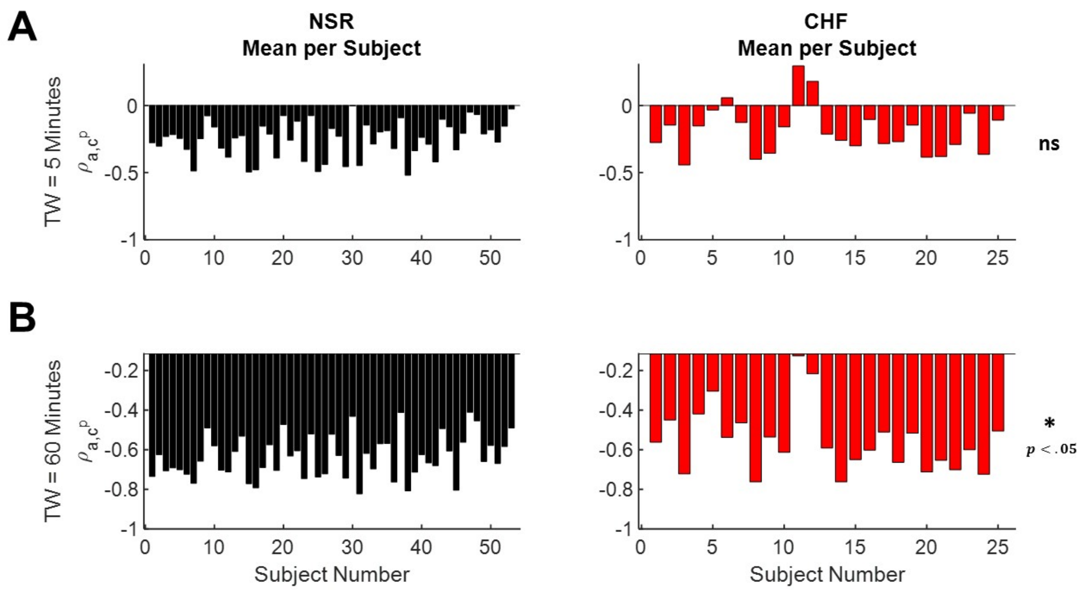

Figure S5. APD and peak Ca tend to be negatively correlated in NSR and CHF. Each subject's mean ρ_{a,c^p} is shown for a short (5 minutes, A) and long (60 minutes, B) time window (TW). ρ_{a,c^p} is significantly different between the two populations for the 60 minute time window (*$p < .05$, unpaired t-test). ρ_{a,c^p}: Correlation coefficient between APD and peak Ca.

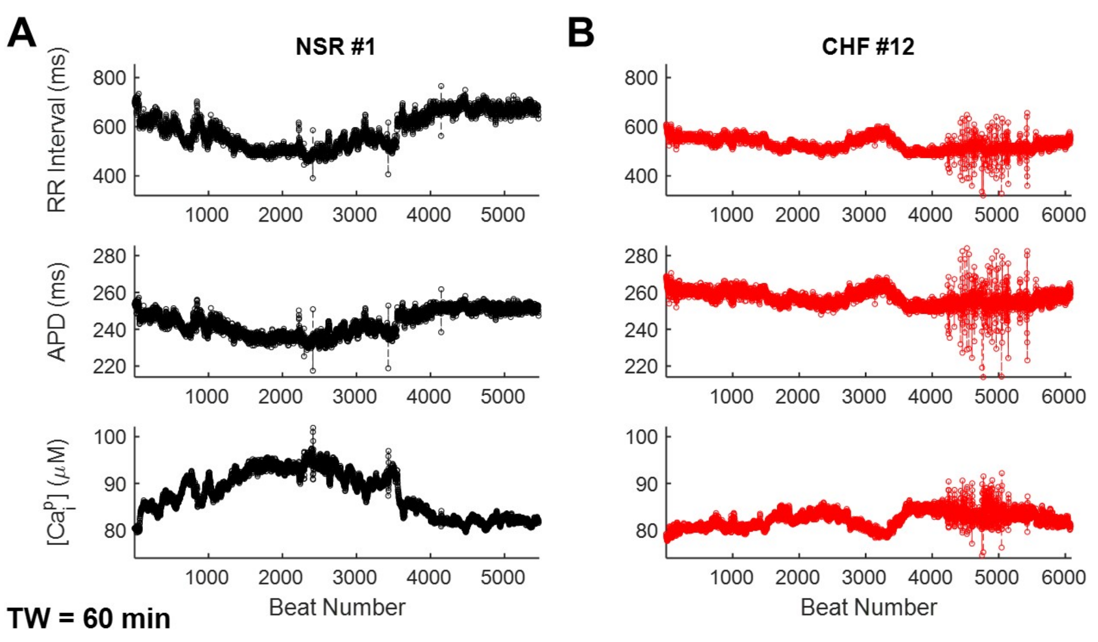

Figure S6. At a longer duration, the trends in NSR electrical activity are consistent with the shorter simulation. In CHF, there is less overall variability though there are periods with similar properties to the 5 minute simulation. Traces of a 60 minute RR sequence (top) and the corresponding APD (middle) and peak Ca (bottom) beat-to-beat values are depicted from (A) NSR #1 and (B) CHF #12. Time window (TW) = 60 minutes.

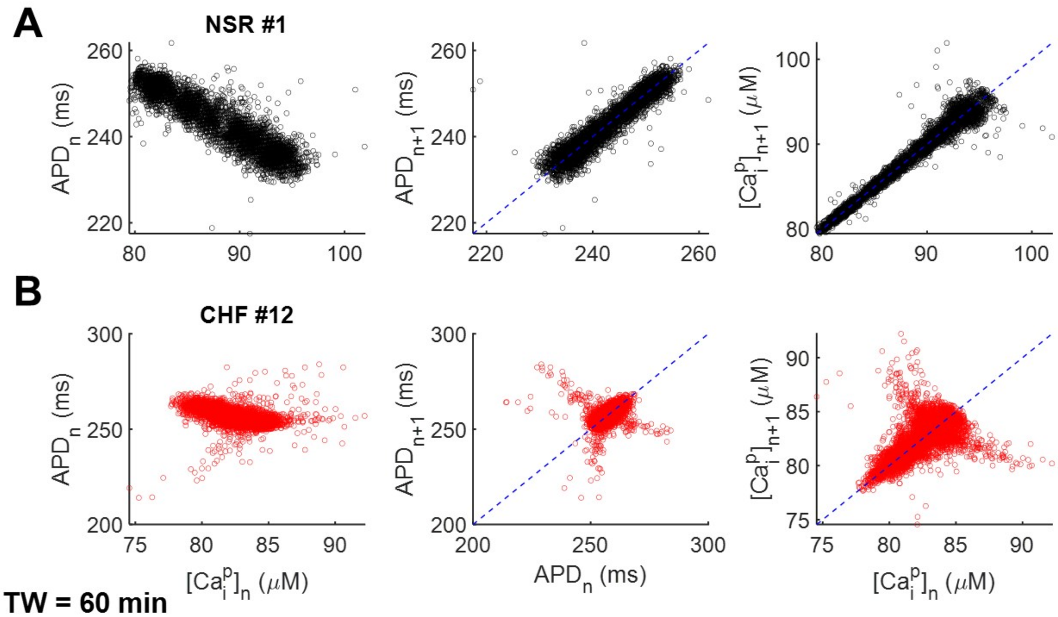

Figure S7. The relationship between APD and peak Ca and the correlations between consecutive APD and peak Ca values are consistent at a longer time window of 1 hour in NSR and CHF. Scatter plots of APD vs. peak Ca (left), successive APD values (middle), and successive peak Ca values (right) are shown for the (A) NSR #1 and (B) CHF #12 simulations depicted in Fig. S6. The blue dashed line is the line of equality. Time window (TW) = 60 minutes.

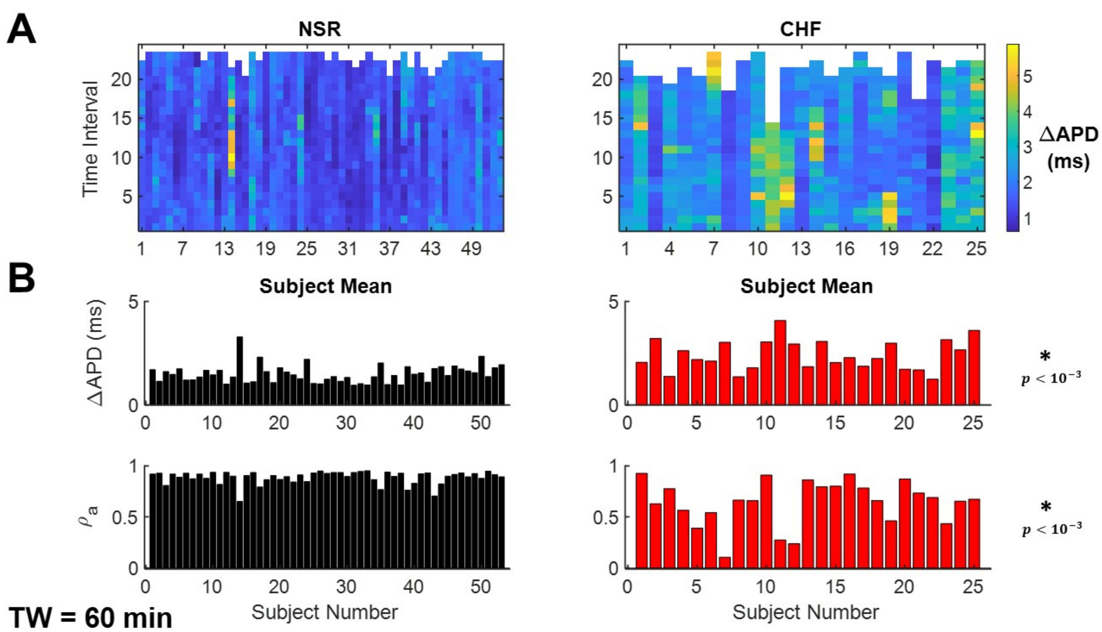

Figure S8. Consistent with shorter simulations, APD alternans formation is more likely in the CHF population. (A) ΔAPD is shown for each one hour segment of every 24 hour RR sequence in both populations. (B) The temporal mean of ΔAPD and ρ_a are depicted for each subject in the NSR (black) and CHF (red) populations. The populations have a significantly different temporal mean for ΔAPD and ρ_a ($*p < 10^{-3}$, unpaired t-test). Time window (TW) = 60 minutes.

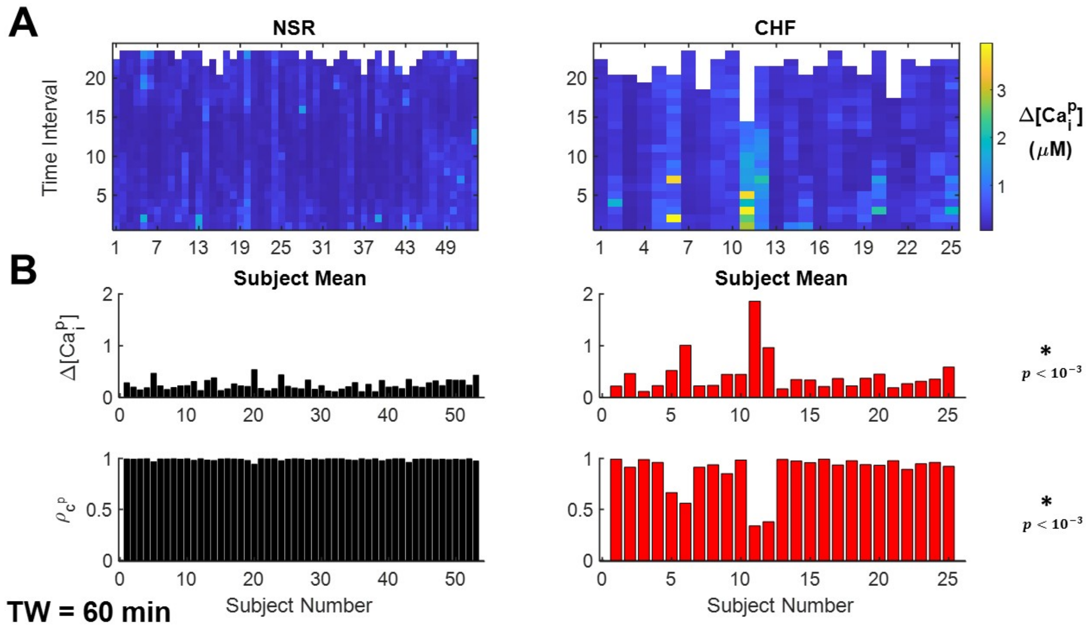

Figure S9. Similar to the 5 minute time window, peak Ca alternans formation is more prevalent in CHF. (A) $\Delta[Ca_i^p]$ is shown for each one hour segment of every 24 hour RR sequence in both populations. (B) The temporal mean of $\Delta[Ca_i^p]$ and ρ_{c^p} are depicted for each subject in the NSR (black) and CHF (red) populations. The populations have a significantly different temporal mean for $\Delta[Ca_i^p]$ and ρ_{c^p} ($*p < 10^{-3}$, unpaired t-test). Time window (TW) = 60 minutes.

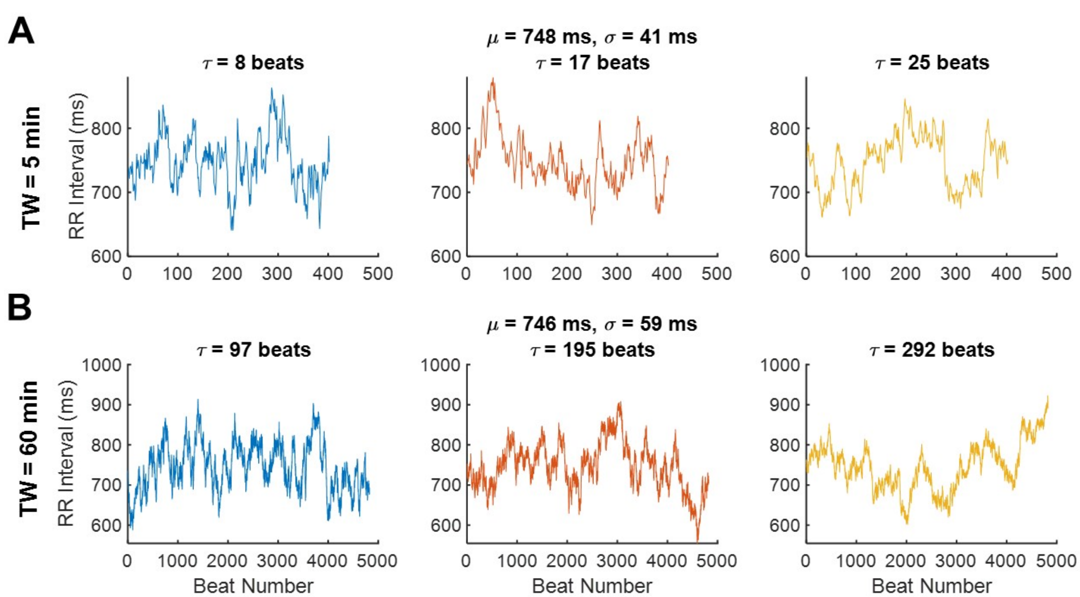

Figure S10. Influence of τ on synthetic sequences. Individual plots of synthetic sequences displayed in column 3 of Fig. 6 for a time window (TW) of (A) 5 minutes and (B) 60 minutes.

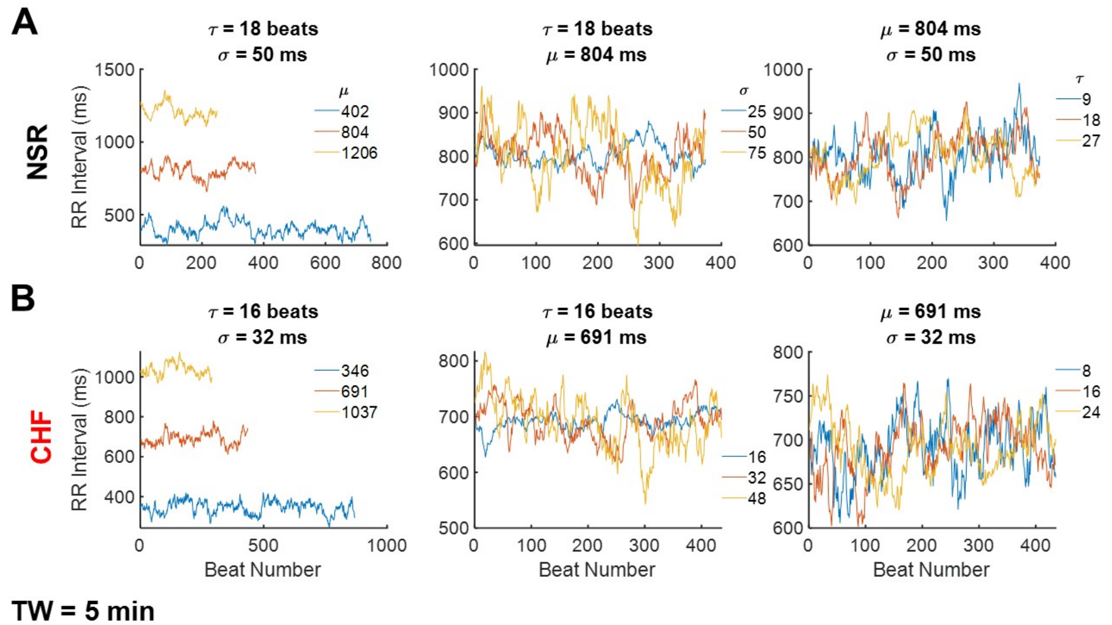

Figure S11. RR interval synthetic sequences are plotted as a function of beat number for different combinations of statistical properties, where two properties are the population-specific mean and the third property is 50%, 100% and 150% of its corresponding mean. Plots are shown for (A) NSR and (B) CHF. Time window (TW) = 5 minutes.

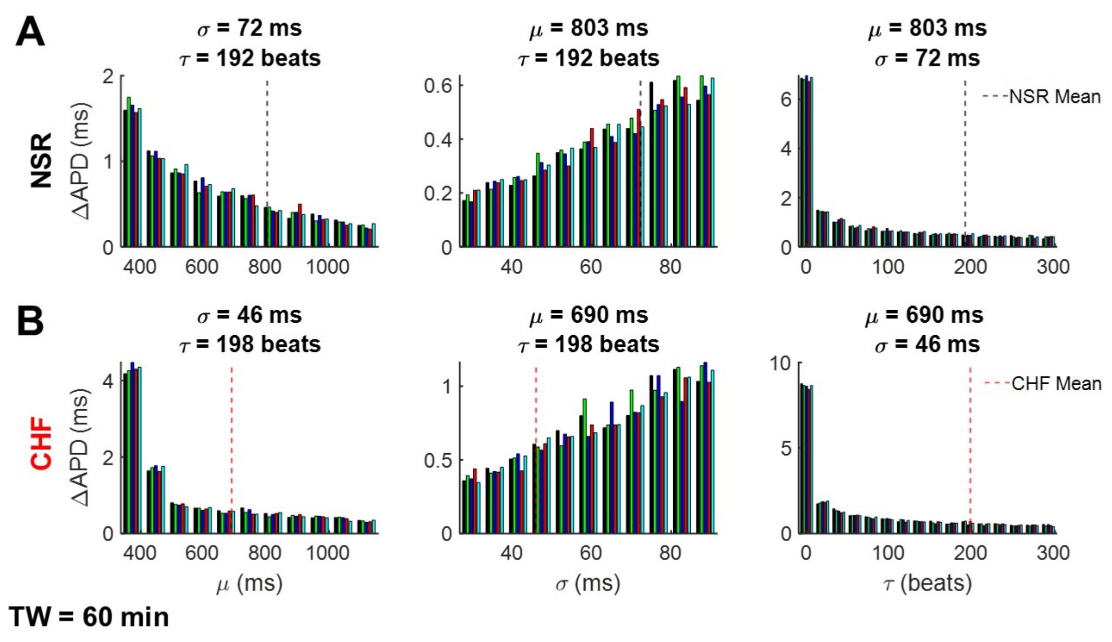

Figure S12. The influence of each statistical property at a long time window is consistent with trends seen in 5 minute simulations. ΔAPD is shown for 5 synthetic sequences for different combinations of statistical properties, where τ (left), σ (middle), and μ (right) are broadly varied and the remaining two parameters are the population mean. The third NSR and CHF mean parameter value is shown in black and red, respectively. Results are shown for both the (A) NSR and (B) CHF models. Time window (TW) = 60 minutes.

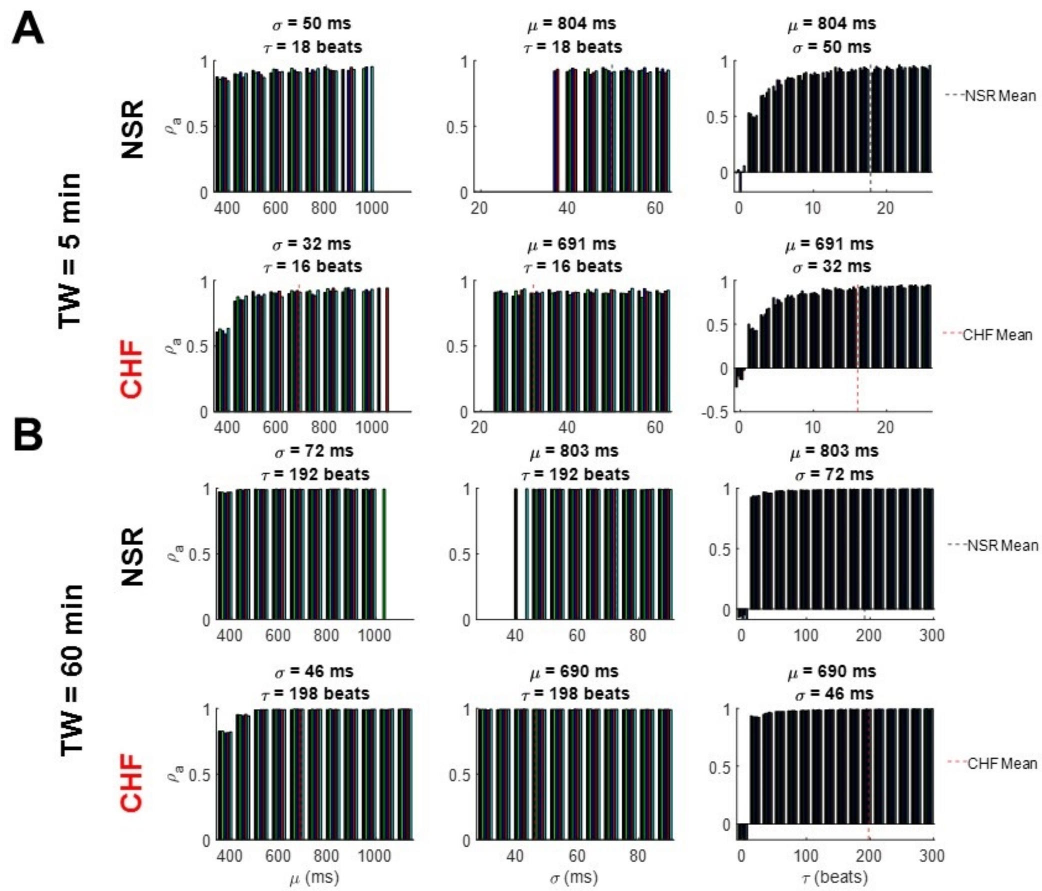

Figure S13. Increasing the autocorrelation time promotes consistency in APD. ρ_a is shown for 5 synthetic sequences for different combinations of statistical properties, where τ (left), σ (middle), and μ (right) are broadly varied and the remaining two parameters are the population mean using the NSR and CHF models. The third NSR and CHF mean parameter value is shown in black and red, respectively. Values are shown for time windows (TWs) of (A) 5 and (B) 60 minutes.

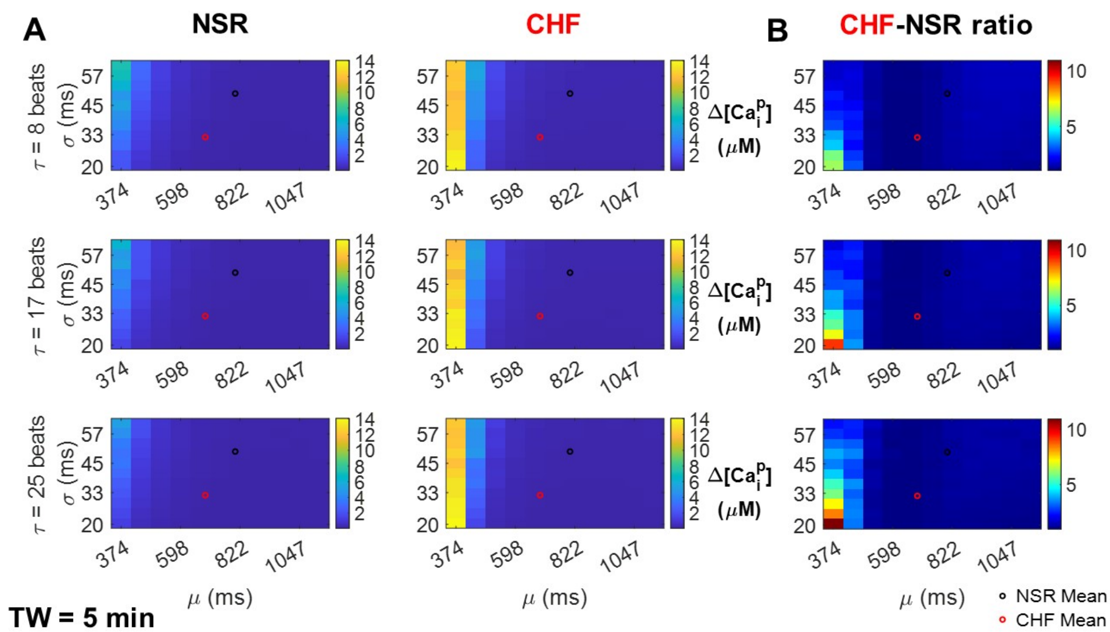

Figure S14. For a specific synthetic sequence, the CHF model leads to greater peak Ca alternations, compared with the NSR model. (A) The $\Delta[Ca_i^p]$ value is plotted for different values of μ (x-axis), σ (y-axis), and τ (row) using the NSR (left) and CHF (middle) models. The mean NSR and CHF μ and σ are depicted in black and red circles. (B) The corresponding ratio of CHF to NSR $\Delta[Ca_i^p]$is also shown (right). Time window (TW) = 5 minutes.

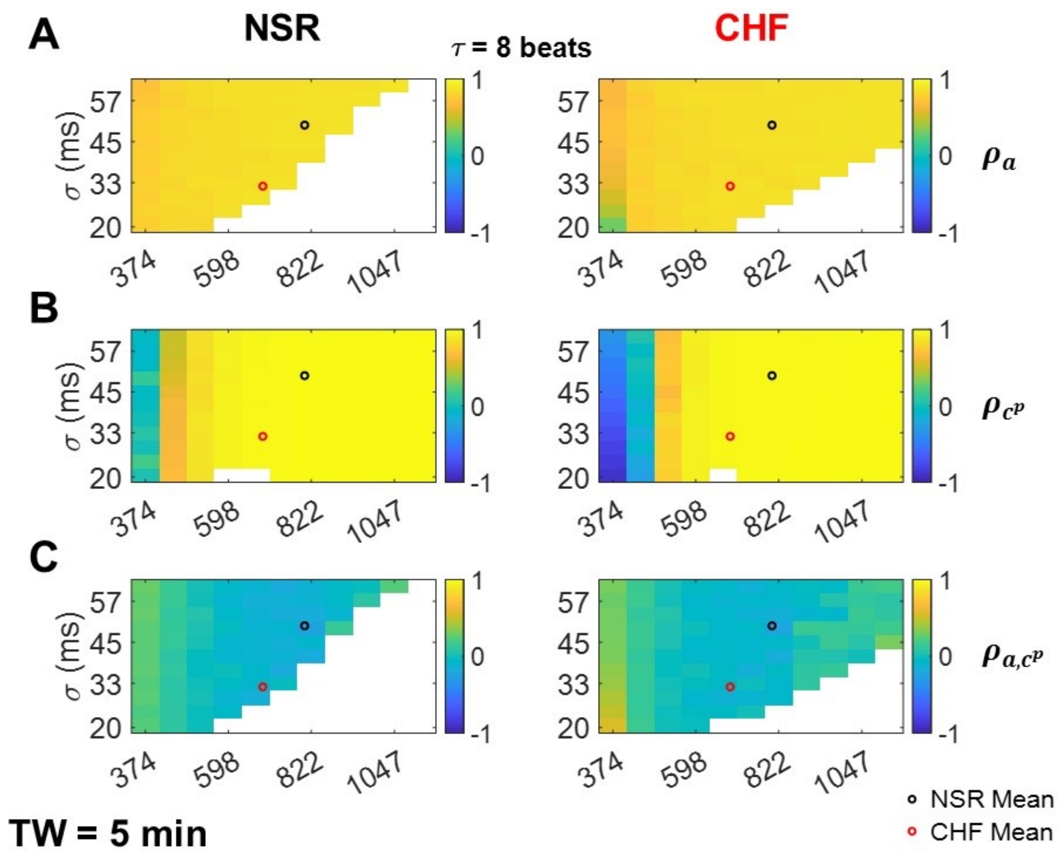

Figure S15. The ρ_a (A), ρ_{c^p} (B), and ρ_{a,c^p} (C) values are plotted for $\tau = 8$ beats and different values of μ (x-axis), and σ (y-axis) using the NSR (left) and CHF (right) models. The mean NSR and CHF μ and σ are depicted in black and red circles. Time window (TW) = 5 minutes.

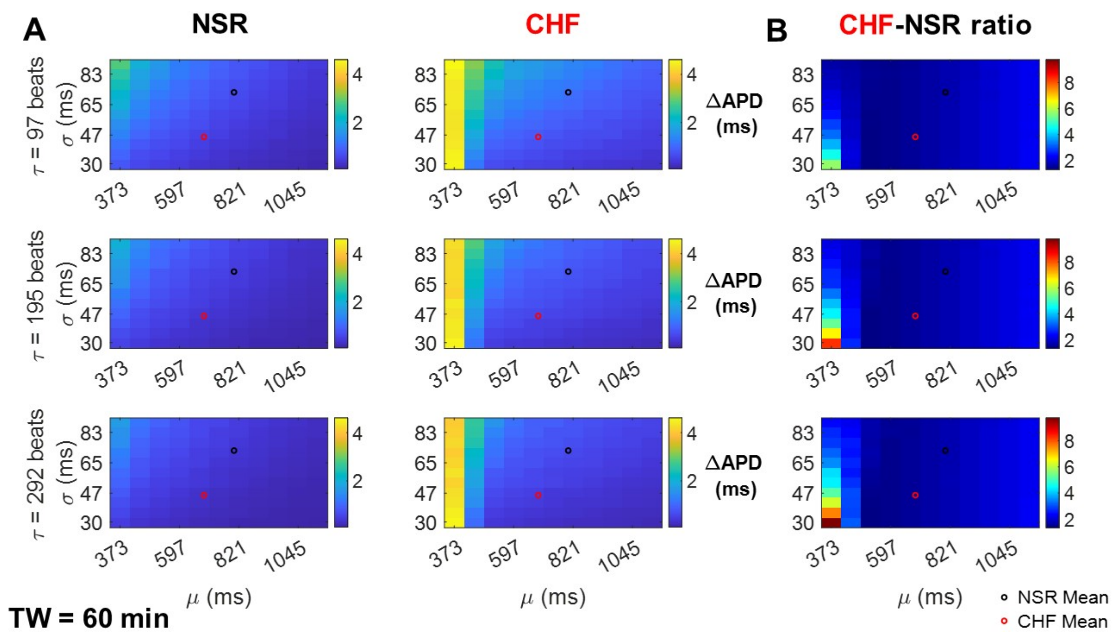

Figure S16. The effect of model parameters on ΔAPD are similar on both a short and long time scale. (A) The ΔAPD value is plotted for different values of μ (x-axis), σ (y-axis), and τ (row) using the NSR (left) and CHF (middle) models. The mean NSR and CHF μ and σ are depicted in black and red circles. (B) The corresponding ratio of CHF to NSR ΔAPD is also shown (right). Time window (TW) = 60 minutes.