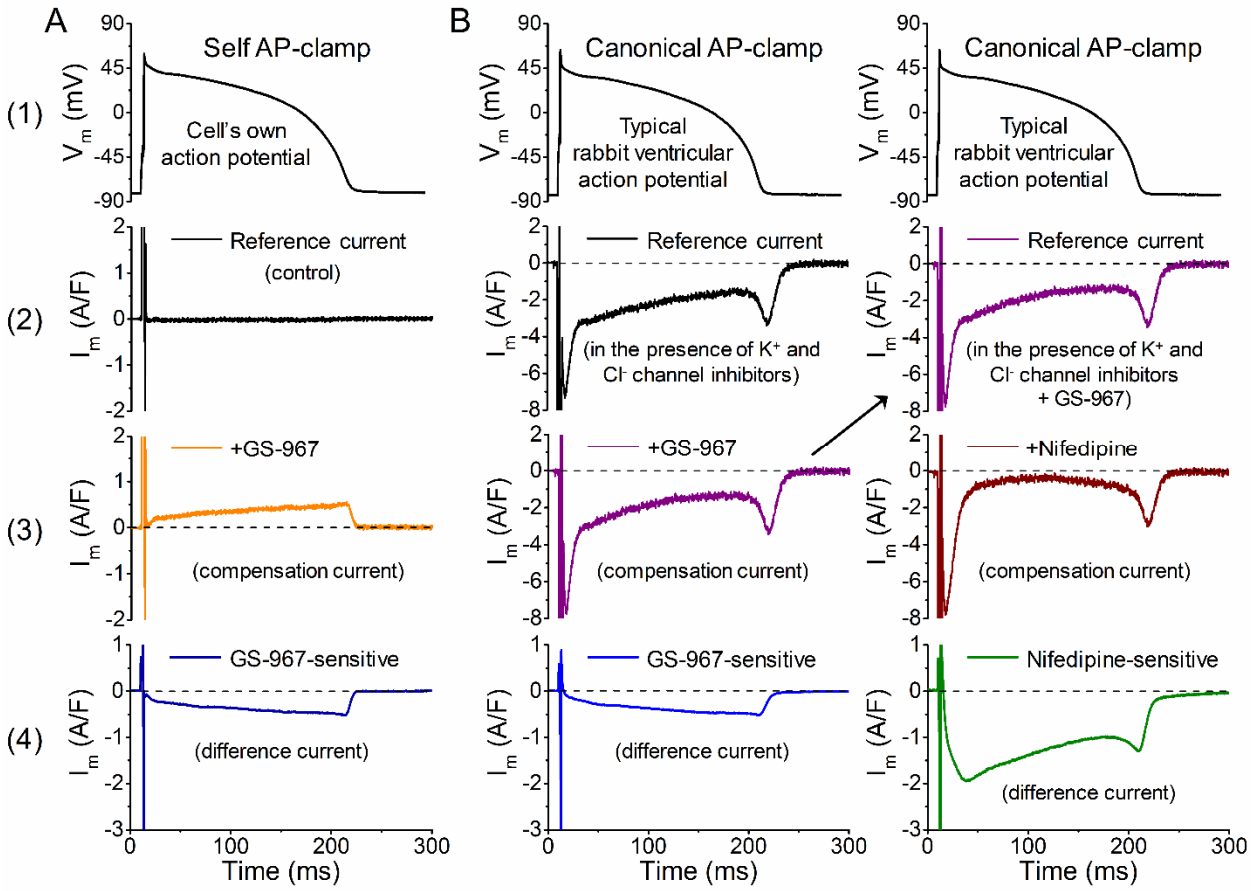
SUPPLEMENTAL MATERIAL

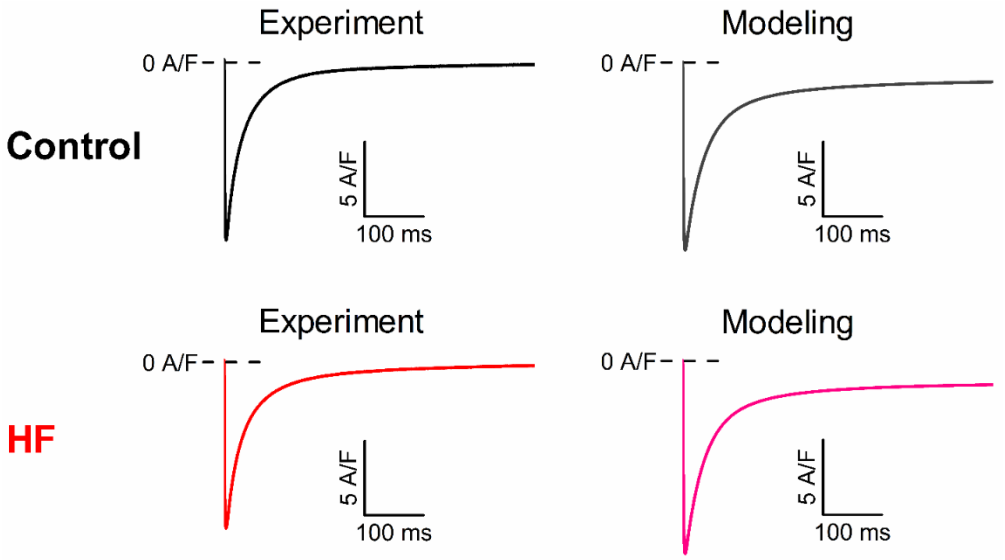
Supplemental Table. Inactivation parameters of L-type Ca^{2+} current (I_{CaL}) in control and heart failure (HF).

	Control		HF	
I_{CaL} parameter	Experiment	Model	Experiment	Model
Peak (A/F)	12.0±0.9	12.7	11.4±1.1	13.1
τ fast (ms)	16.4±0.4	28.5	19.6±0.6	28.4
Amplitude fast (%)	78.2±1.1	76.8	80.7±1.9	76.6
τ slow (ms)	86.9±4.2	119.7	106.8±6.5	114.6
Amplitude slow (%)	21.8±1.1	23.2	19.3±1.9	23.4

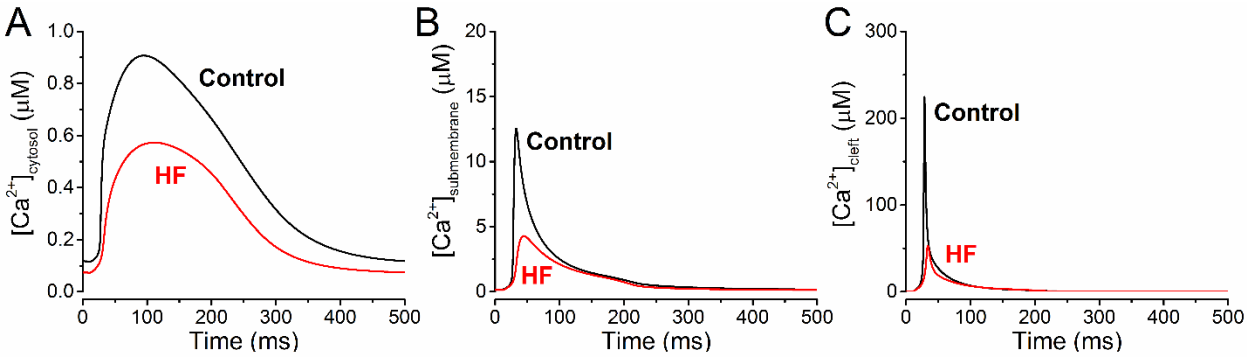
Inactivation parameters of I_{CaL} were assessed at 0 mV by biexponential fitting of the current decay. I_{CaL} parameters measured in isolated cardiomyoyctes are expressed as mean±SEM. n=6 cells from 3 animals for both control and HF. See Methods for details of I_{CaL} modeling.



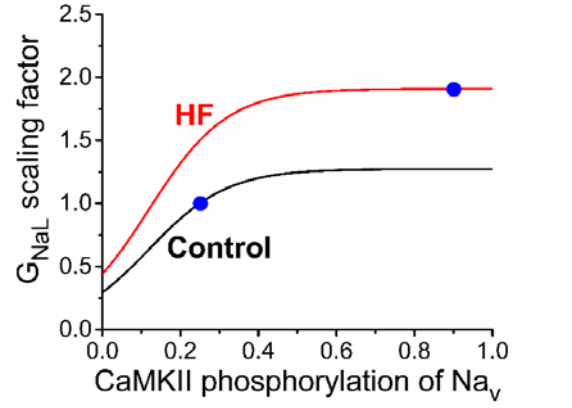
Supplemental Figure I. Action potential (AP)-clamp technique.
Representative traces show the basic steps of self AP-clamp (**A**) and canonical AP-clamp (**B**) experiments. First, using an AP as voltage command (1) a reference current is recorded (2). Next, when the drug is applied and reached its steady-state effect, a compensation current is recorded specific to the drug action (3). The drug-sensitive current is obtained as the difference current (i.e. subtracting the compensation current from the reference current) (4). In self AP-clamp (**A**) the cell's own steady-state AP is applied and the reference current should be zero. When the cell is pretreated with different ion channel inhibitors and a prerecorded, typical rabbit AP (canonical AP-clamp, **B**) is applied, the reference current is no longer flat. However, the reference current still must reach a steady-state indicating stable seal conditions. Under AP-clamp, all ionic currents were recorded as difference currents after their specific blocker had reached steady-state effect (3-min perfusion). 60 consecutive traces were recorded (to evaluate the stability of the reference and compensation currents) and averaged in each case before and 3-min after drug application. 1 µmol/L GS-967 and 10 µmol/L nifedipine were used to measure late Na^+ current (I_{NaL}) and L-type Ca^{2+} current (I_{CaL}), respectively.



Supplemental Figure II. Modeling of L-type Ca^{2+} current (I_{CaL}) in control and heart failure (HF). Representative I_{CaL} traces measured at 0 mV with square pulse voltage protocol in isolated cardiomyocytes (left) and in silico (right) in control (black/grey) and in HF (red/pink). I_{CaL} was measured in the presence of 5 mmol/L EGTA ($[Ca^{2+}]_i$=100 nmol/L) in the pipette. Inactivation parameters of I_{CaL} are shown in Figure 4E and Supplemental Table.



Supplemental Figure III. Physiological Ca^{2+} transient in control and heart failure (HF).
Physiological Ca^{2+} transients have been obtained with our updated rabbit ventricular myocyte model that integrates detailed descriptions of electrophysiology, Ca^{2+} and Na^{+} handling, PKA and CaMKII signaling, and myofilament contraction. Simulated Ca^{2+} transients under AP-clamp at 2 Hz pacing in control and HF in the cytosol (**A**), in the submembrane compartment (**B**), and in the dyadic cleft (**C**).



Supplemental Figure IV. Modeling the CaMKII-dependent modulation of late Na^+ current (I_{NaL}). Relationship between the CaMKII-dependent phosphorylation of voltage-gated Na^+ channel (Na_V) and the conductance of late Na^+ current (G_{NaL}). The scaling factor that multiplies the basal G_{NaL} value of 0.0527 is shown (control in black, HF in red). Basal G_{NaL} is increased by 50% in HF. By design, the scaling factor is 1 for control with physiologic Ca^{2+} transient at 2 Hz pacing. CaMKII-dependent Na_V phosphorylation is ≈25% in control and ≈90% in HF with physiologic Ca^{2+} transient (blue circles).