SUPPLEMENTARY FIGURES

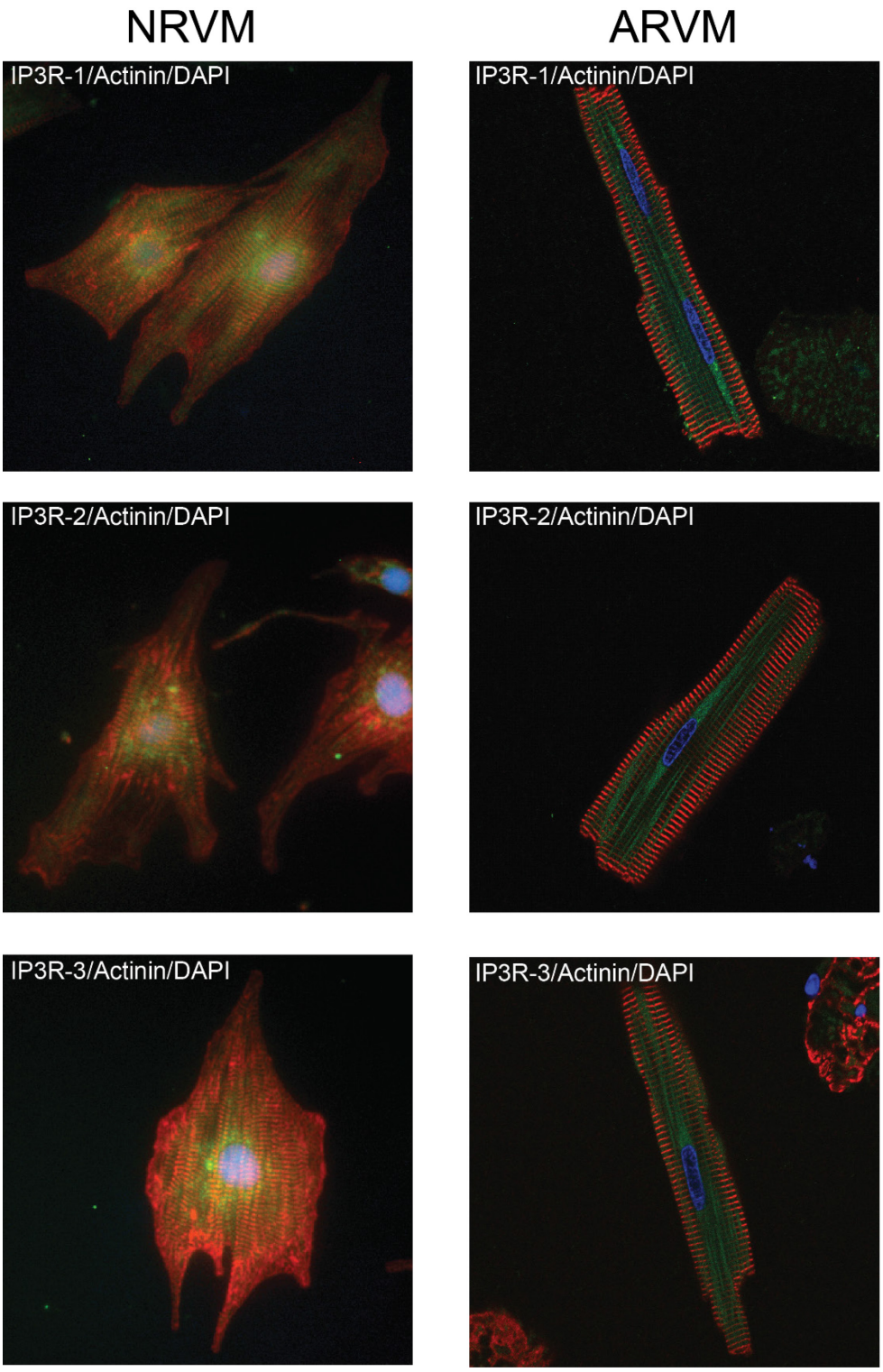

Fig S1. Enlarged merged images from Figure 1.

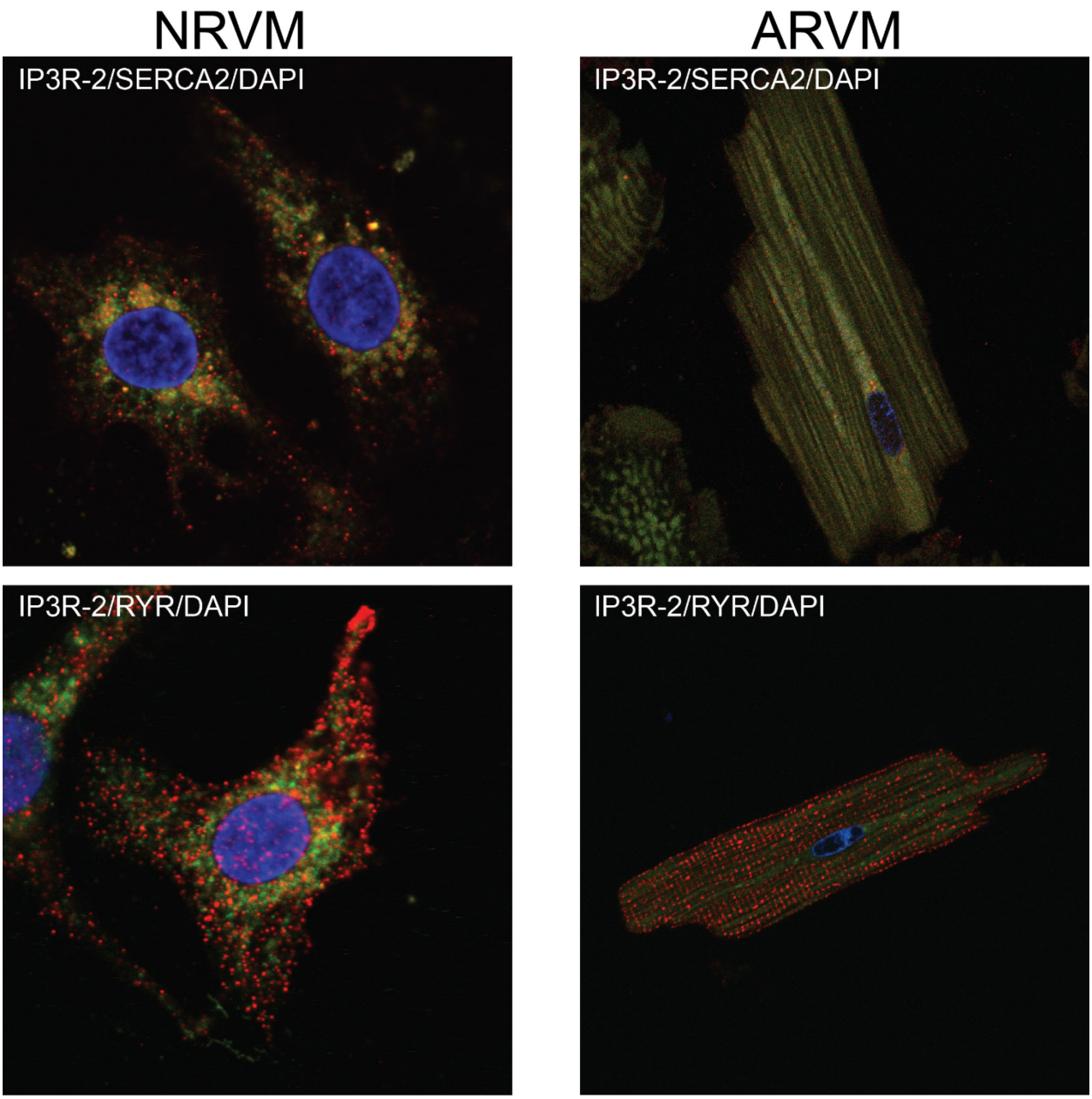

Fig S1. Enlarged merged images from Figure 2.

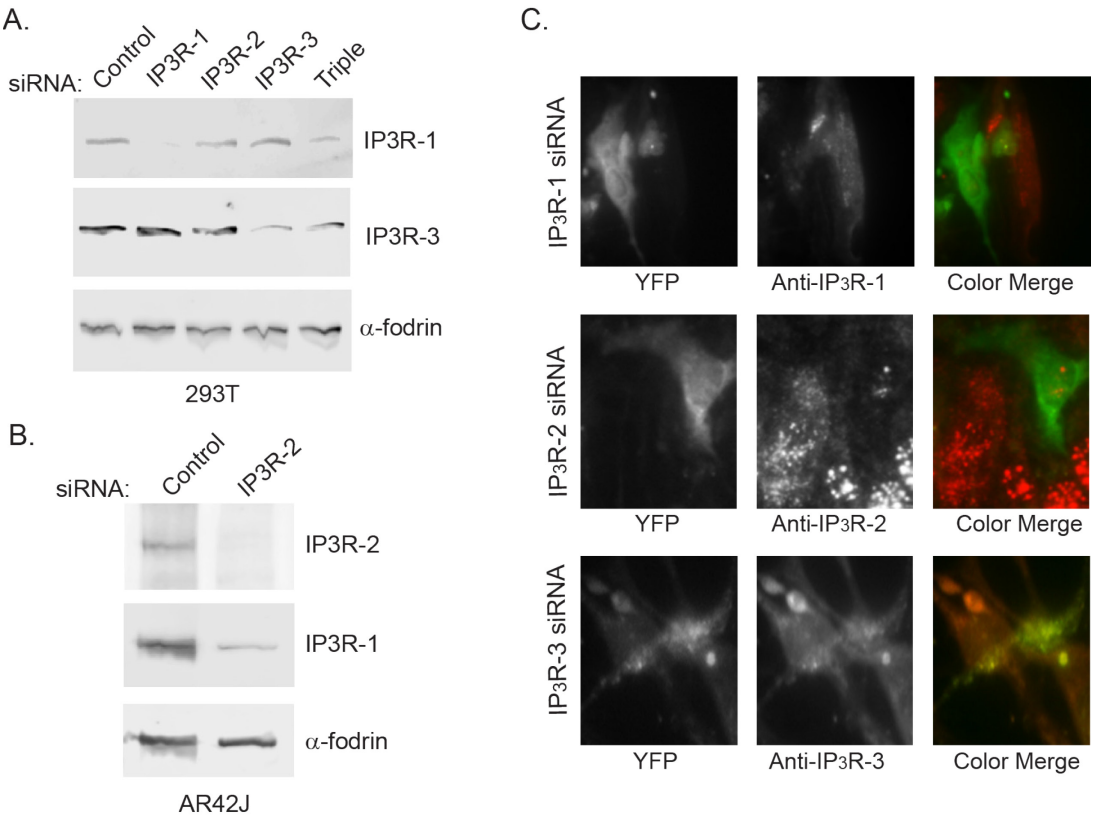

Fig S3.siRNA-mediated knockdown of IP_3R-1, -2 and -3. Western blot analysis of 293T (A) and AR42J (B) cell lines transfected with control siRNA and siRNA oligos specific for each IP_3R isoform as indicated. IP_3R-1 siRNA significantly reduced endogenous IP_3R-1 expression in 293T where control siRNA did not. Similarly IP_3R-3 siRNA significantly reduced IP_3R-3 expression. Both siRNAs were specific for the individual isoforms. Triple IP_3R siRNA transfection inhibited the expression of both IP_3R-1 and -3 in 293T cells (A). IP_3R-2 expression was below detection levels in 293T cells. (B) To probe the efficiency of IP_3R-2 siRNA, we used AR42J cells which express high amounts of this isoform. IP_3R-2 siRNA completely inhibited IP_3R-2 expression, and also partially reduced IP_3R-1 levels. IP_3R-3 expression was below detection levels in AR42J cells. In both panels, alpha-fodrin was used as loading control. (C) IP_3R expression levels in neonatal rat ventricular cardiomyocytes co-transfected with siRNA to the individual isoforms and YFP to identify transfected cells. In the color merge panel, separation of green and red channels is indicative of knockdown.

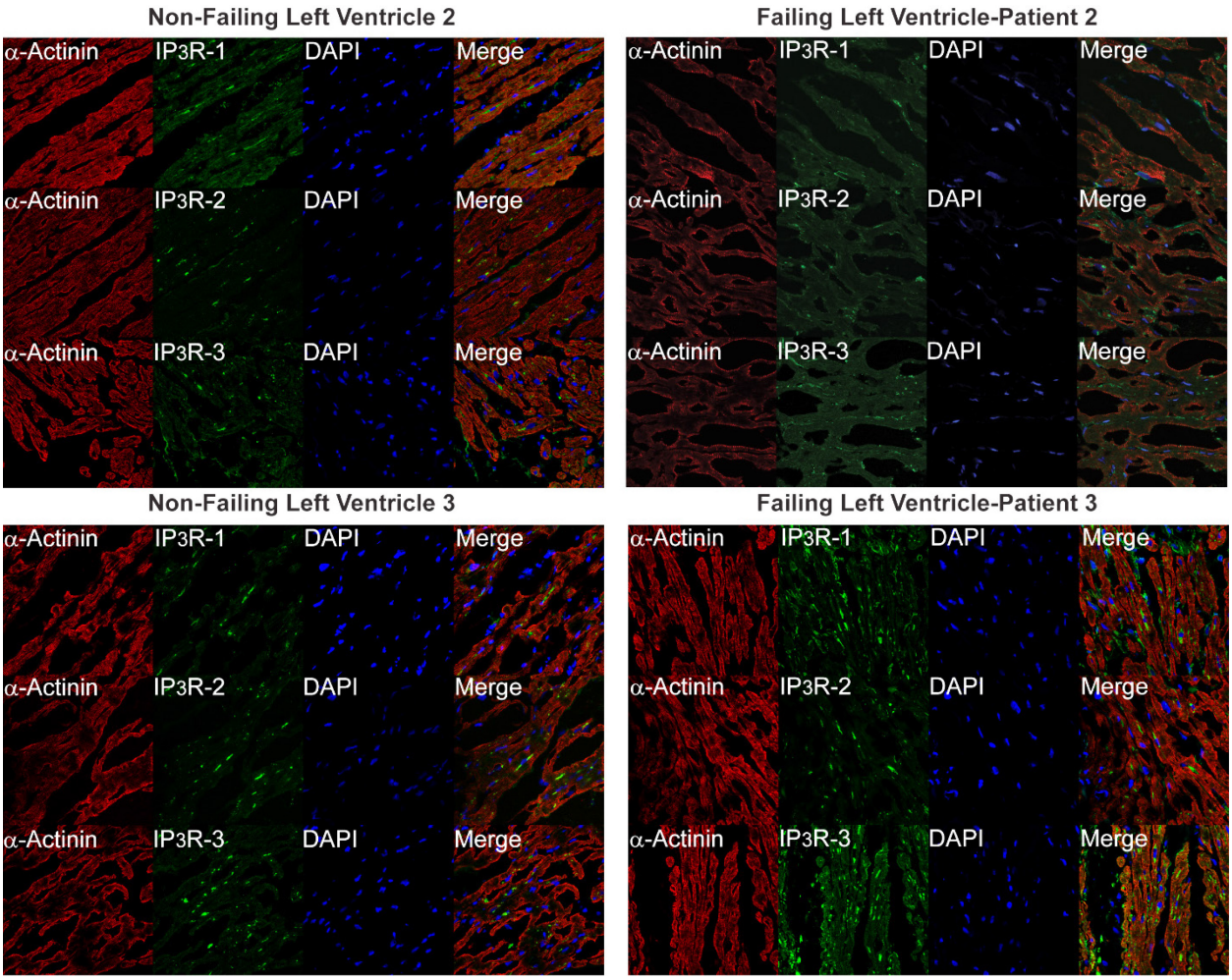

Fig. S4. Expression of IP_3R isoforms in non-failing and end stage heart failure samples. Immunofluorescence staining of non-failing human left ventricle (Control 2 and 3) and left ventricular heart failure samples (Patient 2 and 3). Column 1 is stained with α-actinin to label sarcomeres. Column 2 is stained with indicated IP_3R antibodies. Column 3 is DAPI staining of the nucleus. Column 4 is the merged images of each row.

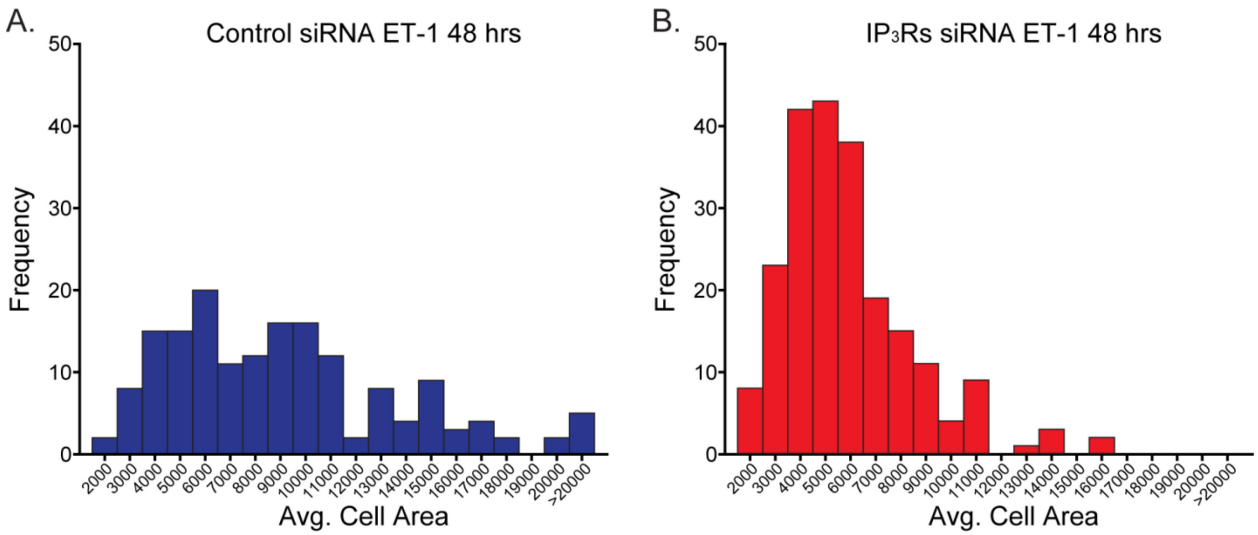

Fig. S5. Histogram of cardiomyocyte cell size distribution after ET-1 treatment of control and triple IP_3R knockdown of NRVMs. Neonatal ventricular cardiomyocytes cell size distribution in control (Panel A) and triple IP_3R siRNA transfected cells (Panel B) treated with ET-1 for 48 hrs. Control cells have a larger cell size distribution compared to triple IP_3R KD cells.

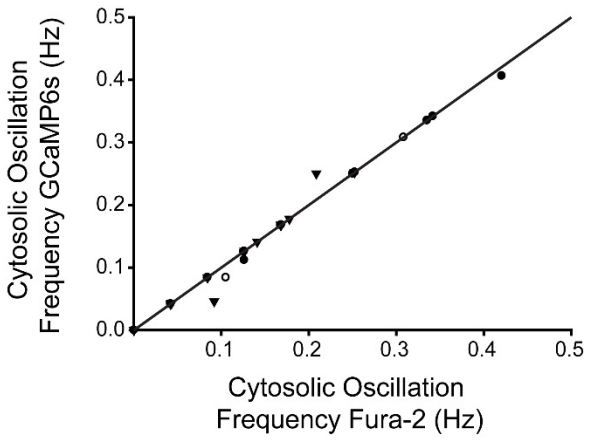

Fig S6. Plot of cytosolic GCaMP6s versus Fura-2 oscillation frequency. Cytosolic GCaMP6s was imaged simultaneously with cytosolic Fura-2 oscillation in neonatal cardiomyocytes and relative oscillation frequencies from each indicator were quantified. Each symbol represents a single coverslip averaging 5-10 cells for a total of three separate experiments. Frequency data was quantified from 20 seconds bins.

	Control 1	Control 2	Control 3	Patient 1 HF	Patient 2 HF	Patient 3 HF
NYHA Class	1	1	1	4	3.5	4
Age	43	19	36	57	64	60
Sex	F	F	M	M	M	M
Hypertension	-	-	-	Stage 1	Stage 1	-
LVEDD	-	3.6	4.5	7.2	6.7	5.9
LVPWd	-	0.7	1	1.4	1.3	0.6
EF	60%	68%	60%	20%	20%	20%

Supplementary Table 1. Clinical characteristics of patient samples. Control samples were obtained from hearts that were declined for transplantation due to non-cardiac reasons. Patient 1-3 samples were obtained from patients that suffered with end stage heart failure. NYHA indicates New York Heart Association; Stage 1 hypertension, systolic pressure ranging from 140 to 159 mm Hg or a diastolic pressure ranging from 90 to 99 mm Hg; LVEDD, left ventricular end diastolic diameter- normal range 4.2-5.9 cm; EF, Ejection Fraction, normal EF ranges from 55-70%; LVPWd, Left ventricular posterior wall end diastole and end systole-normal range 0.6-1.1 cm. A dash indicates data not available.