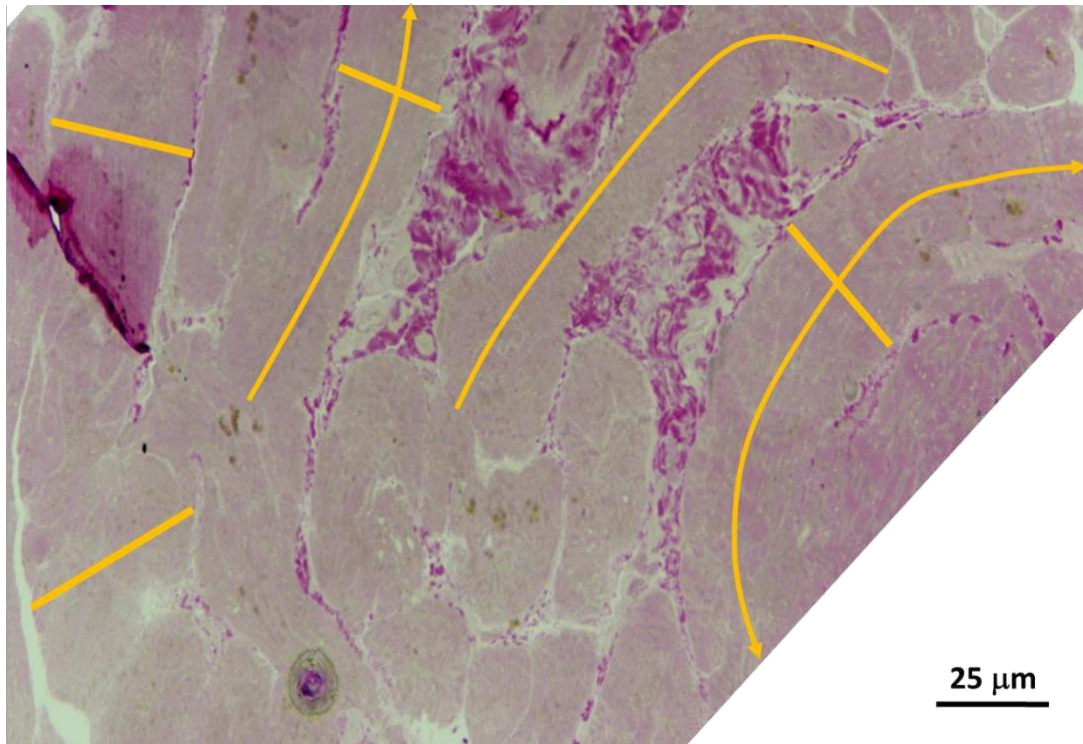


## **Supplemental material**

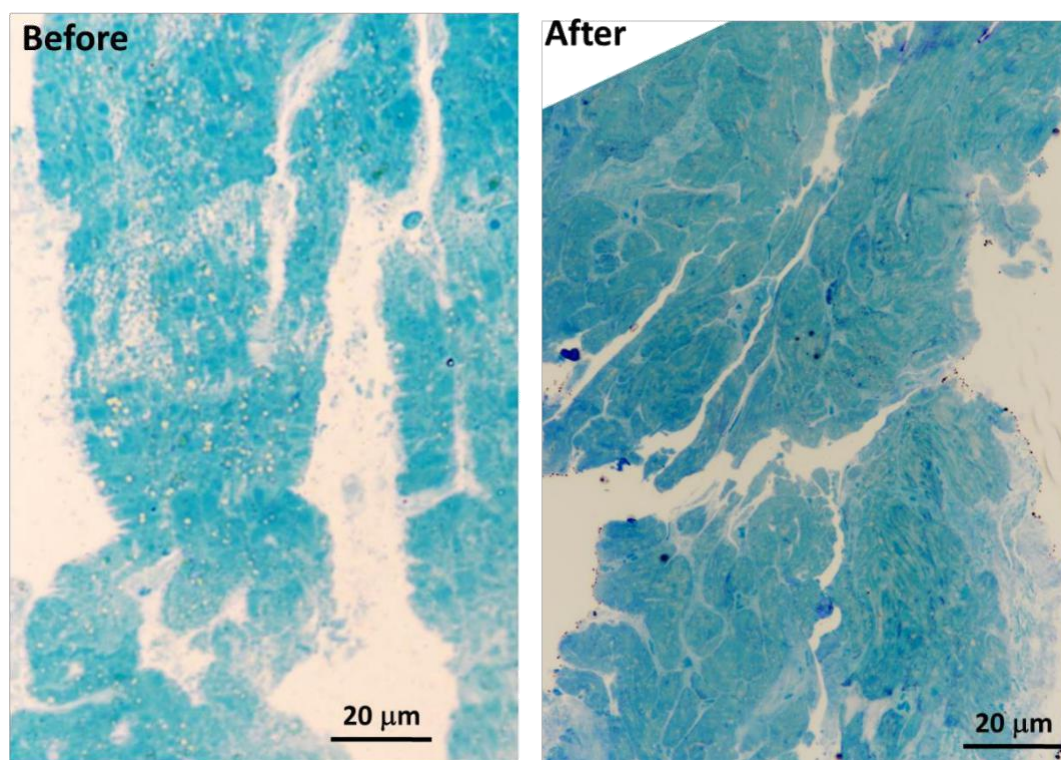
**Supplemental Table S1. Transmission electron microscopy features before and after therapy in 8 patients with heart failure baseline and at 6-month follow up.**

<b>Features</b>	<b>Baseline</b>	<b>At 6-month follow up</b>
Myocardiocyte axis	Increased	Decreased/normal
General swelling	evident	Recovered
Presence of large vesicles	Frequent	Absent
Sarcoplasmic reticulum	Dilated	Normal/partially recovered
Golgi cisternae	Irregularly dilated	Dilated (increased function)
Mitochondria	Swollen/vesculated	Orthodox/condensed/energized
Mitochondria dynamics	Abnormal fission/fusion	Apparently normal
Mitochondria distribution	Grouping	Mostly columnar
Intercalated disc	Occasionally disrupted	Apparently recovered
Lateral junctions	Disrupted	Recovered
Sarcomeres	Myofibrillolysis	Recovered
Extracellular space	Dilated/highly enlarged (extracellular oedema)	Normal/partially recovered

**Supplemental Figures showing baseline transmission electron microscopy findings**

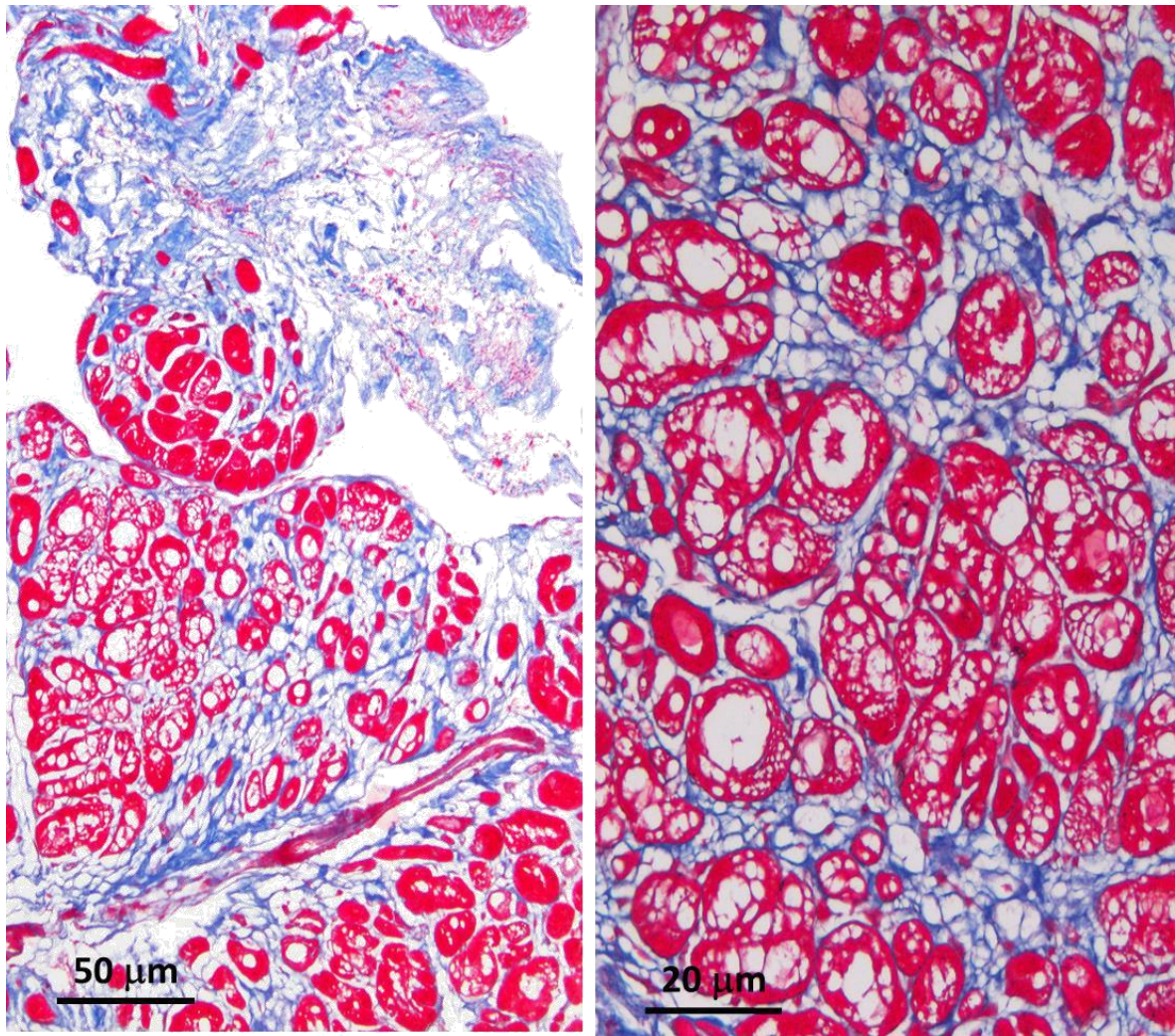


**Supplemental Figure S1. Baseline left ventricular endomyocardial biopsy showing increased myocardiocyte axis and focal fibrosis**

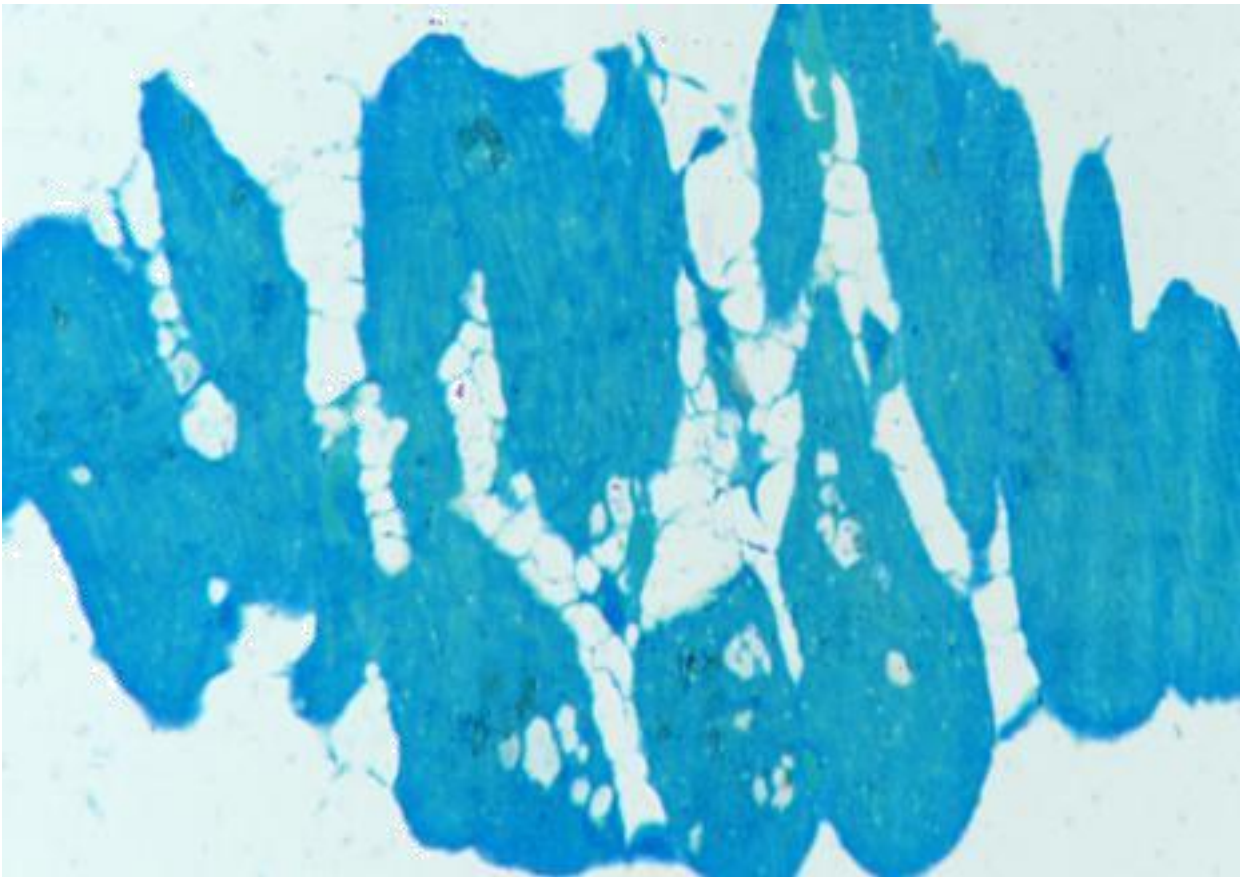


**Supplemental Figure S2. Transmission electron microscopy showing vesiculation before and its recovery after therapy**

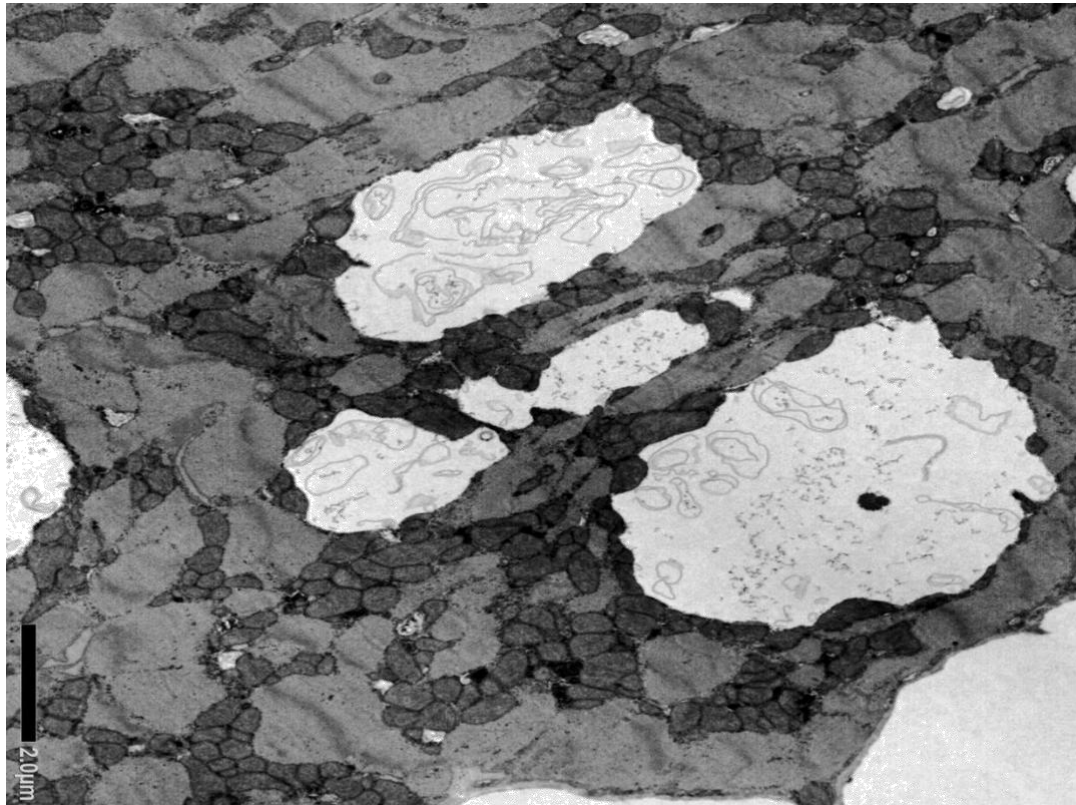




**Supplemental Figure S3. Baseline left ventricular endomyocardial biopsy showing hypertrophy, large/small vesicles, increased extracellular space, fibrosis.**

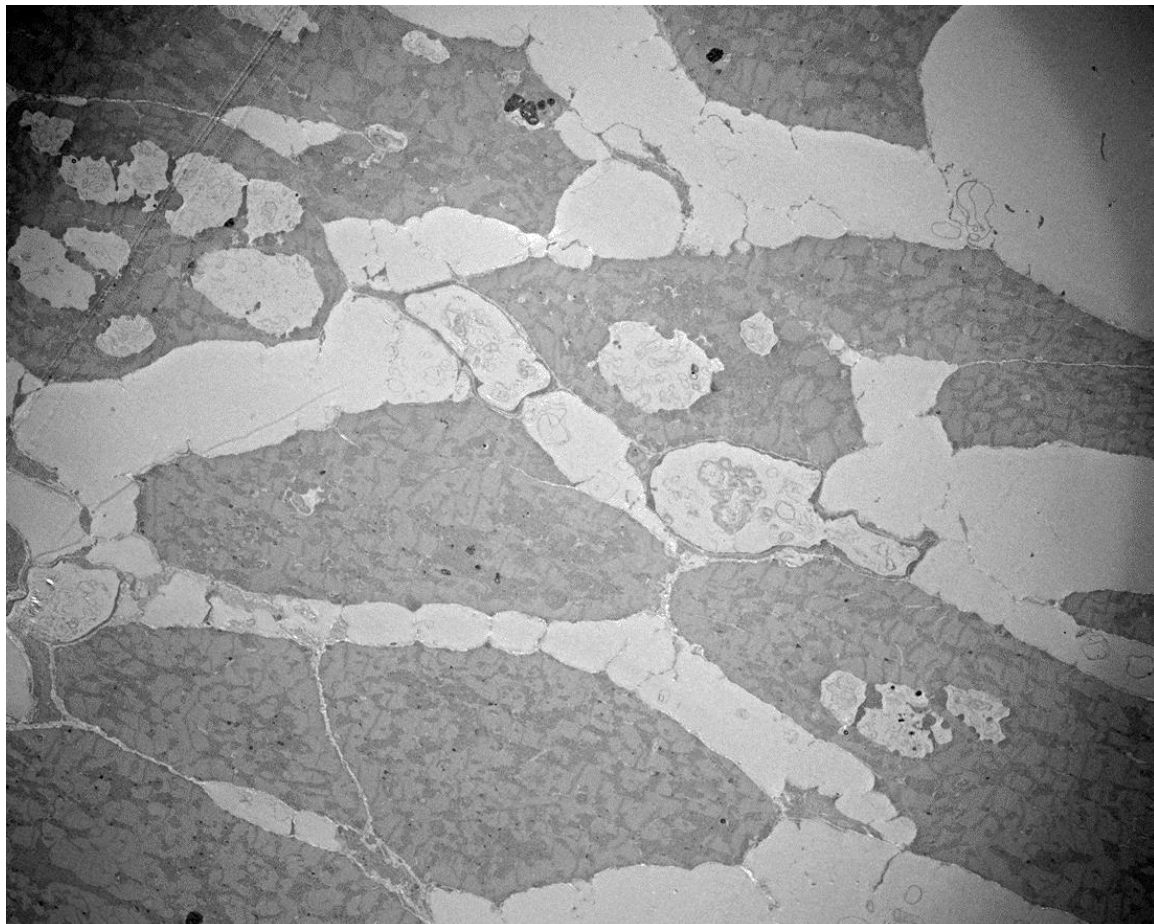


**Supplemental Figure S4. Baseline transmission electron microscopy showing hypertrophy, large vesicles, increased extracellular space (plastic section, Azur II stained).**



**Supplemental Figure S5. Baseline transmission electron microscopy showing vacuolar degeneration: large intracellular vesicles with clear content.**



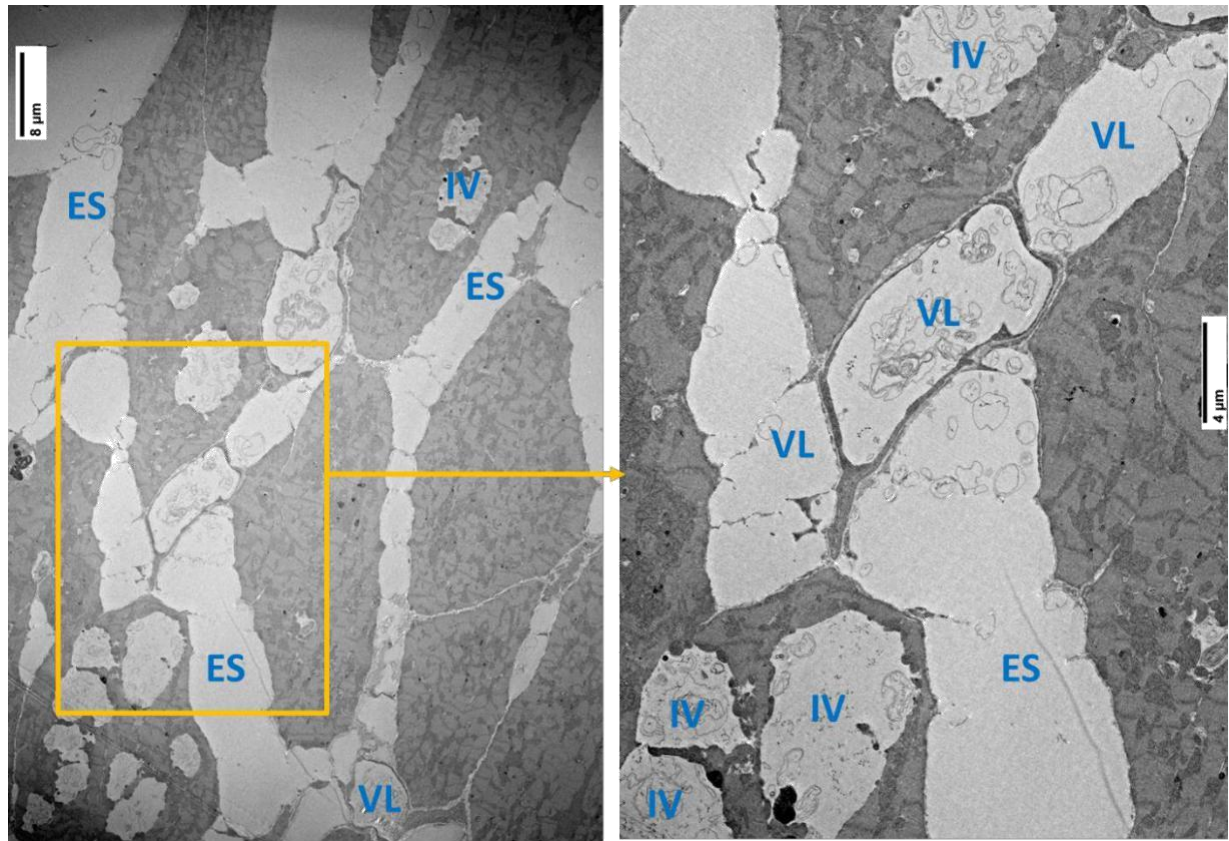


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11:02 2/12/2021

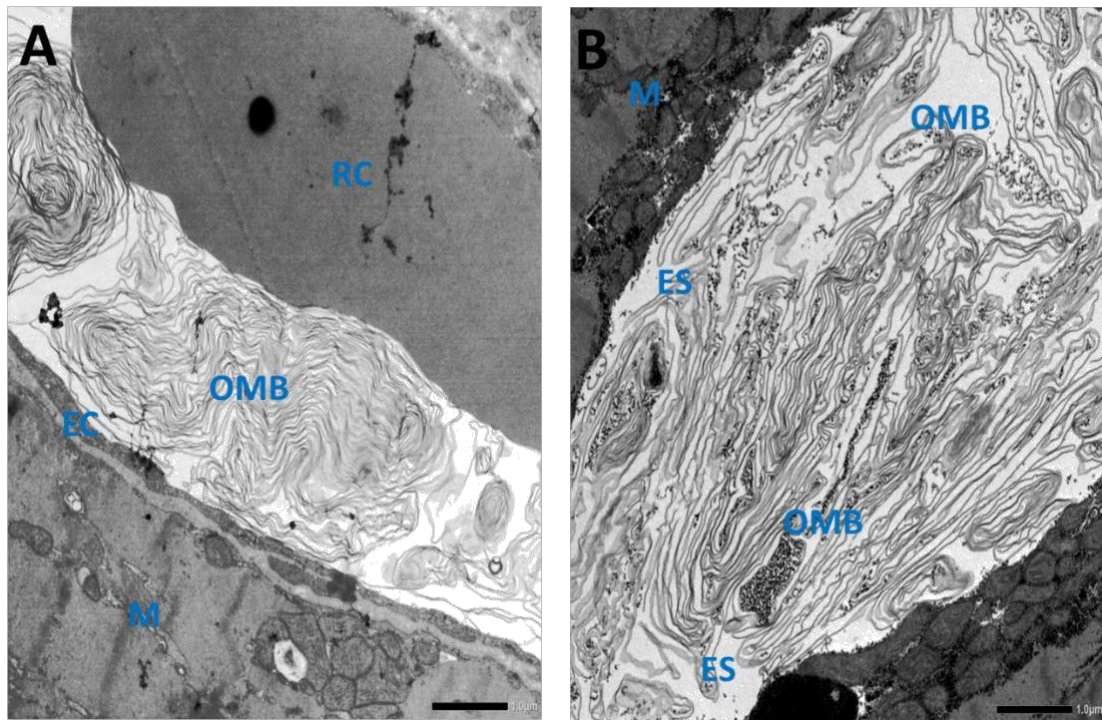
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Gamma: 1.00, No Sharpening, Normal Contrast

8  $\mu\text{m}$   
HV=100kV  
Direct Mag: 500 x  
SR MEBIC

**Supplemental Figure S6. Baseline transmission electron microscopy showing vacuolar degeneration: large intracellular vesicles with clear content enlarged extracellular space with clear content (extracellular edema).**



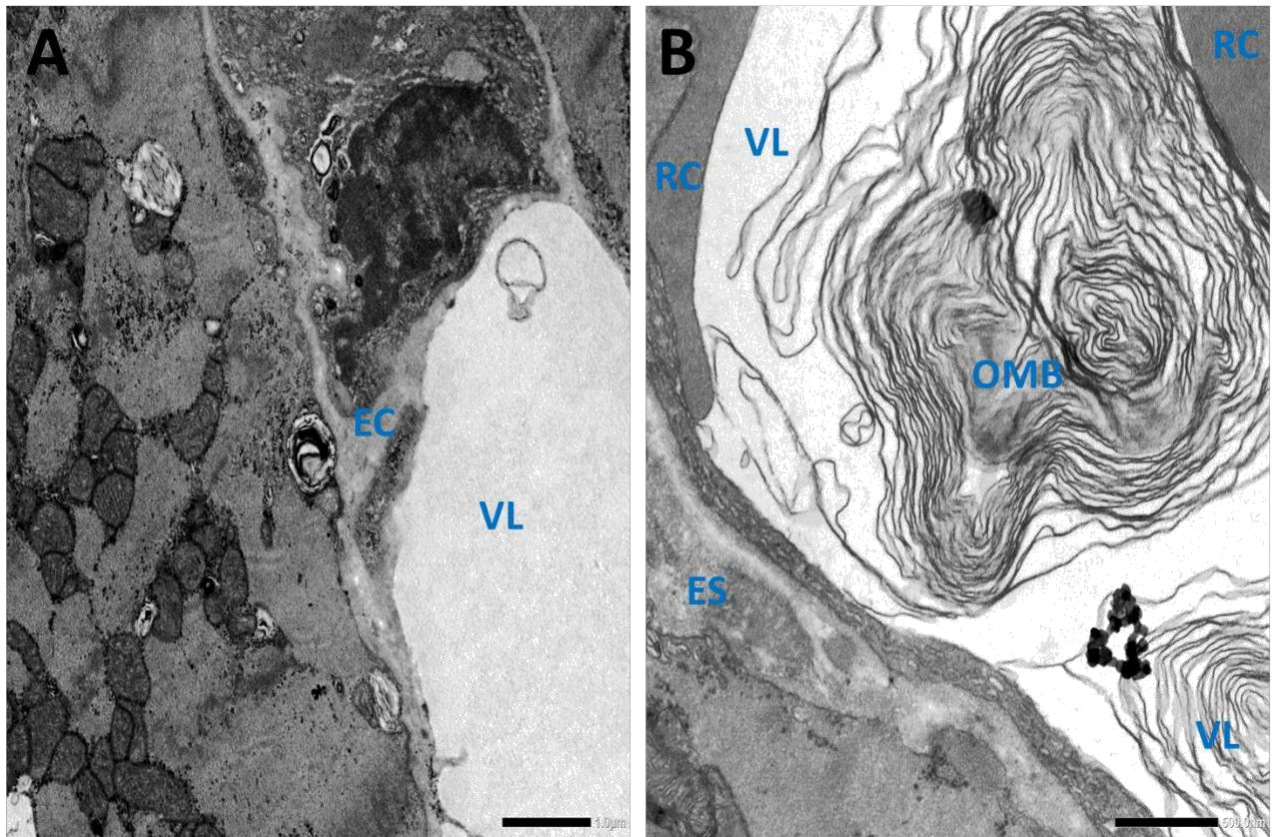
**Supplemental Figure S7. Baseline transmission electron microscopy showing vacuolar degeneration: large intracellular vesicles (IV) with clear content and extracellular edema (large amount of extracellular fluids in extracellular spaces [ES] and vessel lumen [VL]).**



**Supplemental Figure S8. Baseline transmission electron microscopy showing enlarged vessel lumen (VL) with osmiophilic myelin-like bodies (OMB), likely degenerating lipid membranes (A). Extracellular space also containing OMB (B).**

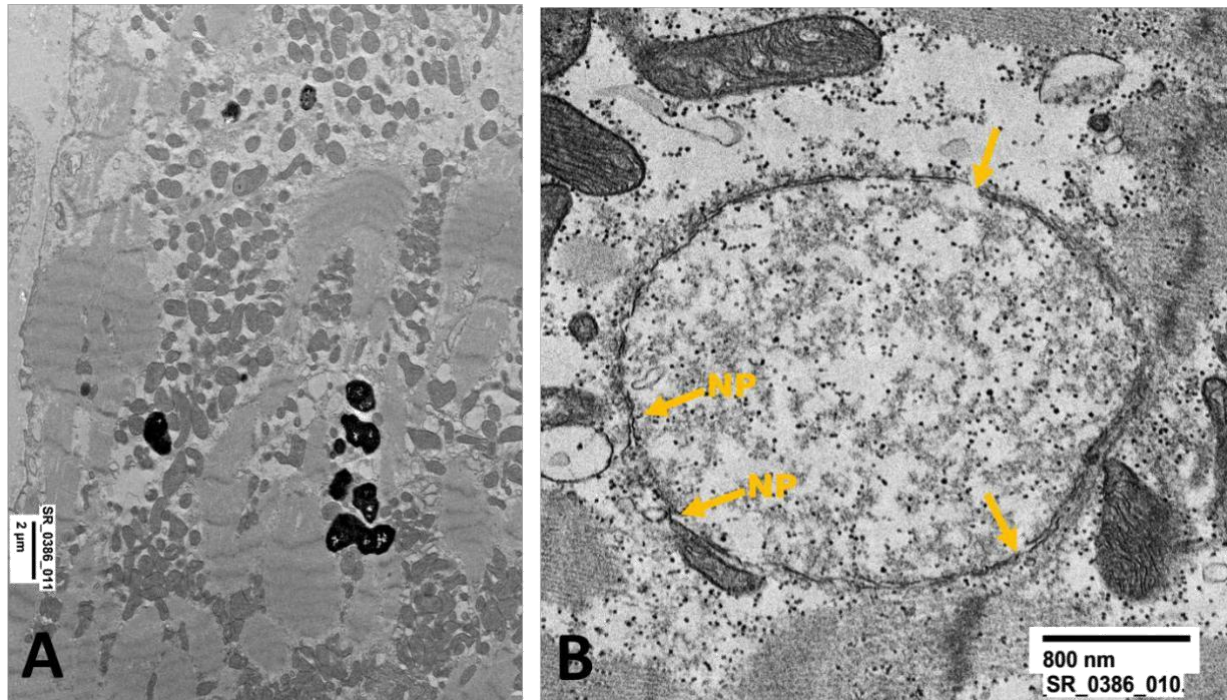
**EC = endothelial cells; RC = Red Cell; ES = Extracellular Space**





**Supplemental Figure S9. Baseline transmission electron microscopy showing enlarged vessel lumen (VL) (A) with electron clear material and/or osmiophilic myelin-like bodies (OMB), likely degenerating lipid membranes (B).**

**EC = endothelial cells; RC = Red Cell; ES = Extracellular Space**

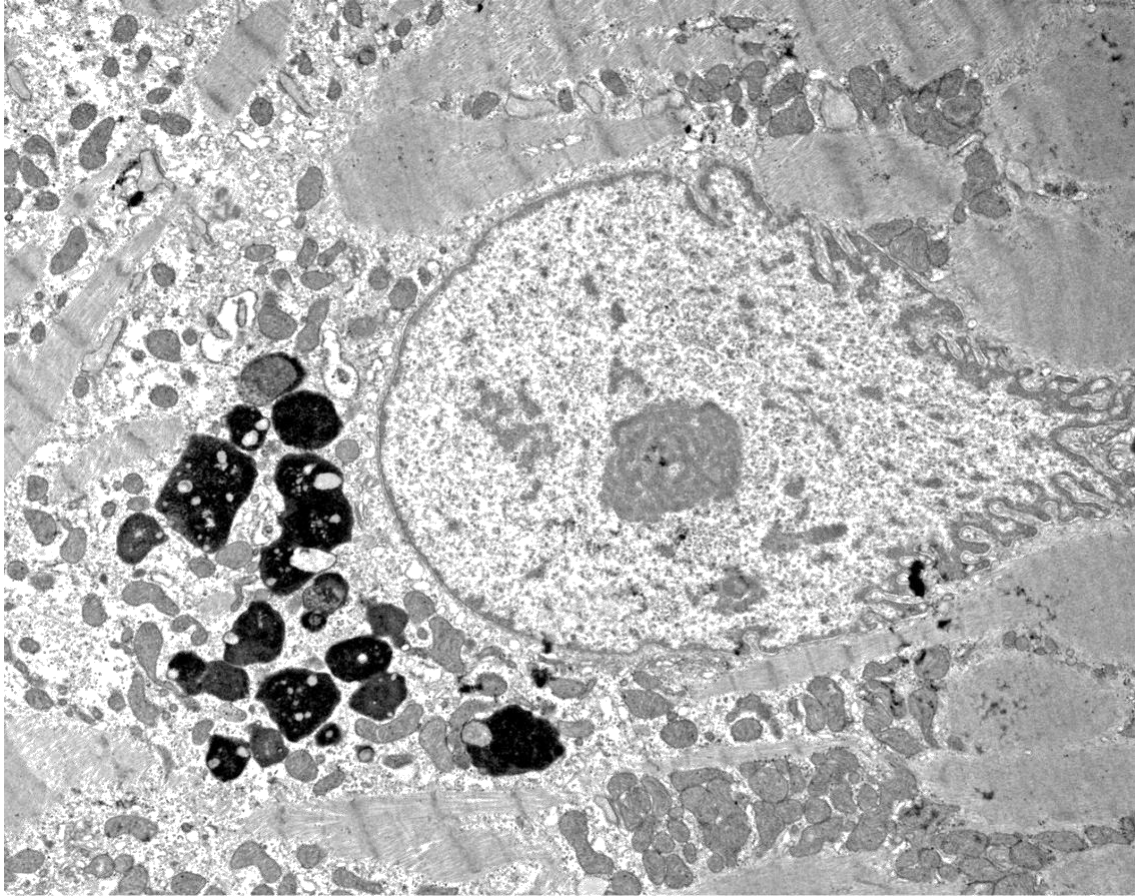


**Supplemental Figure S10. Baseline transmission electron microscopy showing myofibrillolysis and chromatolysis with nuclear membrane damage.**

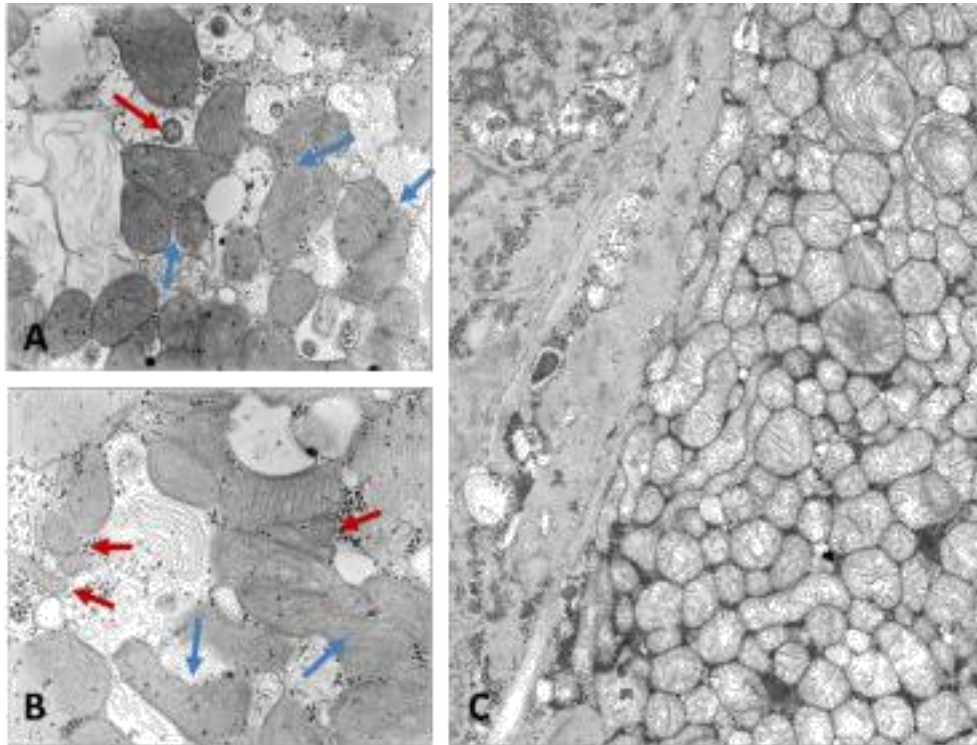
A: Large areas of myofibrillolysis and sarcomere disorganization. Dense lipofiscin.

B: Nuclear damages: chromatolysis, nucleolar disorganization, nuclear membrane damages. NP = nuclear pore; Arrows = membrane fragmentation.





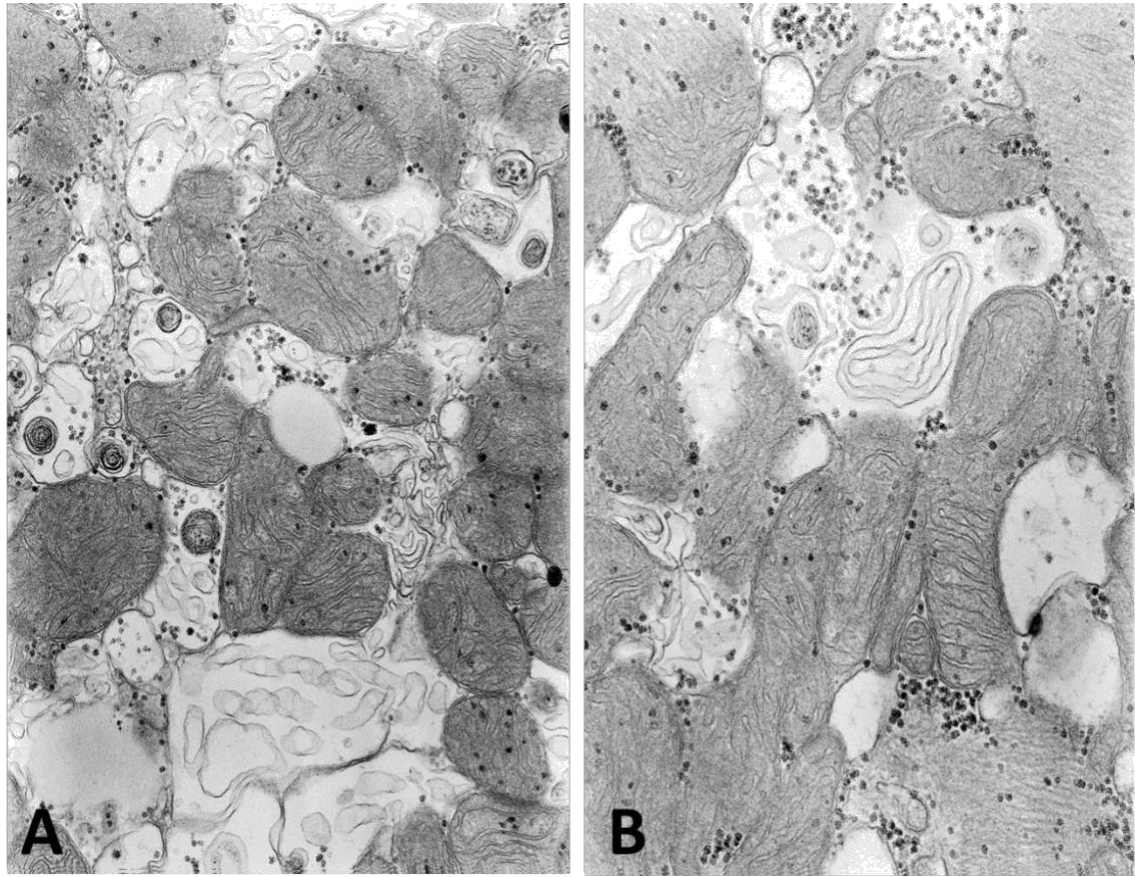
**Supplemental Figure S11. Baseline transmission electron microscopy showing nuclear changes (chromatin fragmentation, abnormal nucleolonema) and cytoplasm changes (areas of myofibrilolysis, abnormal sarcomeres and accumulation of lipofuscins).**



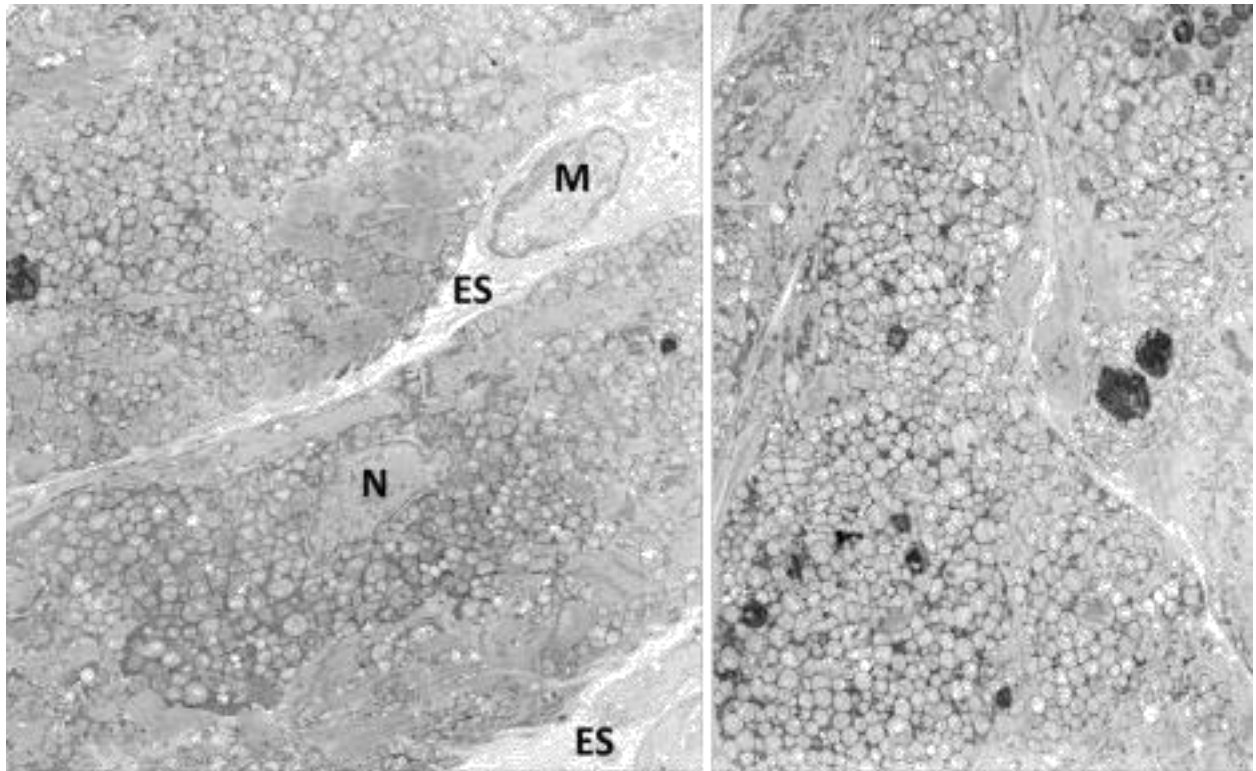
**Supplemental Figure S12. Baseline transmission electron microscopy showing alterations of mitochondrial dynamics/conformation and small vesicles dilatation (sarcoplasmic reticulum, Golgi vesicles, lysosomes, mitochondria).**

A-B. Evidences of altered fission/fusion dynamics, as shown by micro-mitochondria (red arrows) and fusing polymorphic/bizarre mitochondria (blue arrows).

C. A group of densely packed swollen mitochondria. The matrix is electron clear, while cristae are plate-like conformation, although sometimes fragmented.

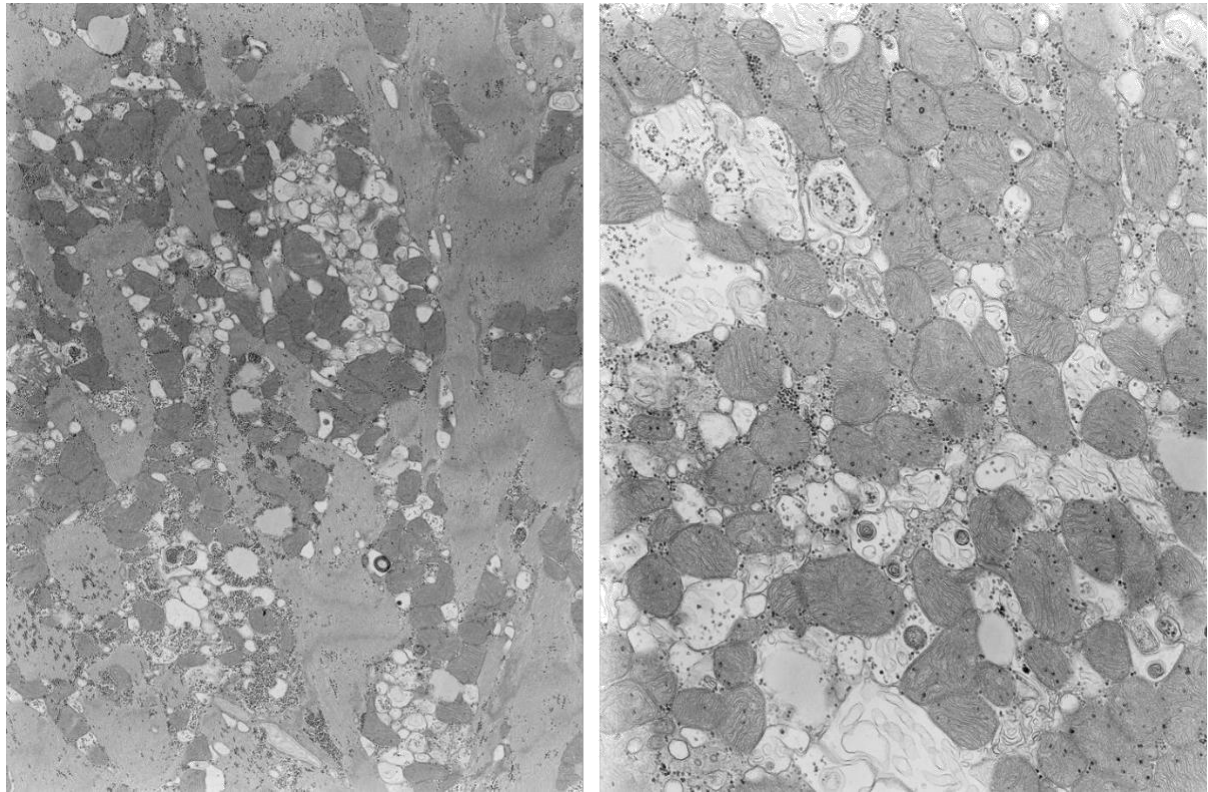


**Supplemental Figure S13. Higher magnification of A and B electron panels of the figure 12.**



**Supplemental Figure S14. Baseline transmission electron microscopy showing alterations of mitochondria.**

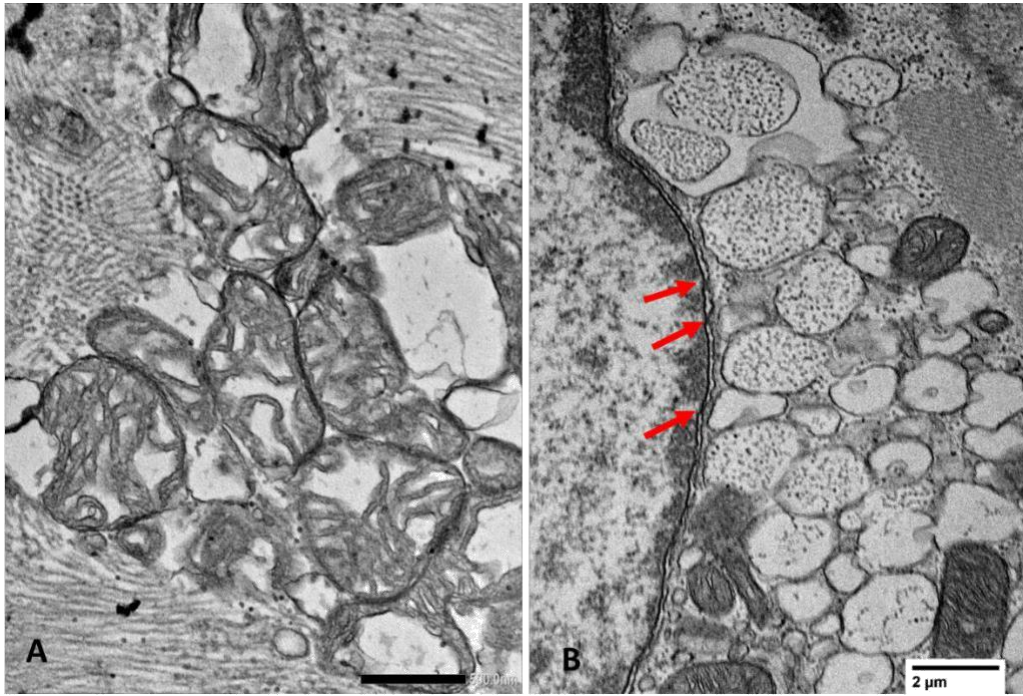
Large groups of swollen mitochondria in a cytoplasm with reduced myofibrillar content and disorganized sarcomeres. Grouping of mitochondria may be responsible for an inefficient supply of high-energy phosphate molecules to the ATP-dependent functions, such as contraction. N = nucleus; ES = extracellular space; M = monocyte or large lymphocyte.



**Supplemental Figure S15. Baseline transmission electron microscopy showing further details of dilated vesicles likely derived from sarcoplasmic reticulum, Golgi apparatus, lysosomes and other organelles.**

The electron clear areas containing glycogen particles are either swollen cytosol or the lumen of an autophagocytic vacuole. Mitochondria are in orthodox/slightly swollen conformation.

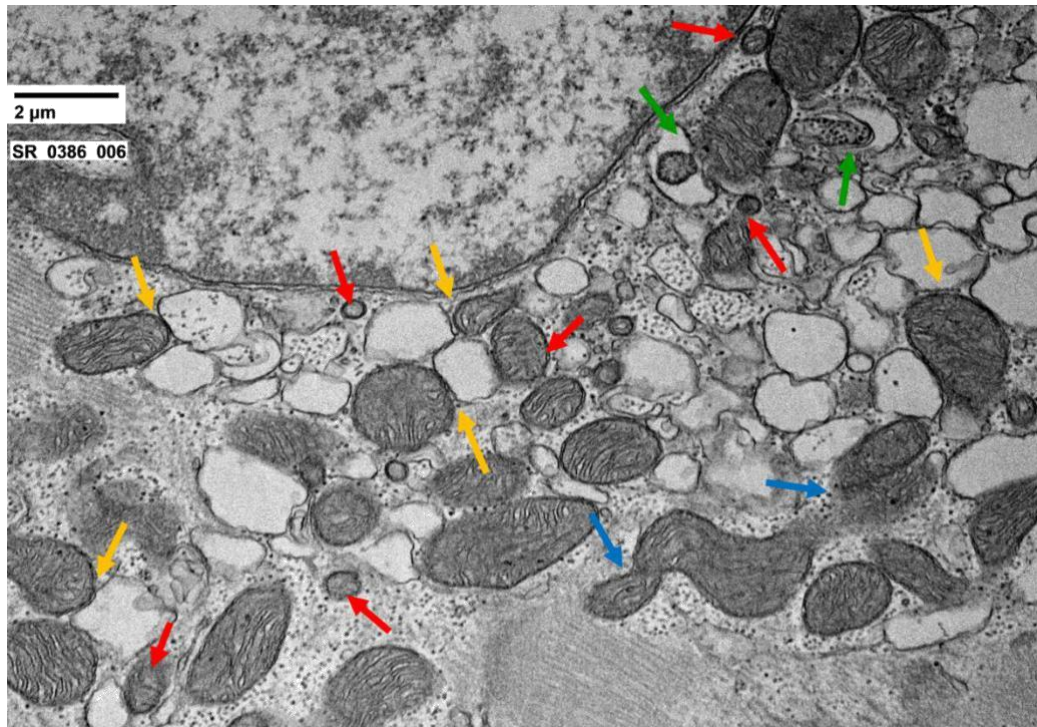




**Supplemental Figure S16. Baseline transmission electron microscopy showing detail of highly swollen mitochondria and other organelles.**

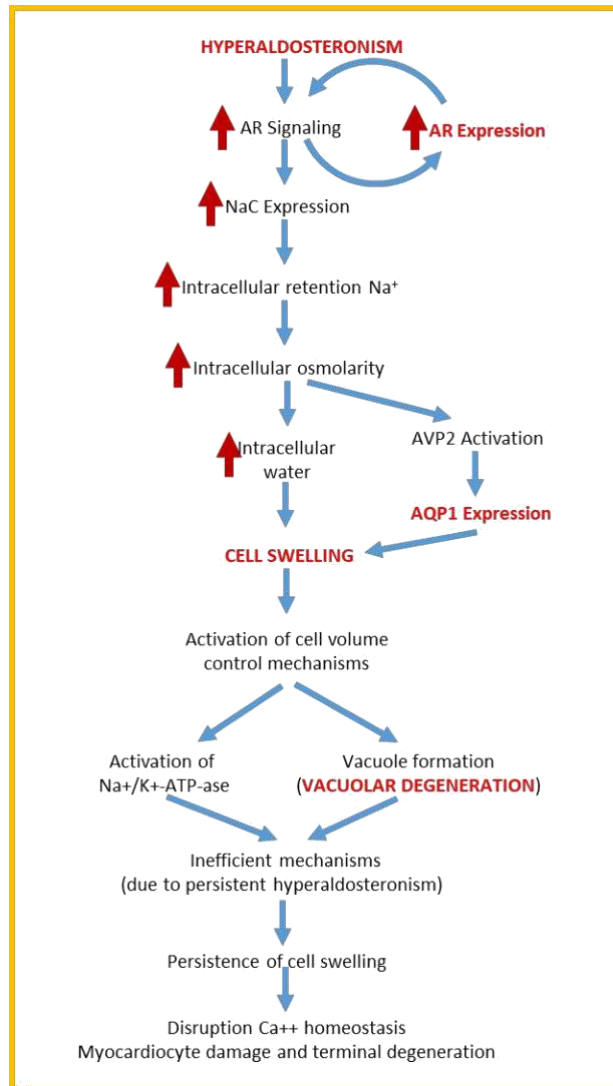
A. Detail of mitochondria: diluted and vesiculated matrix with irregular cristae and damaged outer membrane

B. Detail small dilated vesicles of heterogeneous origin: phagosomes, autophagosomes, cyternae of sarcoplasmic reticulum (strictly interacting with outer mitochondrial membrane) and, possibly, Golgi apparatus (close to nuclear membrane).

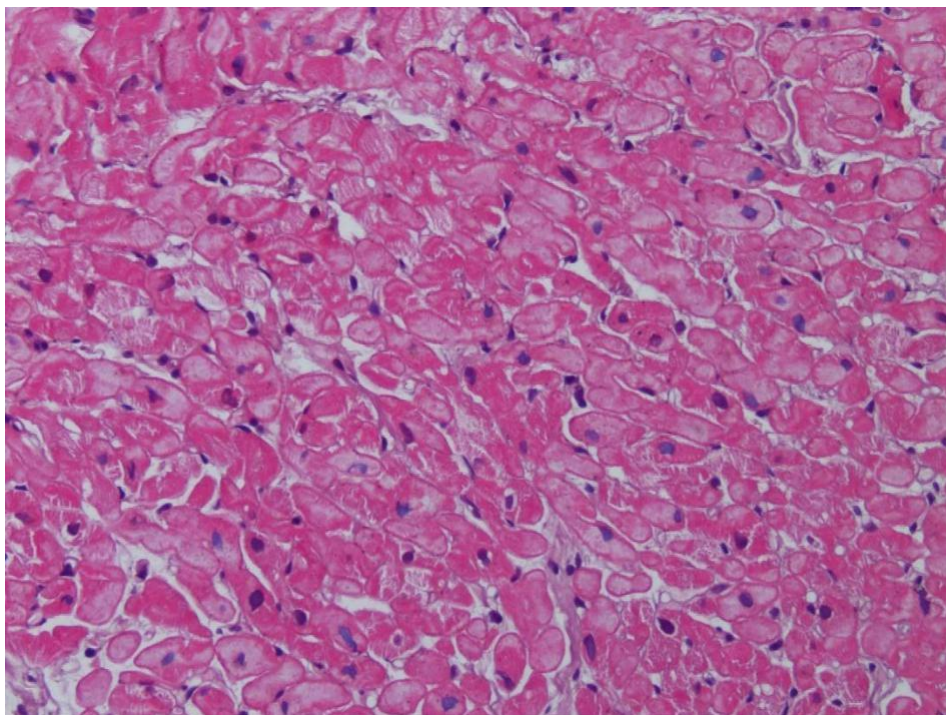


**Supplemental Figure S17. Perinuclear region with small vesicles to that observed in the figure S16.**

Electron microscopy showing a number of details of abnormal dynamics of mitochondria: micro-mitochondria (red arrows), bizarre fusion (blue arrows) close interaction with sarcoplasmic reticulum cisternae (orange arrows) and mitophagy (green arrows).

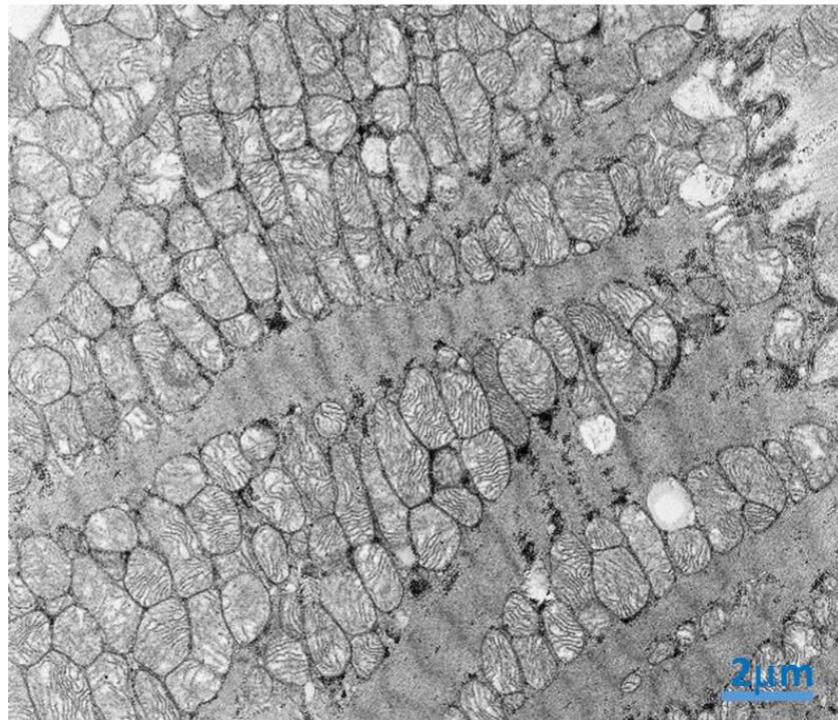
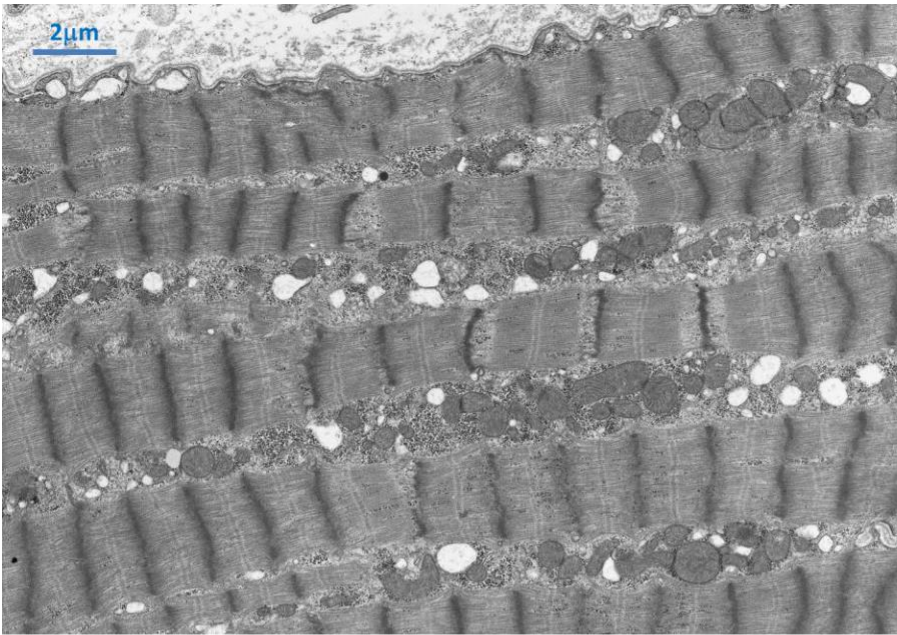


**Supplemental Figure S18. An hypothetical description of the sequence triggered by aldosterone signaling leading to ion/water homeostasis disruption and to the myocardocyte damage.**



**Supplemental Figure S19. Normal myocardium from EMB sample at histology.**





**Supplemental Figure S20. Normal myocardium from a EMB sample at transmission electron microscopy**