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Hypertension and heart failure are accompanied by alterations of the mitochondrial membrane potential in cardiomyocytes

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Background Hypertension is the number one risk factor for the development of heart failure and one of the largest unmet medical needs in cardiovascular medicine. One of the hallmarks of hypertension and heart failure is mitochondrial dysfunction in cardiomyocytes. Although initial studies recognized the importance of different mitochondrial subpopulations, a direct comparison of the role of intrafibrillar (IF) vs perinuclear (PN) mitochondria in cardiac disease is lacking.

Methods/Results We used live cell imaging to investigate changes in mitochondrial membrane potential (??m) of IF vs PN mitochondria. We isolated cardiomyocytes from hypertensive rats, failing mice, and non-failing and failing human hearts. Using a ??m-sensitive dye, we stained the cells and acquired confocal images while subjecting the cells to physiological stress in the form of high-frequency electrical stimulation. Thereby, we demonstrated that ??m was generally more susceptible to alterations in PN mitochondria of diseased hearts than the respective healthy controls. In cells from hypertensive rats, we found depolarization of PN mitochondria upon stress, but not at baseline. However, in cardiomyocytes from both mouse and human failing cardiomyocytes, we found alterations of ??m already at baseline. Application of stress further exacerbated the depolarization of PN mitochondria in failing mice. IF mitochondria showed signs of deterioration only upon high-frequency pacing in failing cardiomyocytes of mice.

Conclusion Taken together, we propose that changes in ??m of PN mitochondria are highly prominent in cardiac disease and may be implicated in the progression of cardiac remodeling. IF mitochondria appear to be affected only under stress conditions in heart failure, indicating incapability to cope with increased workload. Normalization of PN mitochondrial function by ameliorating ??m depolarization emerges as an interesting new strategy to prevent or stall cardiac remodeling.