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# Calcium signalling in cardiac fibroblasts and myocytes in an *in vitro* model of HFpEF

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#### **1. BACKGROUND**

Heart Failure with preserved Ejection Fraction [HFpEF] is a pandemic associated with hypertension and diabetes amongst other co-morbidities<sup>1</sup>. It has been established that fibrosis plays a major role in this form of heart failure<sup>2</sup>. However, the functional mechanisms of cardiac fibroblasts (CFs) in HFpEF and more importantly, how these cells interact with cardiomyocytes (CMs) and impact calcium (Ca<sup>2+</sup>) signalling is limited. This limitation is majorly due to a lack of physiologically relevant cellular models.





#### Aims of study:

- To evaluate the Ca<sup>2+</sup> response of CFs in conditions mimicking diabetes, hypertension, and HFpEF, *in vitro*.
- To assess the impact of sex on the function of CFs.
- To assess the influence of cardiac fibroblasts on the function of cardiac myocytes, under similar pathological conditions.





Imaging by Confocal Microscopy

#### 3. Ca<sup>2+</sup> SIGNALLING IN CARDIAC FIBROBLASTS





ACUTE

CF

#### 4. Ca<sup>2+</sup> SIGNALLING IN CARDIAC MYOCYTES







10 μm 10 μm

Calcium signalling in cardiac myocytes is influenced by cardiac fibroblasts.

Example images of a cardiac myocyte, showing (A) intracellular Ca<sup>2+</sup> activity trace, (B) whole cell, (C) at rest (D) transient during electrical Ca<sup>2+</sup> stimulation and (E) Ca<sup>2+</sup> sparks. (F) The Ca<sup>2+</sup> transient amplitude of CMs, alone, is enhanced under Ang IIinduced hypertensive culture conditions diabetic but not in conditions. This effect in however changed with the presence of cardiac fibroblast. (G) Ca<sup>2+</sup> leak from the sarcoplasmic reticulum is increased in the pathological conditions, and greater with female CFs than males.

activity in the presence of Ang II, which is enhanced in female CFs. This enhanced effect is observed only in hyperglycaemic conditions after (**D and E**) 24 hours and (**F**) 72 hours.



24hr

#### 5. SUMMARY

#### 6. REFERENCE, ACKNOWLEDGMENT and CONTACT

#### Findings suggest that:

- Ca<sup>2+</sup> response in CFs is enhanced in *in vitro* diabetic and hypertensive conditions, relative to time.
- Cardiac fibroblasts influence the electrophysiology of cardiac myocytes, in vitro.
- The Ca<sup>2+</sup> activity of CFs and its influence on the physiology of CMs is sex specific.

#### Future studies:

- What happens to the SR content in these cellular models of pathology?
- What factors drive intercellular communication by both cell types, in cardiomyopathy?
- How do fatty acids influence these cellular interactions, as seen in obese hearts?

**1.** Lejeune S, Roy C, Slimani A, Pasquet A, Vancraeynest D, Vanoverschelde JL, Gerber BL, Beauloye C, Pouleur AC. Diabetic phenotype and prognosis of patients with heart failure and preserved ejection fraction in a real life cohort. Cardiovascular diabetology. 2021 Dec;20:1-2.

**2.** Sweeney M, Corden B, Cook SA. Targeting cardiac fibrosis in heart failure with preserved ejection fraction: mirage or miracle?. EMBO molecular medicine. 2020 Oct 7;12(10):e10865.



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