

Overview

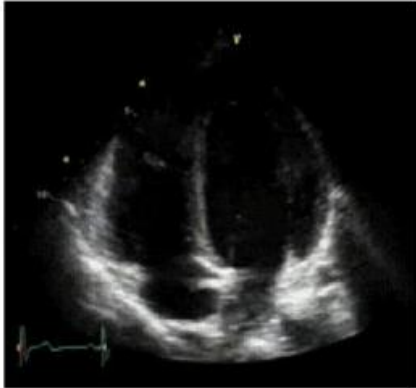
- **Background: heart failure and animal models**
- **Therapeutic concept and administration route**
- **Tachypacing model - methods**
- **Study design**
- **Preliminary results**
- **Conclusions**

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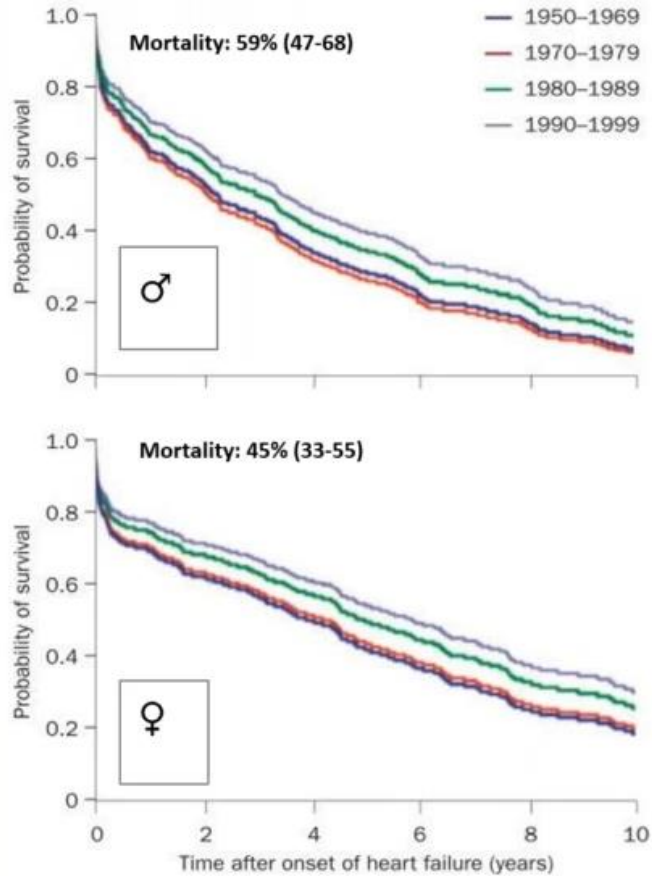
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Background: Heart failure

PhD Student (me)



Heart failure



Bui A. Nat Rev Cardiol. 2011

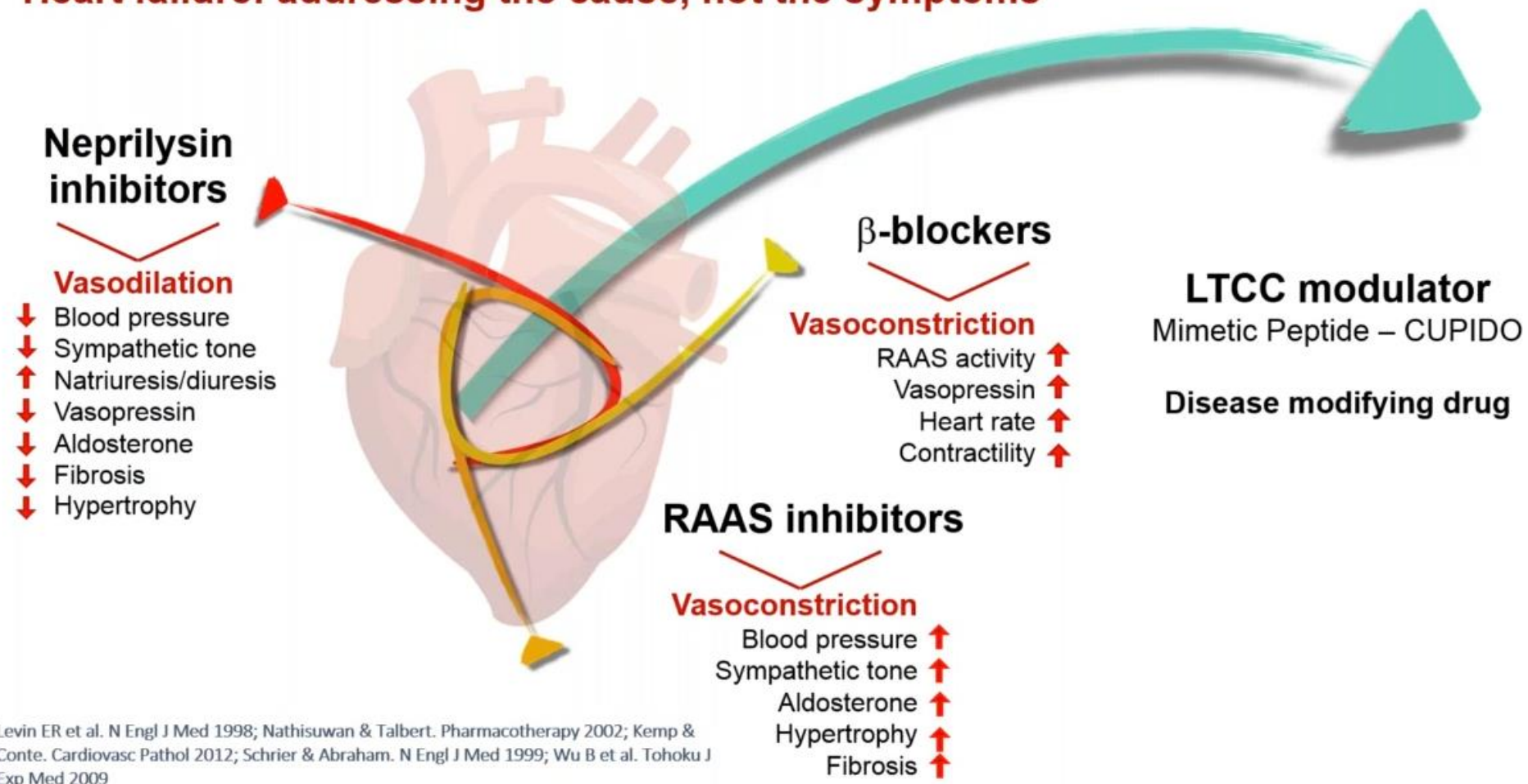
26 million
patients worldwide

Heart Failure with **reduced Ejection Fraction (HFrEF)**

13 million

Heart Failure with **preserved Ejection Fraction (HFpEF)**

Heart failure: addressing the cause, not the symptoms



Levin ER et al. N Engl J Med 1998; Nathisuwan & Talbert. Pharmacotherapy 2002; Kemp & Conte. Cardiovasc Pathol 2012; Schrier & Abraham. N Engl J Med 1999; Wu B et al. Tohoku J Exp Med 2009

“Specialists are people who always repeat the same mistake.”
Walter Gropius, German architect and founder of the Bauhaus School

Animal models for HFrEF?



tachypacing



myocardial infarction

→ LV dilatation
→ reduced EF



toxic
(anthracycline)

- cardiovascular physiology comparable to humans
- Stable weight over months
 - Highly trainable



aortic constriction

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The therapeutic concept



THE BREATH HEART CONCEPT



Administration route

The inhalation method

Vibrating mesh nebulizer

efficient inhalation method

the translation into the clinical setting is limited



Powder Aerosol – Wright Dust Feed Principle

The dry powder is aerosolized using a commercially available device provided by the company Covance

It represents the most efficient solution for dry powder inhalation in chronic animal models



The animals breath spontaneously during inhalation and do not need sedation

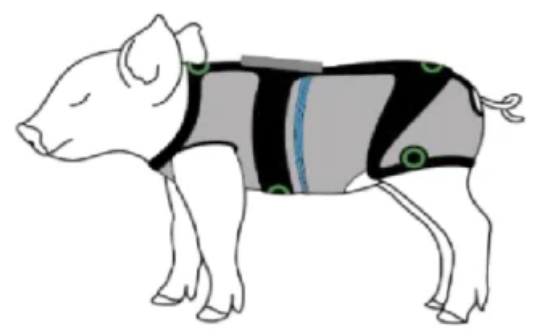
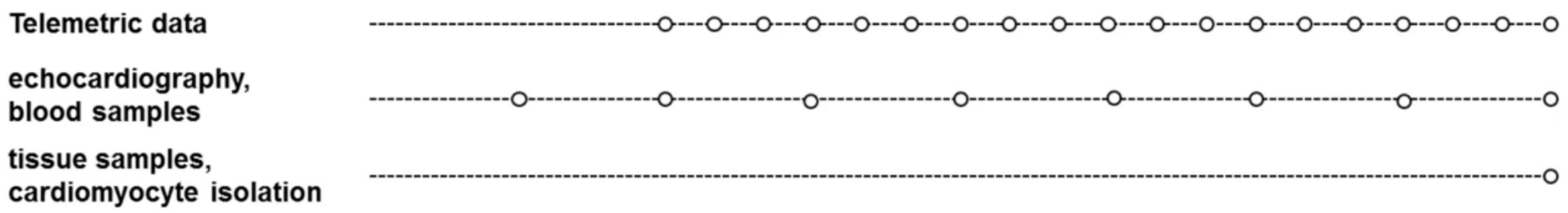
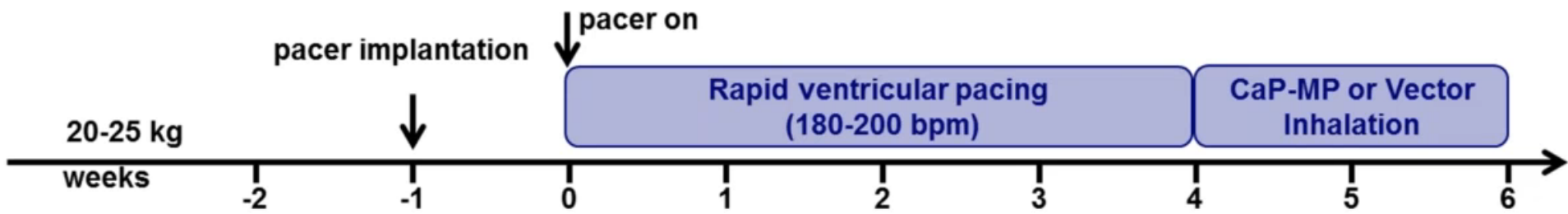
The system has been developed and tested to minimize animal distress



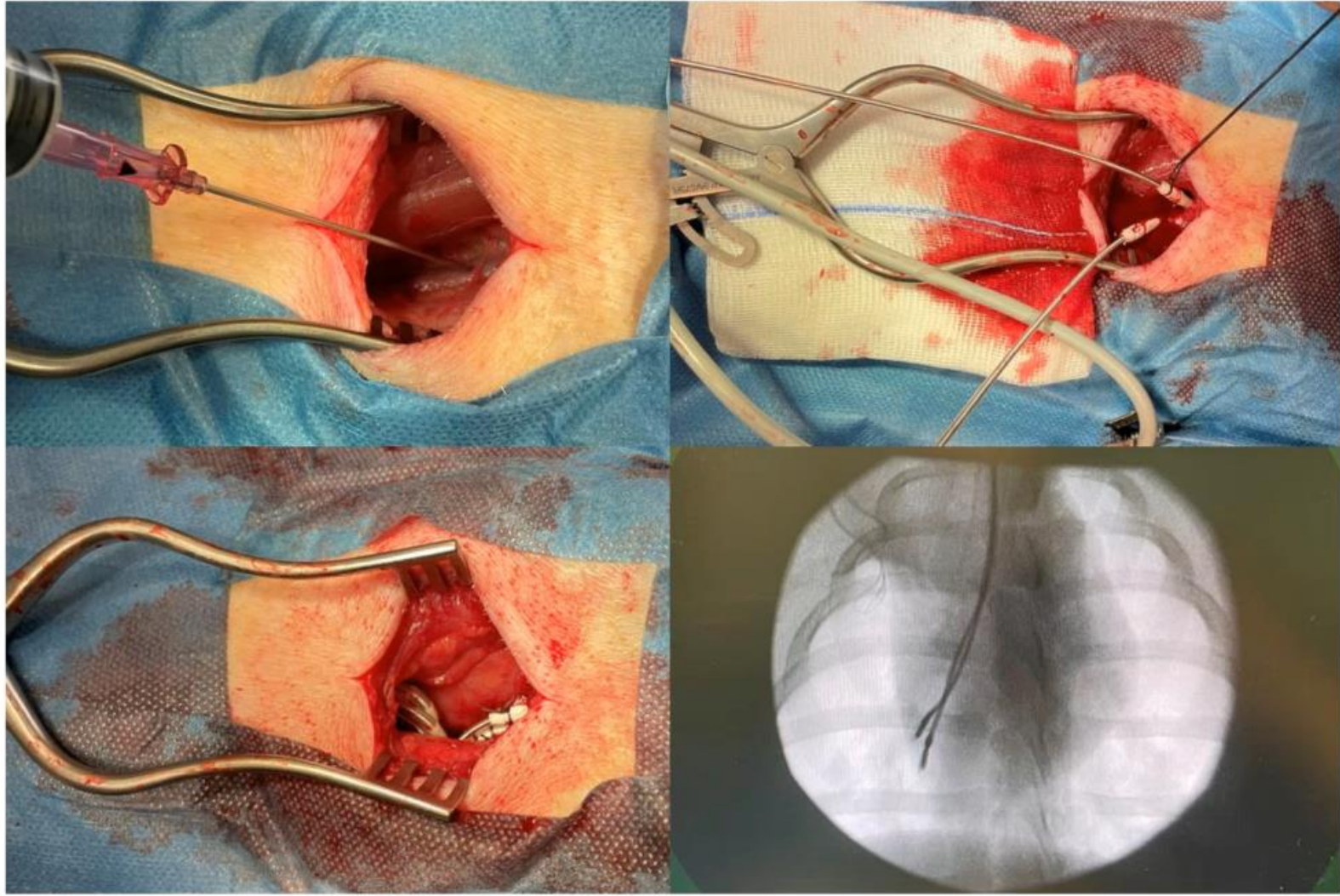
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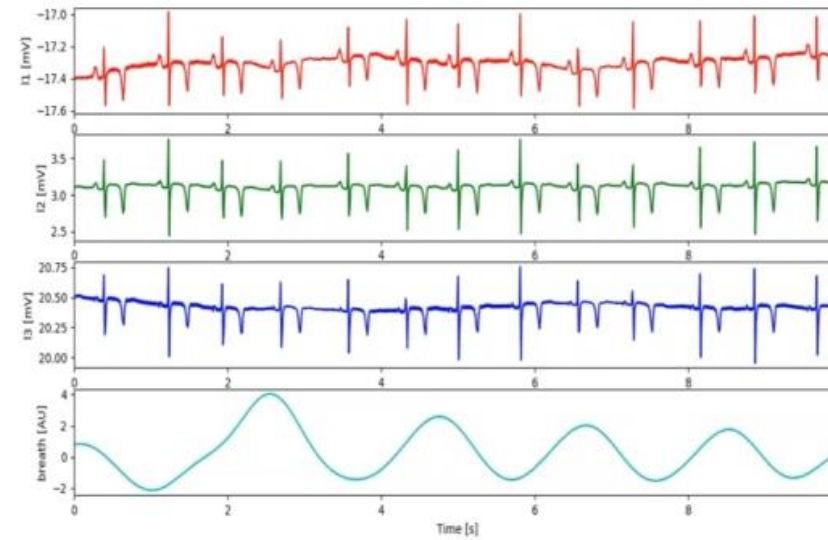


Pacemaker Implantation



Telemetric system

Wearable jackets – pilot version



Telemetric system

Wearable jackets – pilot version



Acquired data are labchart compatible

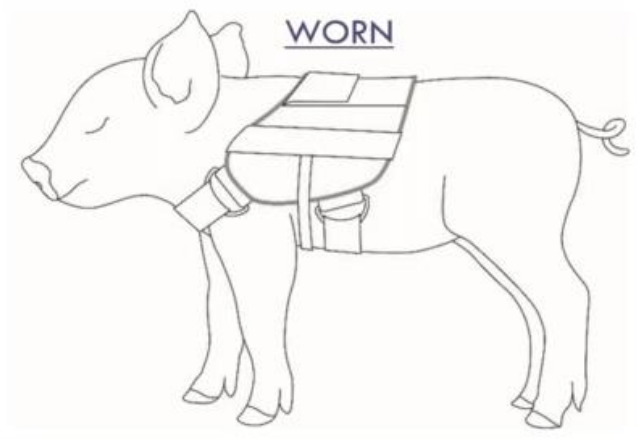
Wearable jackets – new version 1/2



Wearable jackets – new version 2/2



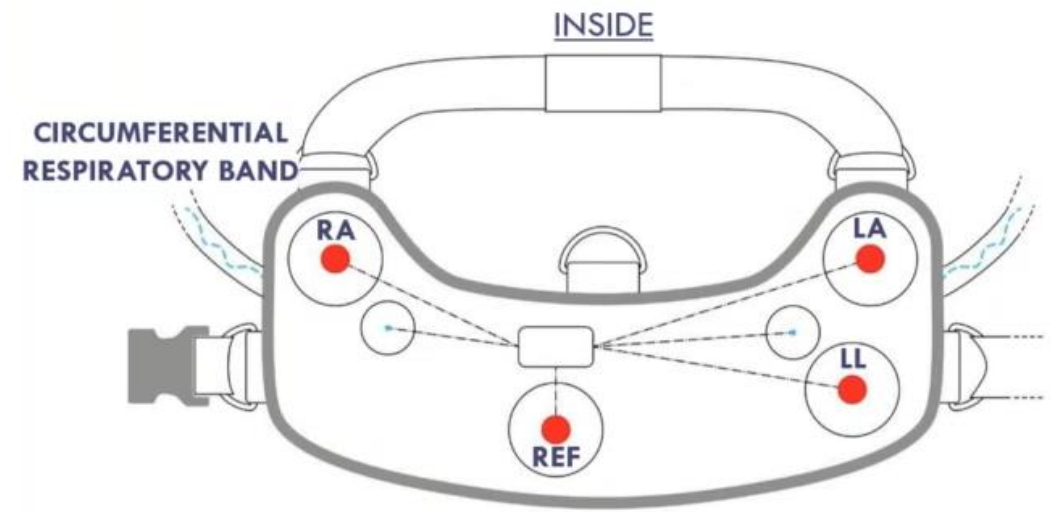
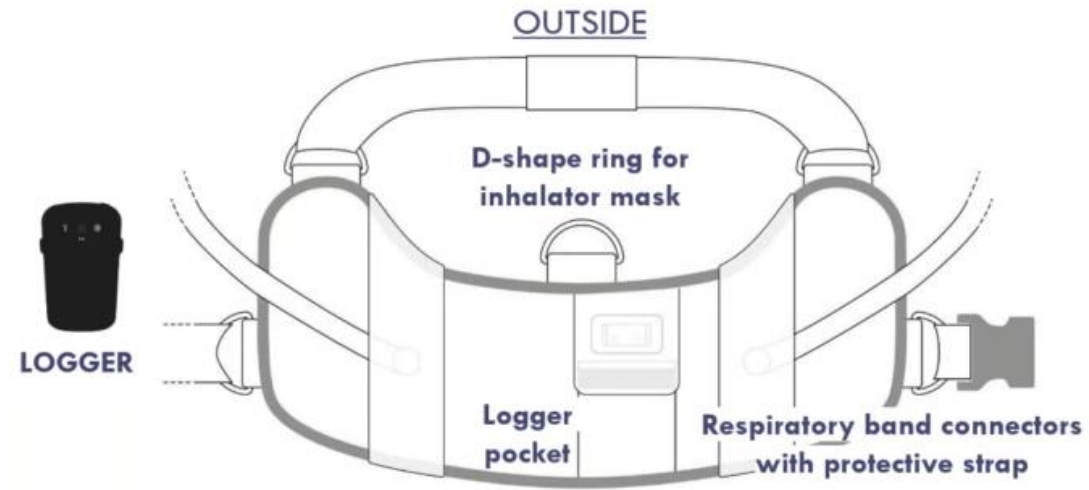
WEARABLE DEVICE
Final configuration



2-LEAD ECG

BREATH SIGNAL

3-AXIS
ACCELEROMETER



Telemetry system: LIFE jackets

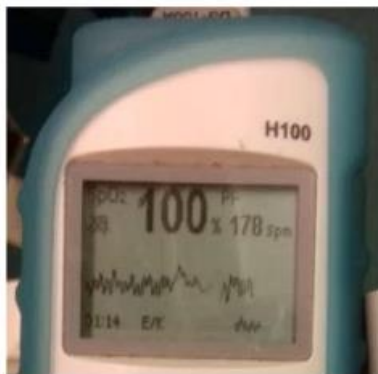


Central venous catheter implantation



Echocardiographic examination

Pacemaker on



Pacemaker off



Examination after 30 min

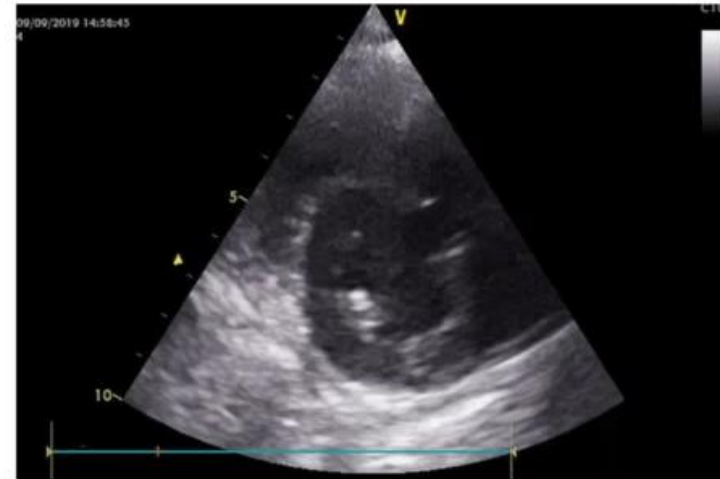
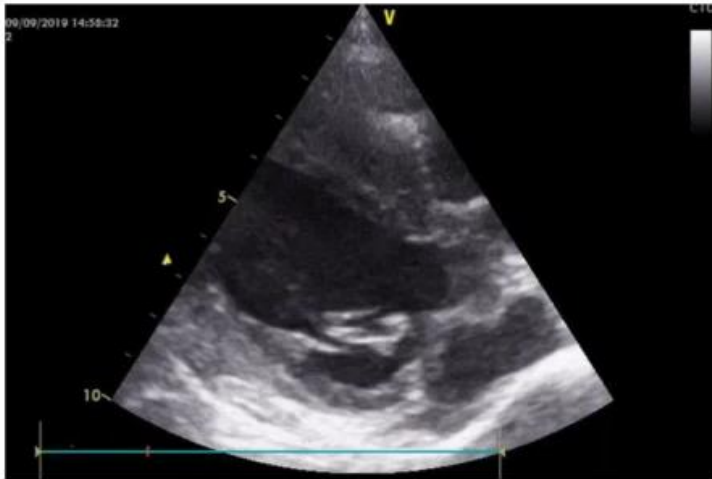


Echocardiographic examination

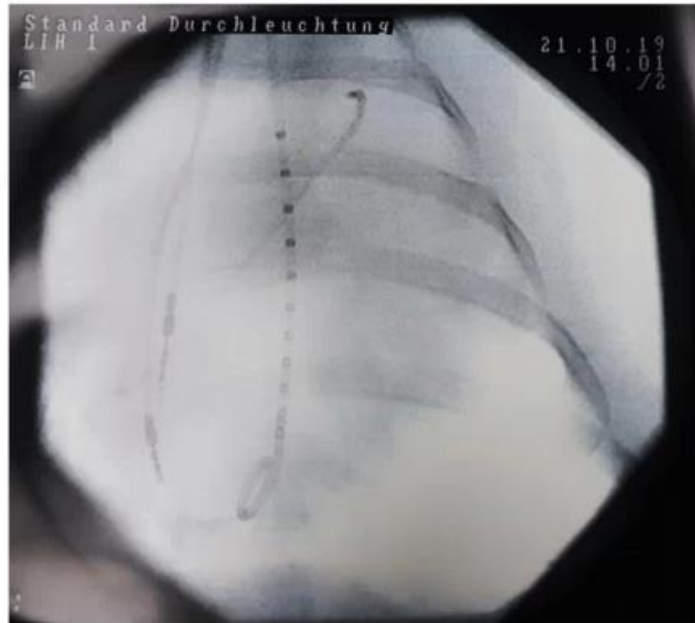


Echocardiography baseline before pacing

EF = 60%



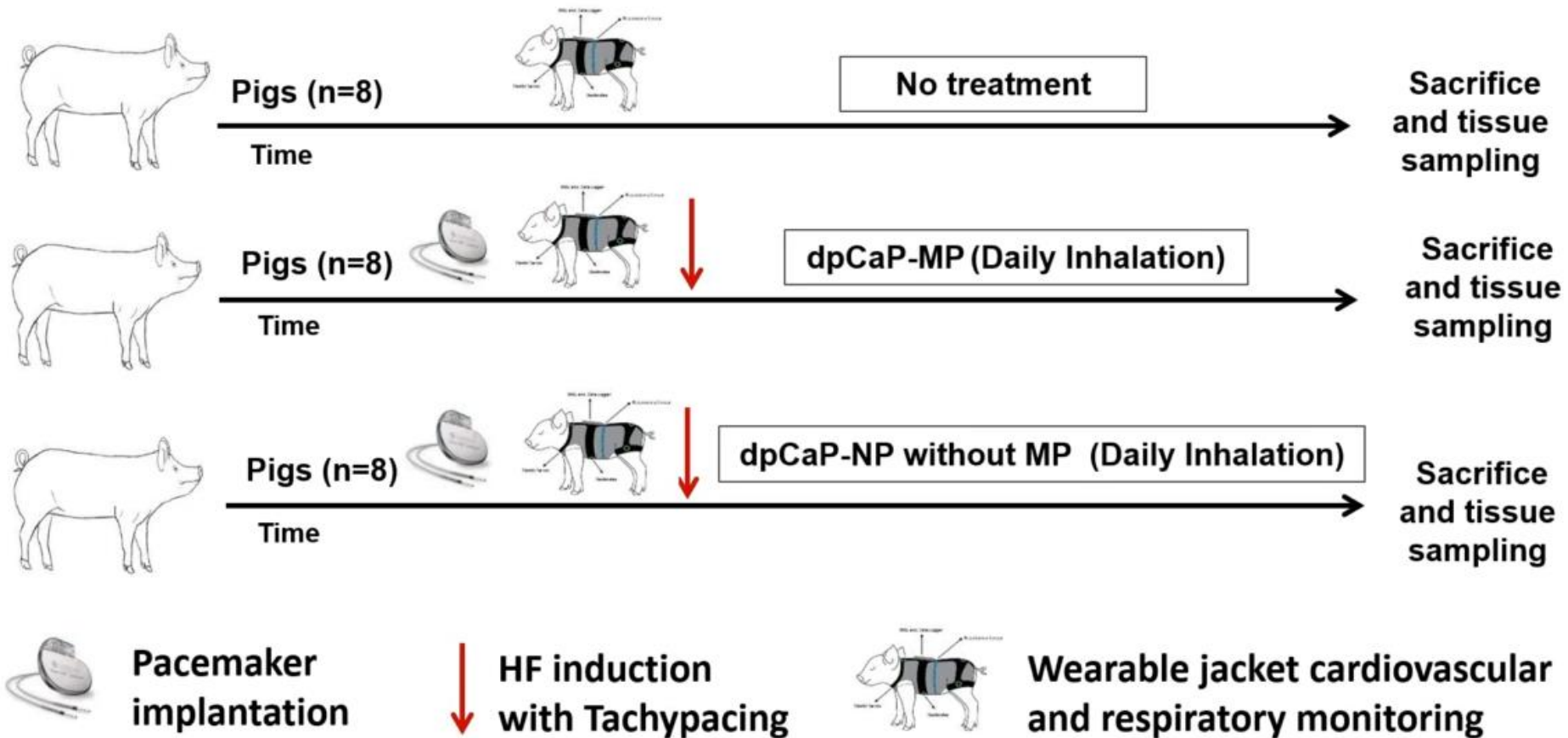
Final invasive measurements – Millar setup



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Study design*



* Sample size calculation performed via GPower V. 3.1, (Effect size $d=0,55$, $\alpha=0,05$ und Power $1-\beta=0,80$)

Study design

Primary endpoints:

Left ventricular ejection fraction (LVEF) *in vivo*

Developed force in muscle strips (trabeculae) and Calcium transient amplitude in single cardiomyocytes – *in vitro*

Secondary endpoints:

% Left ventricular fibrosis (stereology)

Respiratory rate (orthopnea), activity level (6min wt surrogate)

Adverse events and preclinical safety

Overview

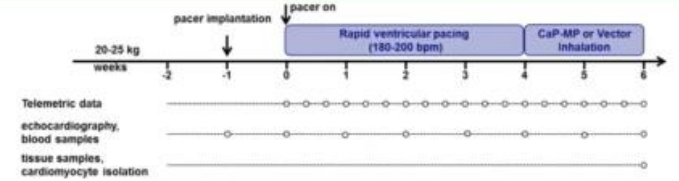
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- ✓ muscle strips – force development
- ✓ Isolated cardiomyocytes (Langendorff) – calcium cycling

Main study, new data

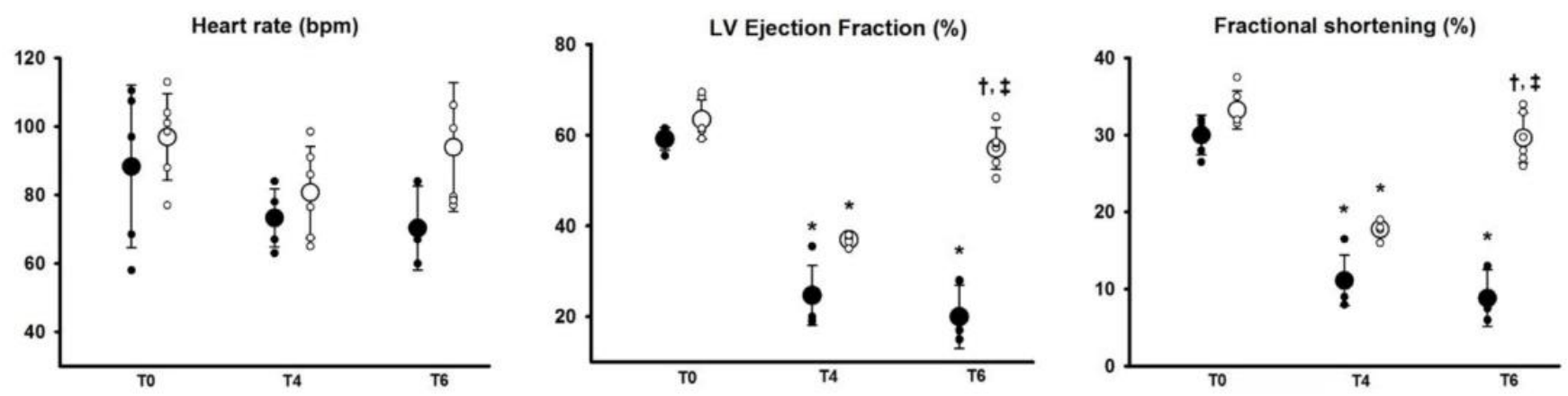
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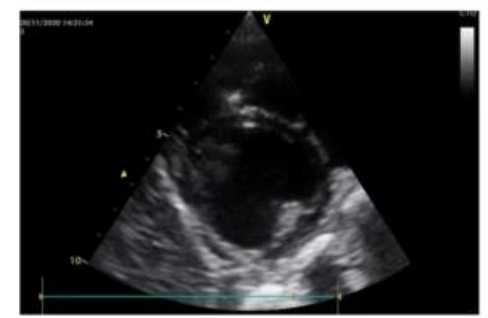
* p<0.05 vs. BL
 † p<0.05 between groups
 ‡ p<0.05 vs T4

- heart failure untreated n=5
- heart failure treated n=6

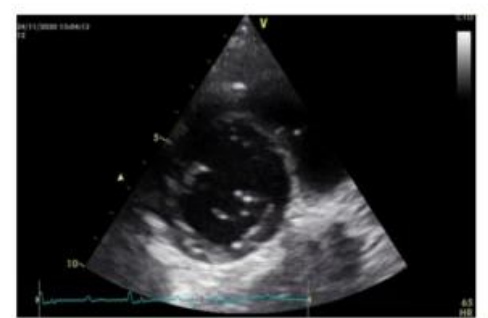
LV systolic function



- heart failure untreated

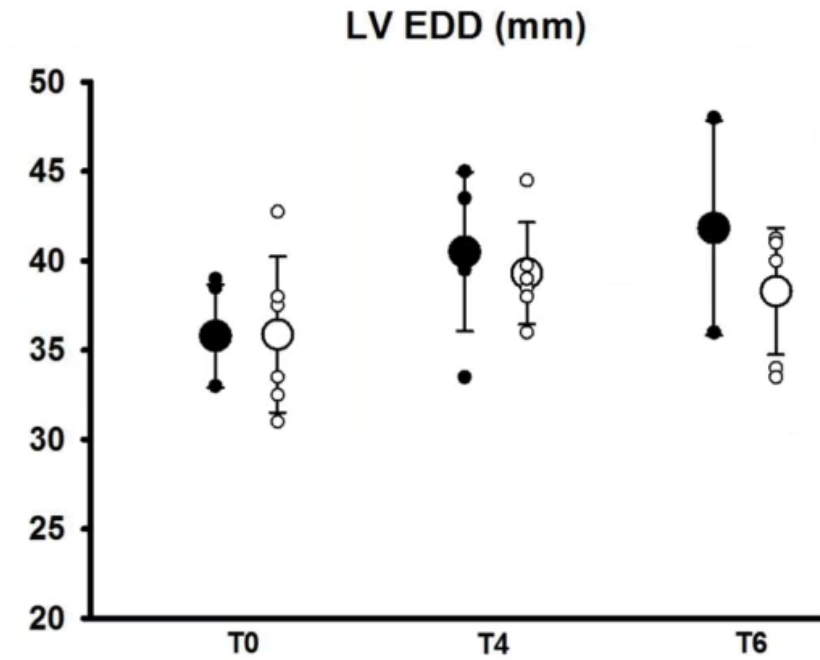
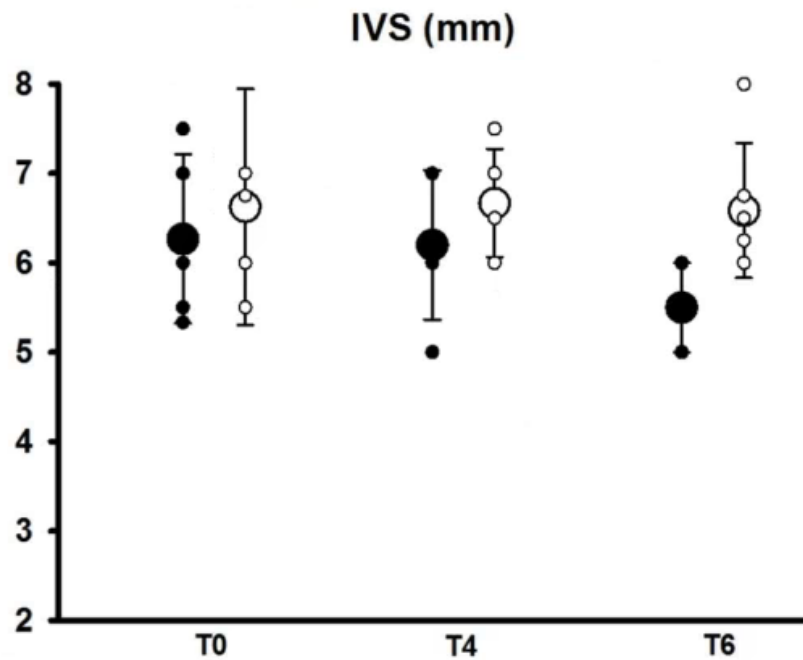


- heart failure treated



- heart failure untreated n=5
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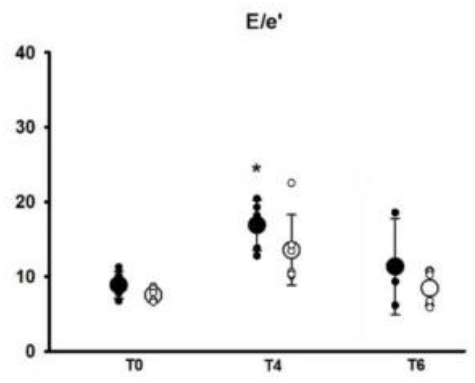
LV structure



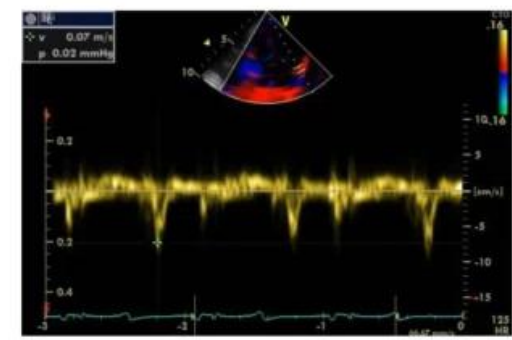
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Tissue doppler indices

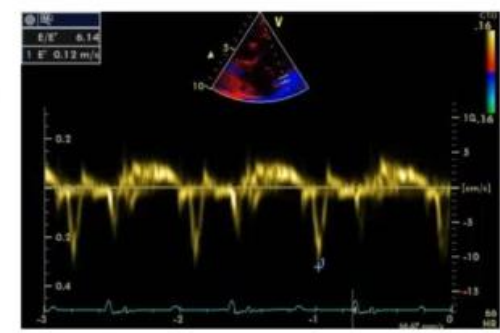
LV diastolic function



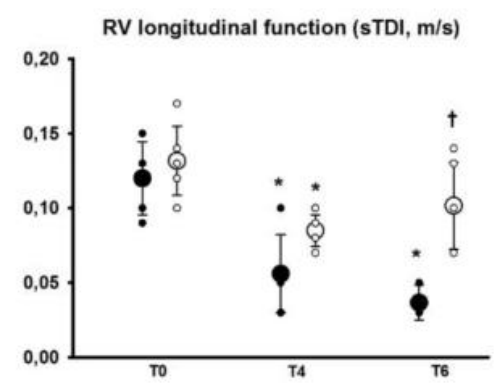
● heart failure untreated



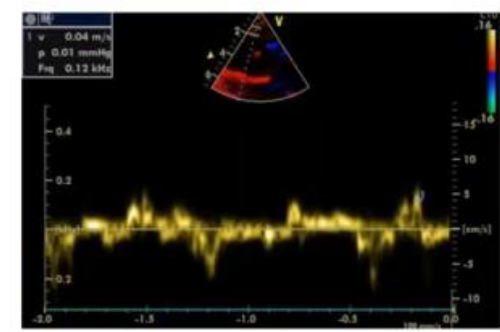
○ heart failure treated



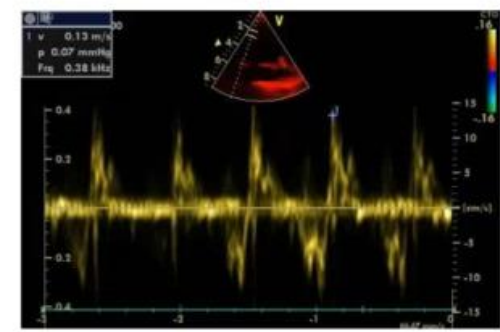
RV systolic function



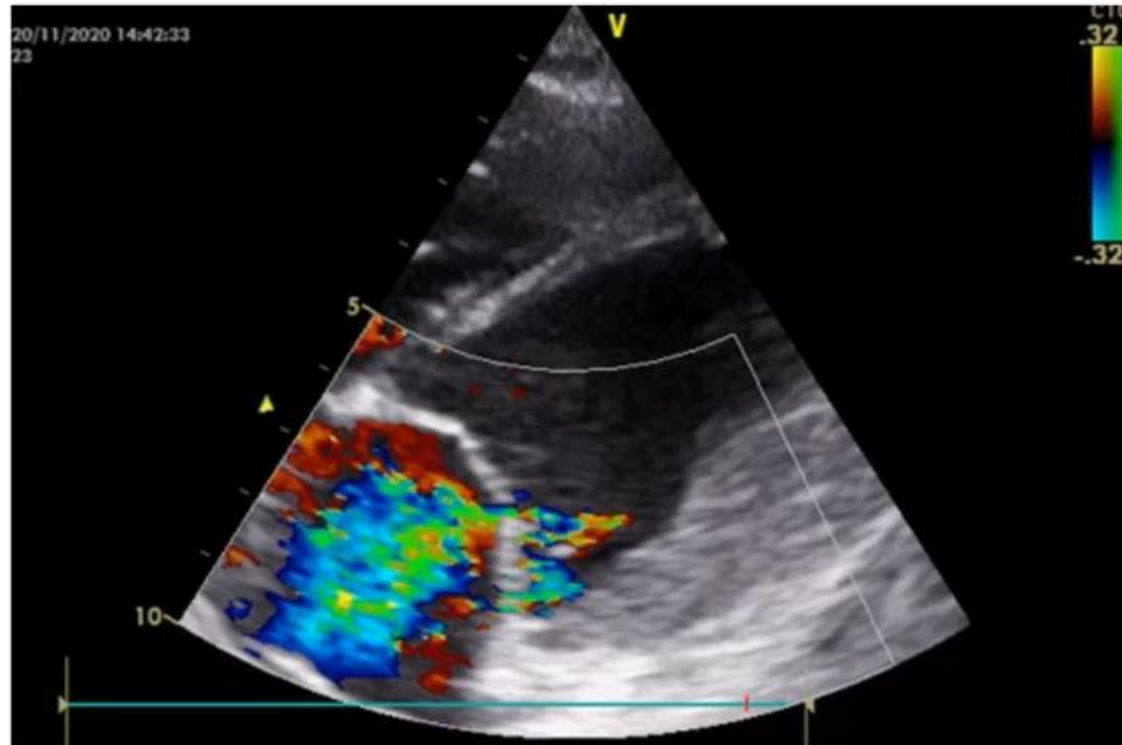
● heart failure untreated



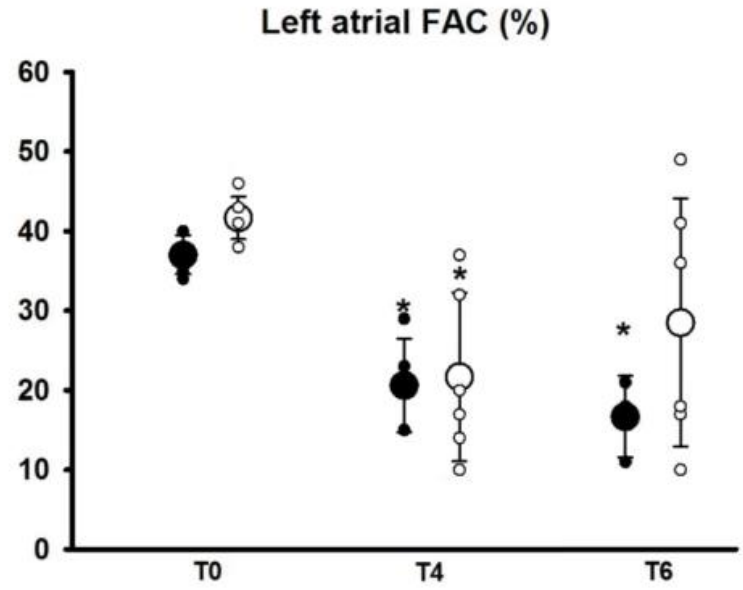
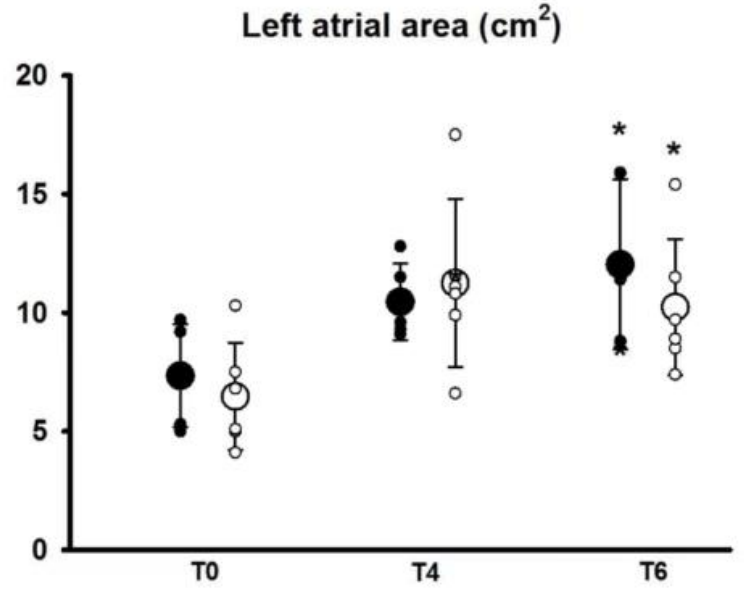
○ heart failure treated



At 6 weeks, 100% of the untreated animals had a mitral valve regurgitation, while only 30% (2/6) in the treated group



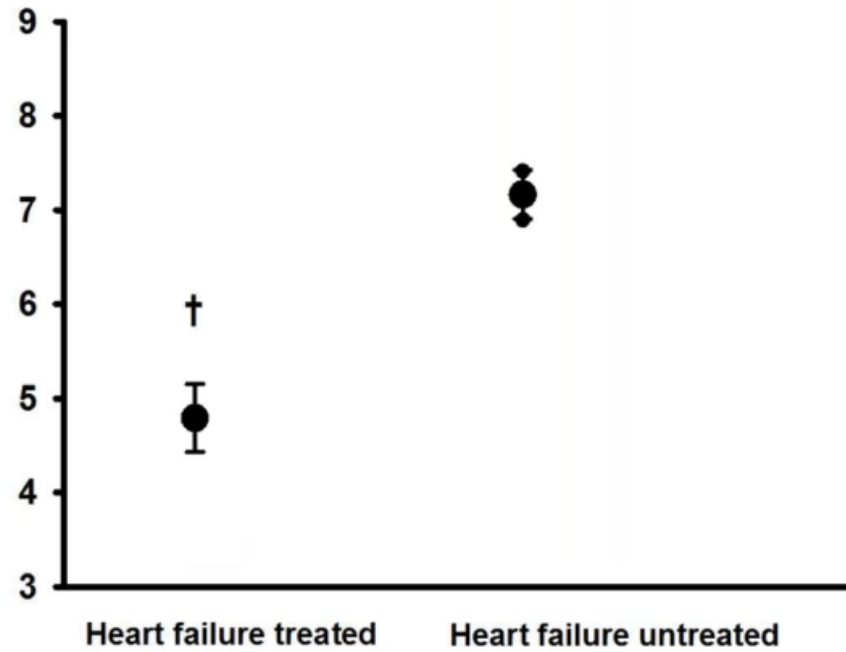
Left atrial remodelling



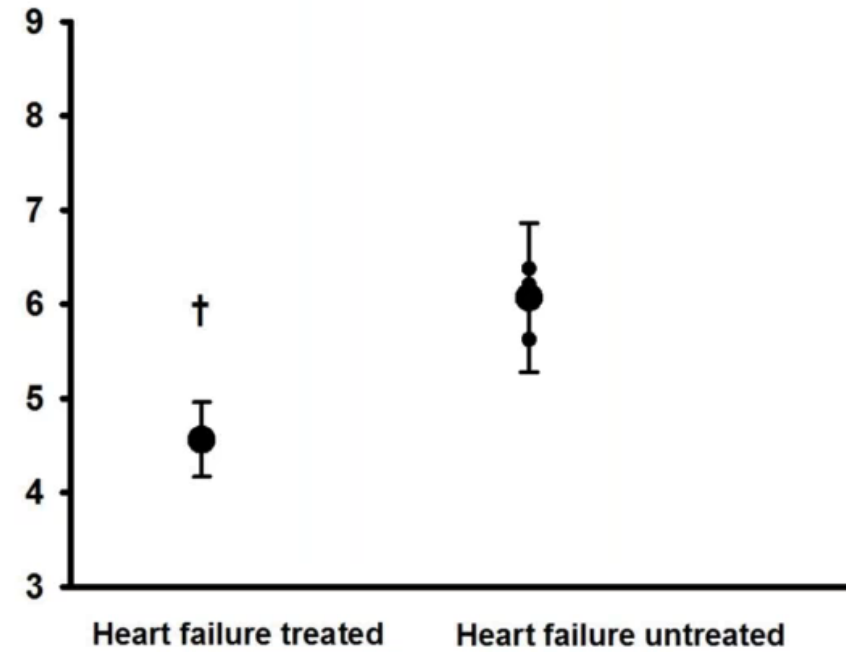
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Lung and heart weight

Lung/body weight (%)



heart /body weight (%)



n=3 each group

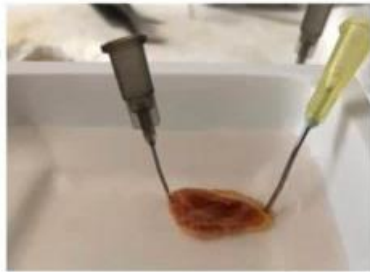


Results

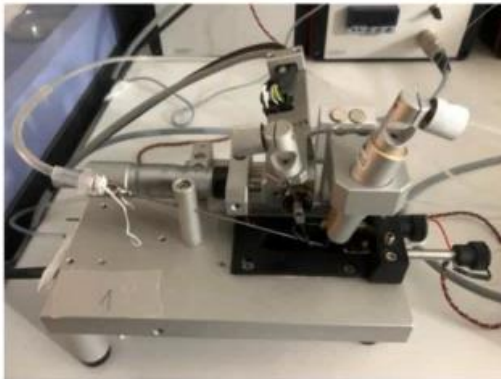
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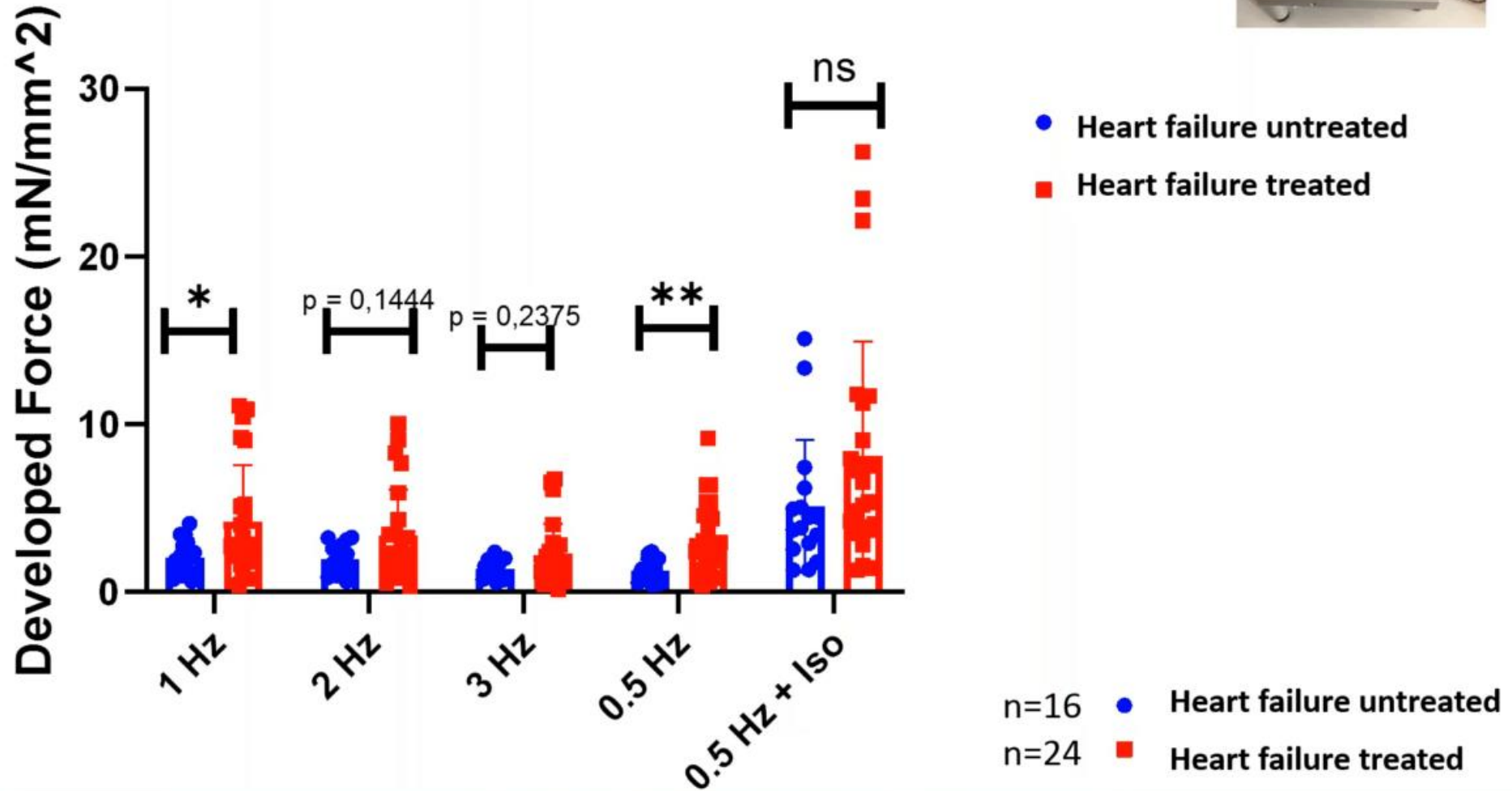
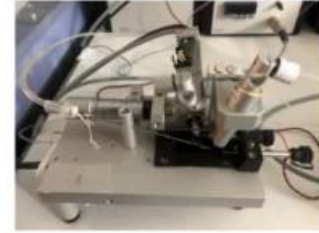
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Preparation

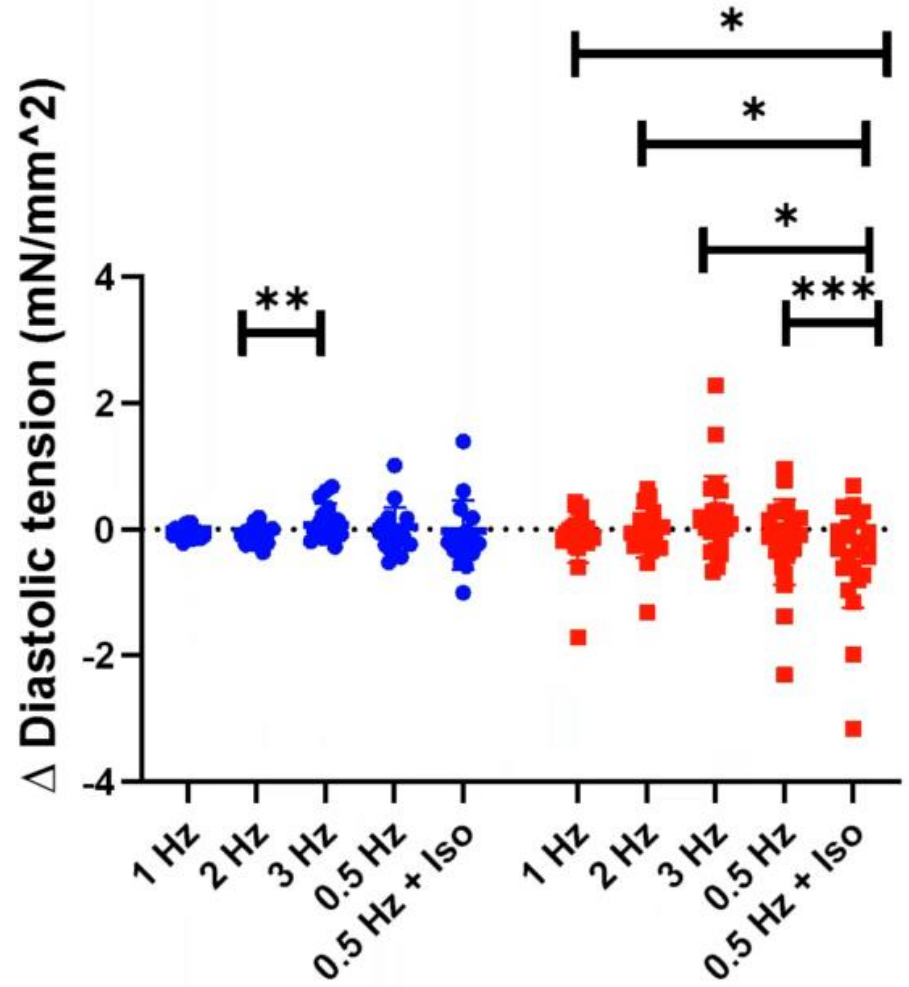


Muscle strips – developed force





Muscle strips – diastolic tension

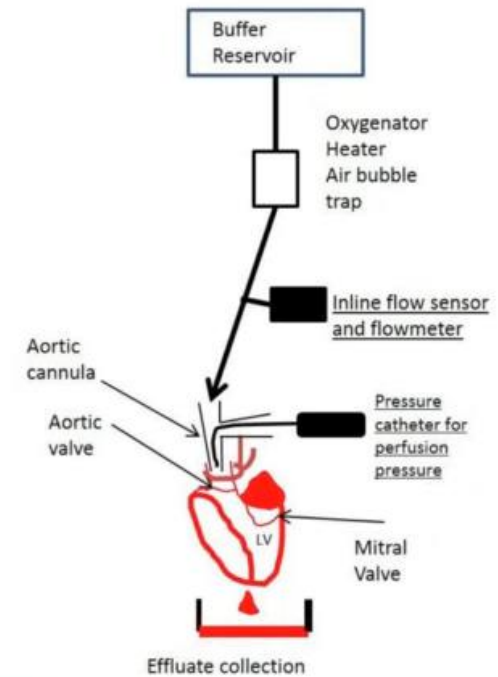


● Heart failure untreated
■ Heart failure treated

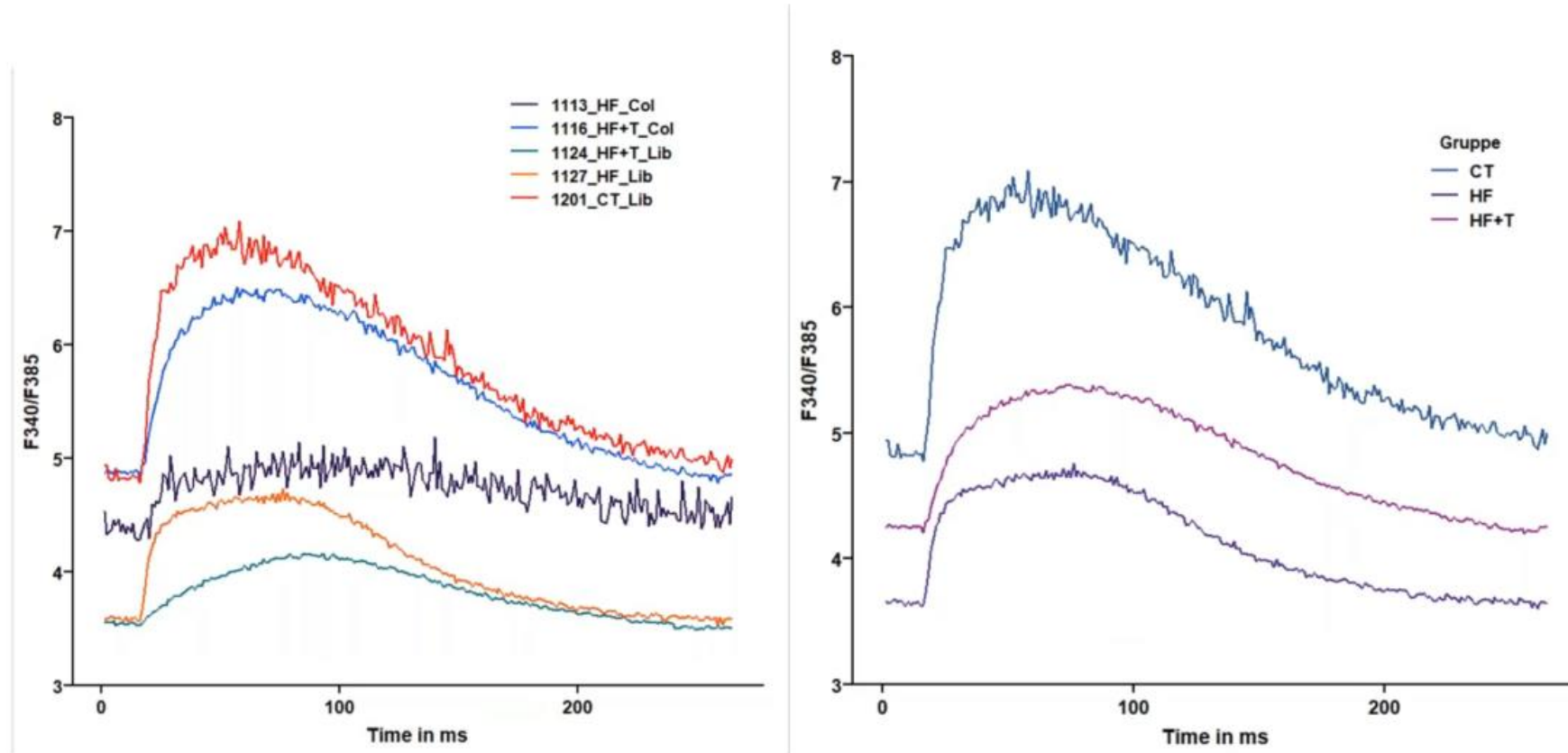
n=16 ● Heart failure untreated
n=24 ■ Heart failure treated

Results

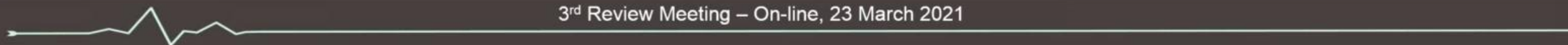
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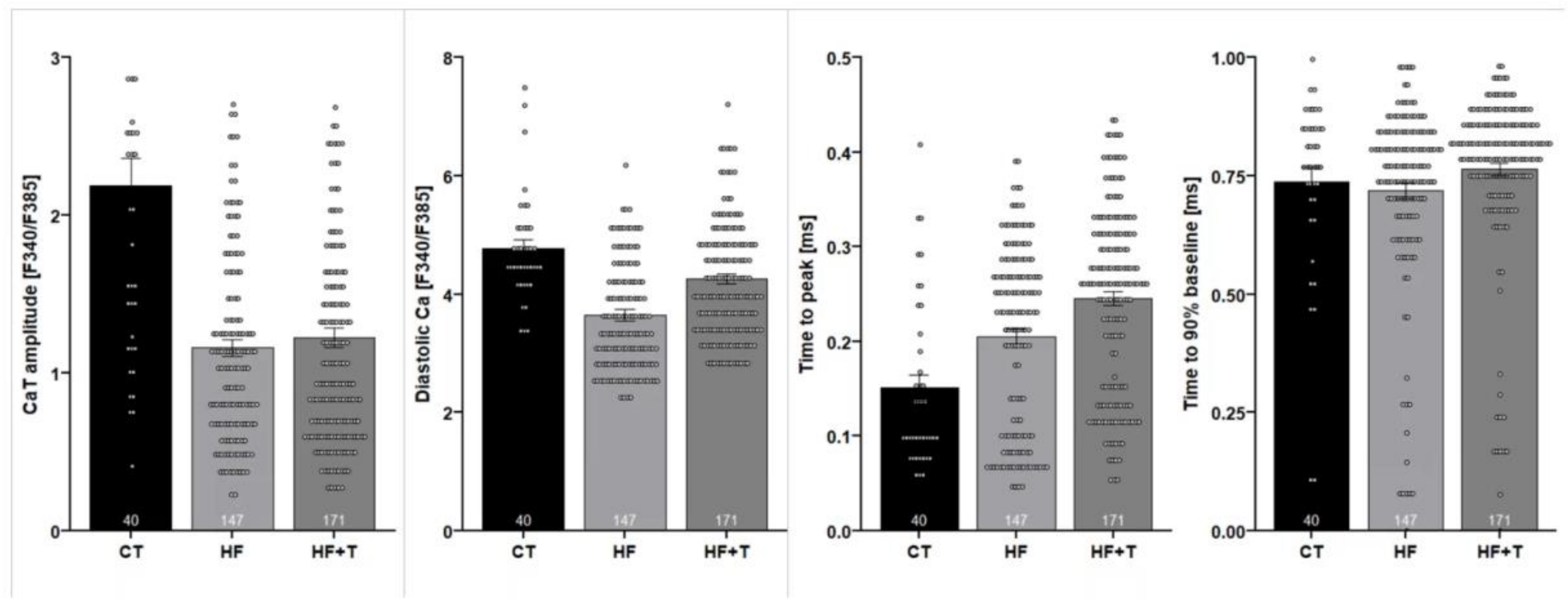
Isolated cardiomyocytes: high-throughput Calcium transient analysis (Cytocypher)



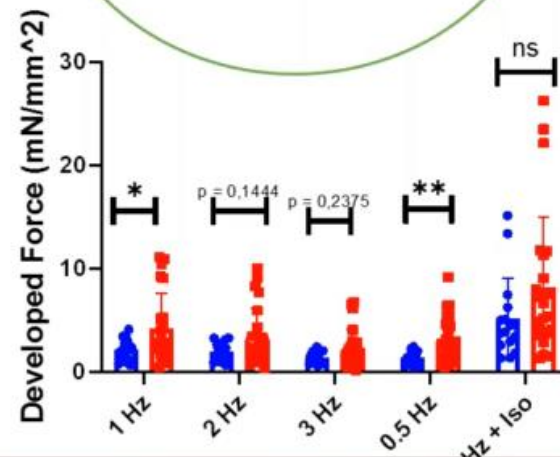
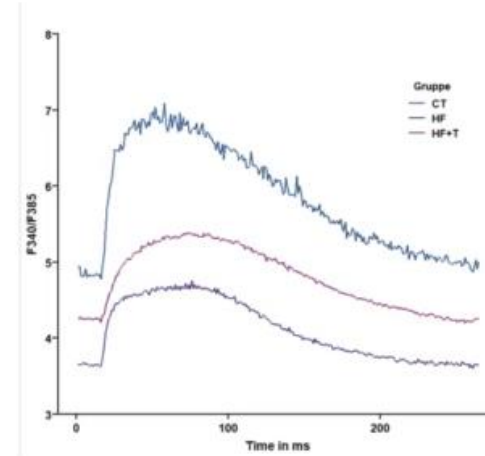
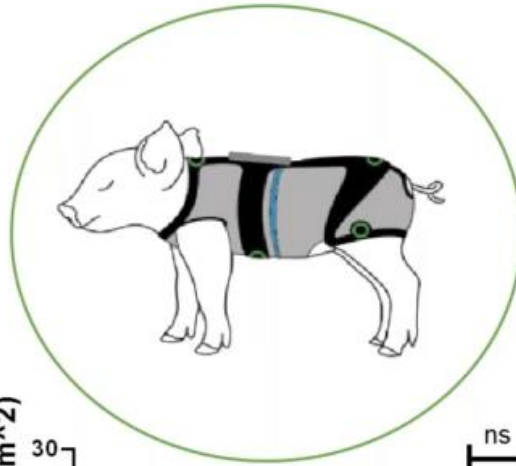
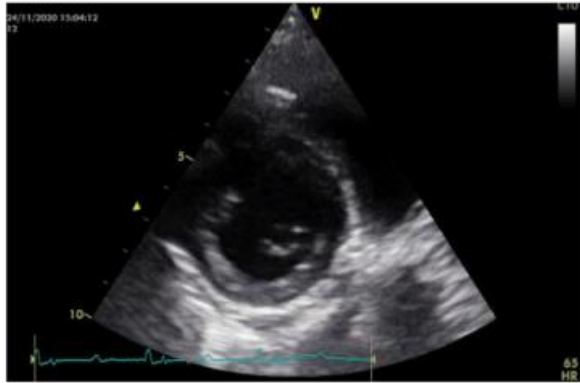
n=5



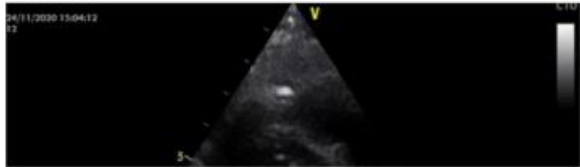
Isolated cardiomyocytes: high-throughput Calcium transient analysis
 . Overview single cells



Concluding remarks

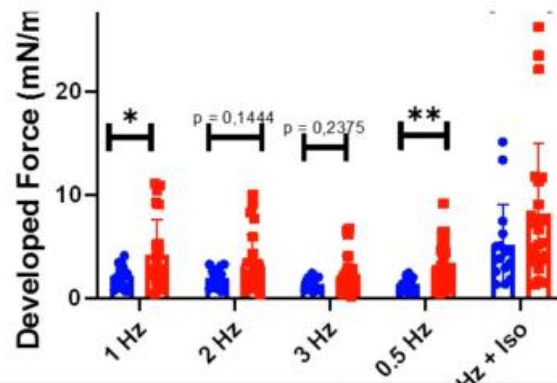


Concluding remarks



„All animals are equal, but some animals are more equal than others“

Animal Farm, G. Orwell



THANK YOU FOR YOUR ATTENTION!

E-mail: alessio.alogna@charite.de

