Cardiac compliance is acutely modulated through cGMP-PKG signalling

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INTRODUCTION

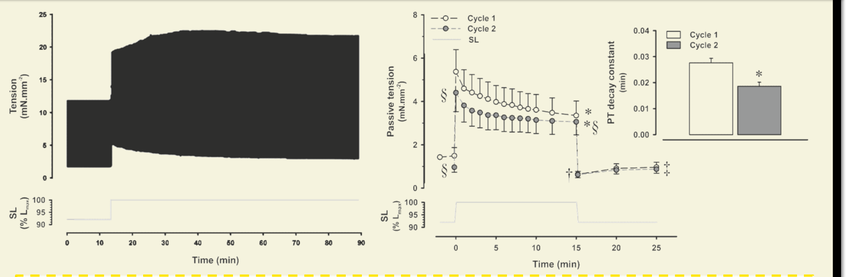
Increased diastolic stiffness due to **titin** hypophosphorylation and low **protein kinase G** (PKG) activity is a hallmark of **heart failure with preserved ejection fraction** (HFpEF). Acute load sensitivity is a well-known factor of decompensation in HFpEF, which has been mainly ascribed to vascular and systolic stiffening, but other factors may be at play.

We aimed to investigate whether there is a diastolic response to acute **volume overload** (VO), cardiac **stretch-induced compliance** (SIC), and to ascertain the potential involvement of titin phosphorylation and cGMP-PKG-signalling in this response in several animal models and in the human heart.

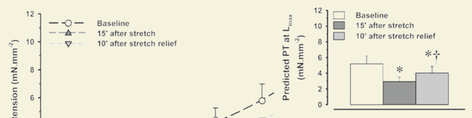
METHODS

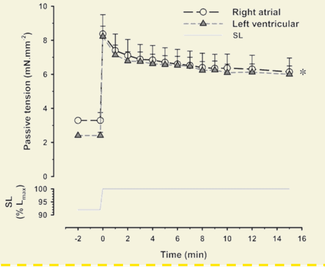
- **Intact rat hearts**, strips dissected from the LV or right atrium of **cardiac surgery patients** and **rabbit papillary muscles** were acutely stretched for 15 minutes.
- **Skinned cardiomyocytes** from the LV of control and stretched hearts were incubated with either **PKG** or **Protein Phosphatase 1**.
- Rabbit muscles were incubated with a **PKG inhibitor**, **a NO synthase inhibitor**, a **NO scavenger** or a natriuretic peptide **(NP) receptor A antagonist**.
- After gel electrophoresis, **Titin phosphorylation** was measured with Pro-Q Diamond stain and indexed to total-protein signals using SYPRO Ruby.
- Myocardial **cGMP** levels and vasodilator-stimulated phosphoprotein **(VASP) phosphorylation** were quantified.
- Hemodynamic **pressure-volume response** to VO was assessed in sham and transverse aortic constriction **(TAC) rats** and was also assessed by echocardiography in **healthy volunteers** and invasively in **cardiac surgery patients** before and after leg elevation and Trendelenburg positioning, respectively.

RESULTS



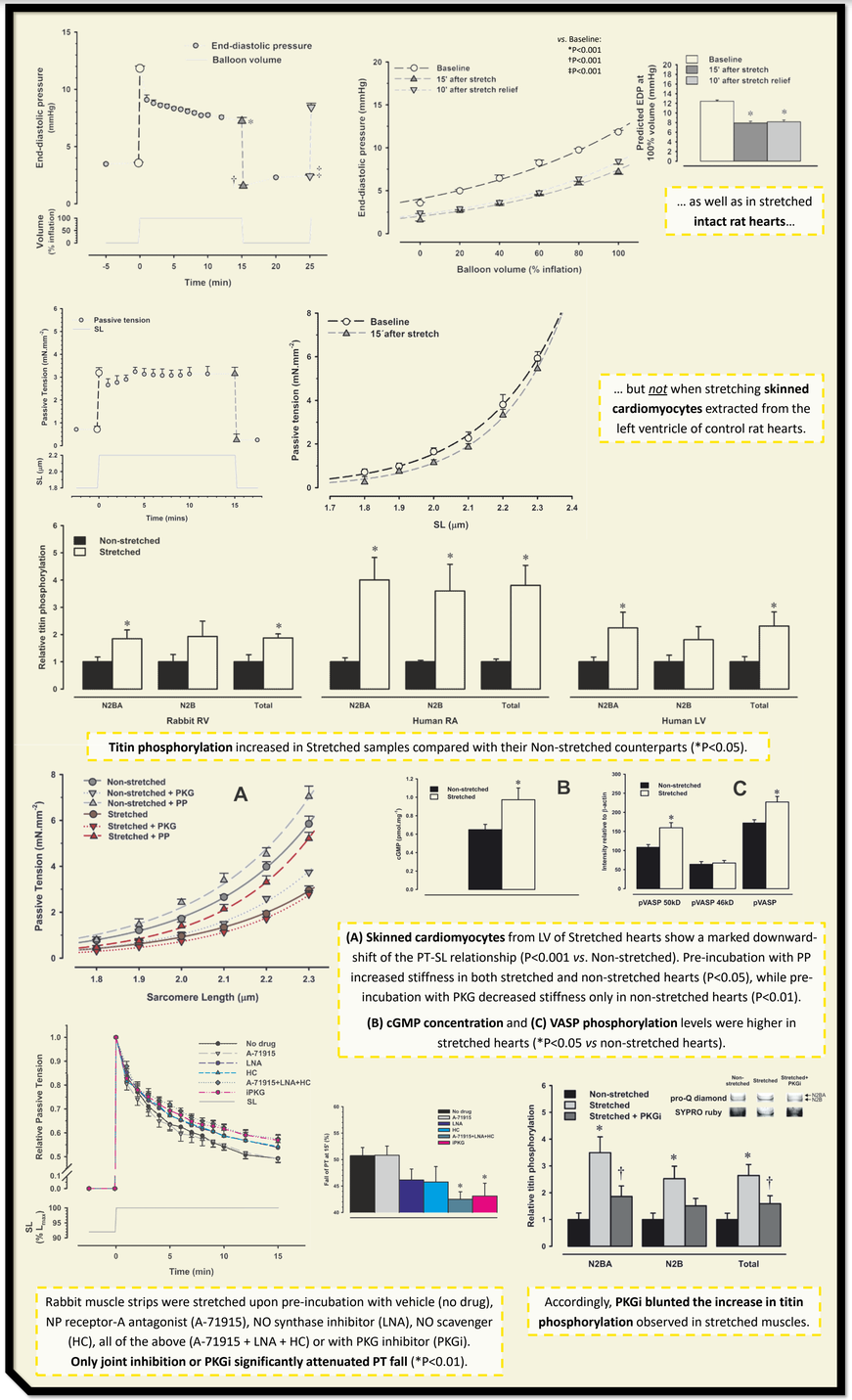
Acute stretch of **isolated rabbit papillary muscles** from a sarcomere length (SL) of 92% to 100% of L_{max} leads to a **decrease in passive tension** (PT) over 15min (* P<0.001), which drops below baseline values after stretch relief († P<0.01). During the following 10 mins, it slightly rises, though remaining below baseline PT (‡ P<0.01). In a second stretch cycle, PT rises significantly less and drops to lower values (§ P<0.001 vs 1st cycle) at a faster rate.

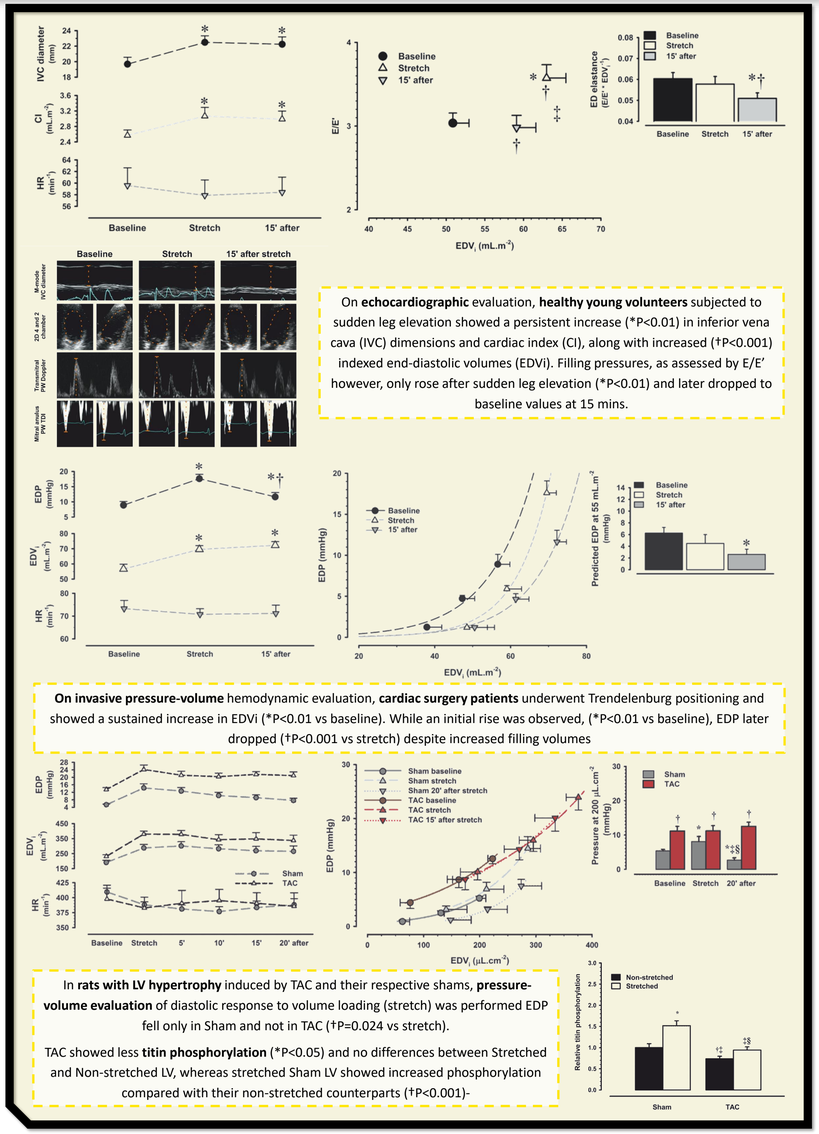




SL-PT relationships were downward shifted after 15 mins of stretch and did not fully return to baseline after 10mins of stretch relief.

The same behaviour was observed in **muscle strips from cardiac surgery patients** (* P<0.001 vs initial PT at L_{max})...





CONCLUSIONS

- **Myocardial compliance increases in response to acute VO by a novel mechanism that is mediated by titin phosphorylation through cGMP-PKG signalling.**
- **The findings translated to human physiology and may be abolished in the hypertrophic heart, suggesting a potential role in the pathophysiology of HFpEF.**

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