In silico analysis of the Frank-Starling mechanism and its relationship with vascular filling therapy

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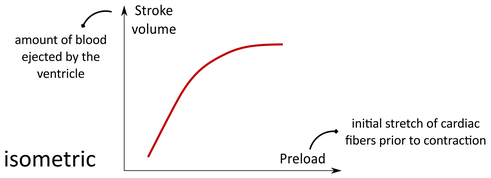
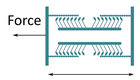
The Frank-Starling (FS) mechanism: an increase in ventricular preload leading to an increase in stroke volume (SV) *within the same heartbeat.*

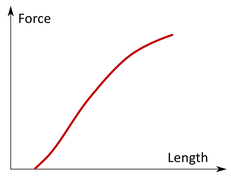


Length-dependent activation (LDA): the maximal isometric produced force increases if sarcomere length increases.

Sarcomere = basic contractile unit of muscle



Maximal sarcomere length = preload

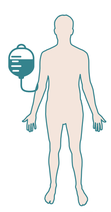


I. Is LDA underlying the FS mechanism ?

II. Is LDA underlying the positive or negative response to vascular filling ?

Vascular filling therapy

= intravenous fluid administration in order to increase the stroke volume

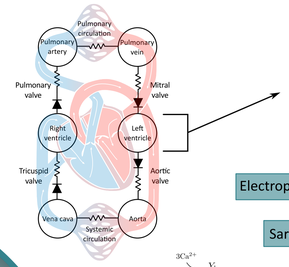


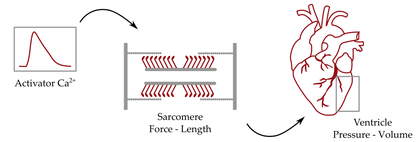
The patient is ***fluid-responsive***, the stroke volume increases

The patient is ***not*** fluid-responsive (the stroke volume does not substantially increase or eventually decreases)

The ***Frank-Starling mechanism*** is assumed to determine the response to fluid therapy

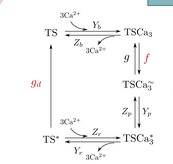
Multiscale model of the cardiovascular system: 6-chamber lumped-parameter model.





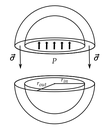
Ventricular contraction is described at the cellular scale

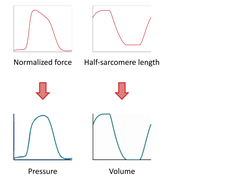
Electrophysiological model + Sarcomere model + Ventricular model ➡ Cellular variables (force and length) are linked to ventricular variables (pressure and volume)



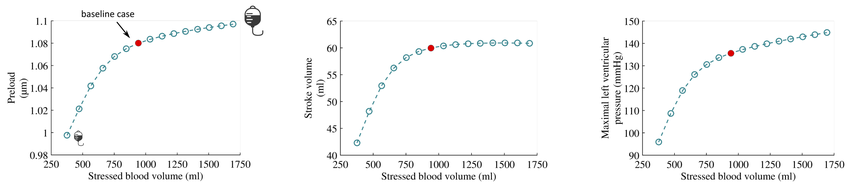
LDA is implemented in the rate constants from the calcium kinetics

$\text{Force} \propto [TSCa_3^{\sim}], [TSCa_3^*], [TS^*]$

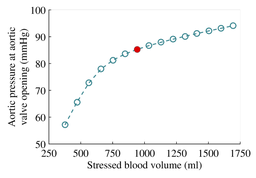




LDA and vascular filling: vascular filling (or emptying) simulations are performed with the model by increasing (or decreasing) the stressed blood volume.

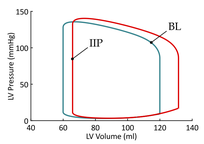


- Preload increases with vascular filling and so does SV.
  ➡ Signature of LDA
- The saturating portion of the curve is not due to a saturating LDA effect (the maximal pressure rises monotonously and does not saturate).
  ➡ Another variable, the afterload, also increases with vascular filling and tends to counterbalance the LDA effect.



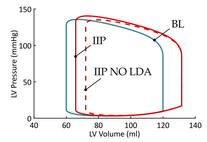
FS mechanism and LDA: an instantaneous increase in preload (IIP) is induced and the stroke volume is compared between the baseline case (BL) and the IIP case.

With LDA



SV increases with IIP, this is the signature of the FS mechanism.

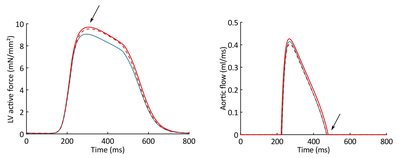
Without LDA



When LDA is turned off, SV does not increase upon IIP.

➡ LDA is the cellular property underlying the FS mechanism.

- The increase in SV is not always correlated with an increase in maximal produced force.
- The timing of contraction is also altered by the preload variations (the blood ejection lasts longer).



➡ **The Frank-Starling mechanism is a multiscale and dynamical LDA-driven response to a change in preload.**

Conclusion

LDA is the cellular mechanism responsible for the increased SV observed upon preload increase. Thus, it is definitely involved in the positive response to vascular filling therapy. However, preload should not be the only monitored variable for predicting the patient response to filling. Afterload should also be considered, as fluid infusions also impact the resistance to blood ejection, which tends to counterbalance the LDA effect and reduce the expected SV increase. These results indicate that there is a saturating limit for vascular filling procedures, which is not related to a saturating LDA effect.

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