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In silico clinical trial simulation shows amelioration of ischemia-reperfusion injury in ST-elevation myocardial infarction via inhibition of reactive oxygen species production

B. Martin, E. Courcelles, A. L'Hostis, L. Etheve, E. Bechet, N. Ceres, E. Jacob, E. Peyronnet, B. M.W. Illigens, M. Hommel, J.P. Boissel

Objectives

Heart disease is the leading cause of death, with about 805,000 myocardial infarctions (MI) a year in the US **[1]**. According to ACC/AHA guidelines, the standard of care is reperfusion of the heart (thrombolysis and/or percutaneous coronary intervention (PCI)). However, restoring blood flow can lead to cardiac ischemia-reperfusion injury (IRI), in part caused by an acute increase of reactive oxygen species (ROS) **[2]**.

Pre-clinical studies have shown cardioprotective effects of ROS inhibition at the mitochondrial C1 level **[3]**, but no clinical trial to date has shown a benefit in patients and no specific drug is available.

We created a model to represent IRI physiology and simulated clinical trials to understand and quantify the clinical benefits of ROS inhibition at the C1 level in myocardial IRI.

The *in silico* clinical trial represented ST-elevation MI (STEMI) patients treated with PCI with goals of understanding the degree and duration of C1 inhibition and quantifying the effect on tissue injury (change in left ventricular (LV) Infarct Size (IS, % volume)), LV ejection fraction (LVEF), creatine phosphokinase (CPK) and troponin I (TnI).

Methods

Model development

The model of myocardial IRI pathophysiology in STEMI patients linked IS to LVEF with 4 submodels: (1) mitochondria, (2) cardiomyocyte, (3) myocardium and (4) ventricular function.

In silico model development followed the standard 3-step approach used by NOVA:

1. *Model Building using a Knowledge and a Computational Model:* Relevant biological entities and their functional relationships were analyzed and translated into ordinary differential equations (ODE). The final model had 496 parameters and 173 ODE states.
2. *Model Calibration* with available pre-clinical and clinical data.
3. *Validation:* The model and its Virtual Population representative of real patients were validated **[4]** with an independent data set for 4 outcomes: IS, LVEF, CPK and TnI. Validation was evaluated with: (a) Spearman rank correlation (through permutation testing) to test the model's capacity to rank patients by their outcome severity; (b) AUCROC to test the model's accuracy in separating patients with severe outcomes from others (a threshold of 0.7 was previously set to define acceptability).

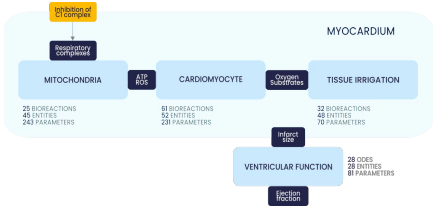

Figure 1: Computational Model structure. Light blue rectangles represent the submodels with the associated number of parameters, variables and reactions. Dark blue rectangles represent the major connections between submodels. Myocardium submodels are duplicated in 10 layers to introduce a spatial discretization of the myocardium.

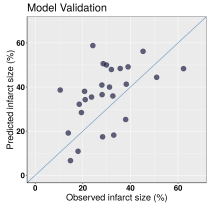

Figure 2: Mean model infarct size prediction (y-axis) vs corresponding 26 real patient's IS (x-axis) extracted from a recent clinical trial dataset (independent validation dataset). The blue line represents the perfect prediction.

Effect model

The Effect Model (EM) **[5]** describes for each patient the rate of disease-related events with (frequency in the treated group = R_T) and without C1 blockade (frequency in the control group = R_C)after PCI initiation. The difference between these rates provides a metric describing the risk difference, referred to as the absolute benefit (AB = R_C-R_T), which is the measure of how much the patient will benefit compared to the control.

Results

1000 virtual patients with STEMI (1 to 12 hours ischemia) treated with PCI were simulated.

Three days post-PCI the simulated mean IS was 31.6% (SD=14.8) and the mean LVEF was 41.7% (SD=10.1). The model's physiological representativeness was confirmed by CPK and TnI showing comparable post-MI dynamics.

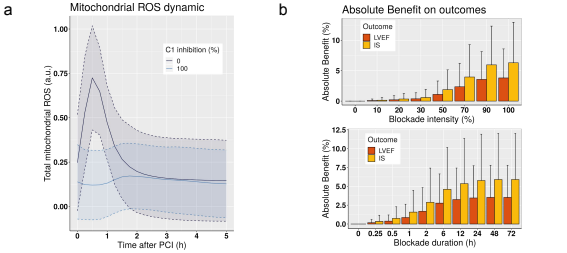

Figure 3a: Simulated Total mitochondrial ROS in arbitrary unit (a.u.) in the entire Virtual Population with C1 blockade (light blue, maximal intensity for 24 hours) and without (dark blue). **Figure 3b:** Comparison of mean Absolute Benefit across the Virtual Population in the different regimens that have been tested for IS (yellow) and LVEF (orange).

In a subset of those virtual patients the effect of increasing degree and duration of C1 inhibition was tested. The maximal effect was found after at least 12hrs of maximal inhibition and led to a mean IS of 26.2% (SD=15.5, p<0.0001 vs control, paired t-test) and a mean LVEF of 45% (SD=10.1, p<0.0001 vs control, paired t-test). The mean Absolute Benefit was 5.8% for IS and 3.3% for LVEF.

Using the EM, an optimal responder group characterized by final TIMI flow grade 3 and LAD occlusion location Mid or Proximal was found with an IS reduction over 10%.

Based on our data, with IS as primary endpoint, we calculated that the necessary sample size for a real trial could be reduced by 75% when optimal responders were selected, i.e. from *n*=236 with the general population to *n*=60 with the selection.

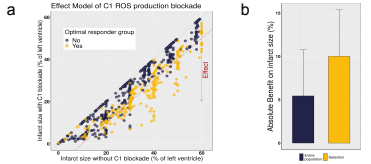

Figure 4a: Simulated Effect Model of blocking ROS production at the C1 level. Patients are selected on the basis of the characterization of optimal responders (inclusion of final TIMI flow grade equal to 3 and lesion location Mid or Proximal). For each virtual patient (represented as a colored dot), infarct size obtained without C1 blockade (x-axis) is compared to infarct size obtained with C1 blockade (y-axis). The difference between these rates yields the Absolute Benefit. The farther the patient is from the bisector, the higher its benefit. The red dashed line reflects the infarct size reduction threshold of 10% of the left ventricle. **Figure 4b:** Comparison of the Absolute Benefit in the entire population (black) and the responder subgroup (yellow).

Conclusion

A model of IRI was created in which the mathematics of the model accurately represents known physiology. Multiple (different) datasets were used to build and test the model and submodels.

Results of the *in silico* trial simulated with the IRI model show that ROS inhibition at the C1 level ameliorates the ROS burst and reduces IRI leading to clinically important improvements.

The approach is generalizable and can be used to study new targets and optimize treatment strategies. For example, characterization of optimal responders has been used to reduce sample size of clinical trial designs and to identify patients benefiting most from a given treatment plan.

In silico clinical trial simulation is a promising approach that can support go/no-go decisions made by clinical researchers, biopharma and regulatory agencies.

Summary

Simulated clinical trials were run using a disease model of cardiac ischemia-reperfusion injury (IRI). The simulation suggested that:

1. Myocardial Infarction (MI) was reduced by reactive oxygen species (ROS) inhibition: 5% infarct size (IS) reduction
2. Best responders characterized by: final thrombolysis in myocardial infarction (TIMI) flow grade of 3, and left anterior descending (LAD) artery lesion location of proximal or mid: 10% IS reduction. This insight allowed reducing the number of patients by 75% in an upcoming trial design.

References

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Contact: Bastien Martin, bastien.martin@novadiscovery.com