In silico clinical trial shows the efficacy of the inhibition of reactive oxygen species production in ST elevated myocardial infarction

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BACKGROUND

Myocardial reperfusion injury [1], is caused by increased oxygen supply after ischemia, which induces a burst of reactive oxygen species (ROS). Scavenging the highly toxic ROS has been tested in clinical trials without clear success to date. We hypothesized that blocking ROS production at the level of the complex 1 (C1), the beginning of respiratory chain, will reduce the explosive damage of the overwhelming ROS production during the reperfusion and bring a relevant clinical benefit.

We ran an in silico clinical trial to test C1 modulation and evaluate the intensity and duration needed for a clinical benefit in ST Elevation Myocardial Infarction (STEMI) treated with percutaneous coronary intervention (PCI).

Model development

The model was composed of 4 submodels: mitochondria, cardiomyocyte, myocardium and ventricular function bridging infarct size (IS) to left ventricular ejection fraction (LVEF). For each submodel, a Knowledge Model and a Computational Model were developed. **Biological entities and their functional relationships were collected in a series of assertions, then translated into ordinary differential equations (ODEs)** (Figure 1). The model was calibrated with information extracted from publications, pre-clinical and clinical data. Variability was introduced through a Virtual Population made of virtual patients obtained through statistical sampling in model parameters distributions. Each virtual patient was the input to a single run of the model.

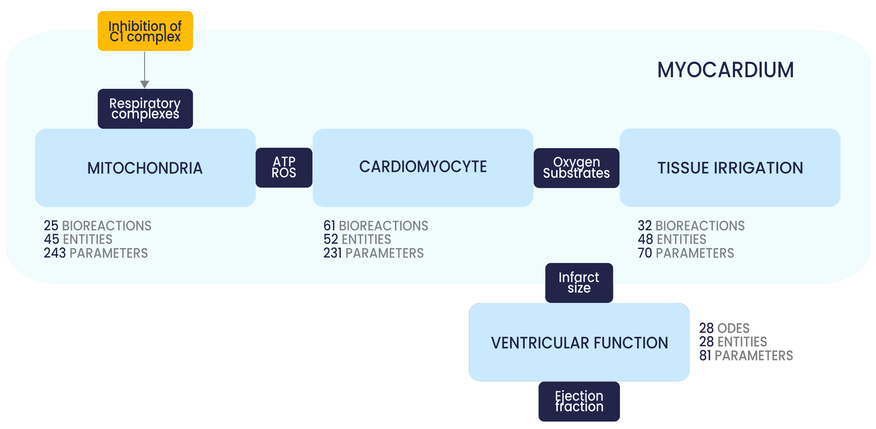
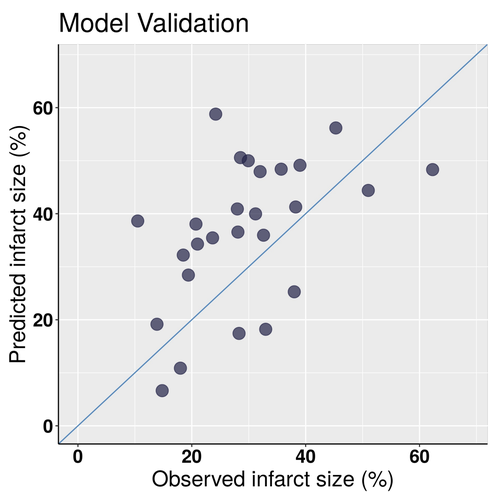


Figure 1: Computational Model structure. Light blue rectangles represent the submodels with the associated number of parameters, variables and reactions. Dark blue rectangles represent the major connexions between submodels. Myocardium submodels are duplicated in 10 layers to introduce a spatial discretization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

Simulations

The model was validated with a protocol aligned with the recent FDA guidelines [2] and a virtual population representative of real patients on four outcomes: creatine phosphokinase, troponin I, IS (Figure 2) and LVEF with an independent dataset. Validation was done on two metrics: (a) spearman rank correlation evaluating the model capacity to rank patients on the basis of their outcome severity, and (b) Receiver Operating Characteristic (ROC) AUC evaluating the model capacity to identify patients with a severe outcome among others (a threshold of 0.7 was previously set to define acceptability).



A specific feature of in silico experiment is that each virtual patient is its own control. A simulation protocol was defined in order to explore two components of the modulation of C1 ROS regimen: (i) intensity of the blockade (8 intensities from 0 to 100%) and (ii) blockade duration (9 durations from 15 min to 72 hours).

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

RESULTS

1000 virtual patients were simulated during STEMI (1 to 12 hours ischemia) followed by PCI. Three days post-PCI the simulated mean IS was 31% (SD ± 15%) and the mean LVEF was 41% (SD ± 10%) in the control group.

Optimal regimen

200 virtual patients were simulated to study (a) the effect of an increasing C1 inhibition and (b) the duration of inhibition. **The maximal inhibition (100%) over a minimal duration of 24h led to an IS reduction of 5%.** Interestingly, a short inhibition duration delayed the burst of ROS compared to control.

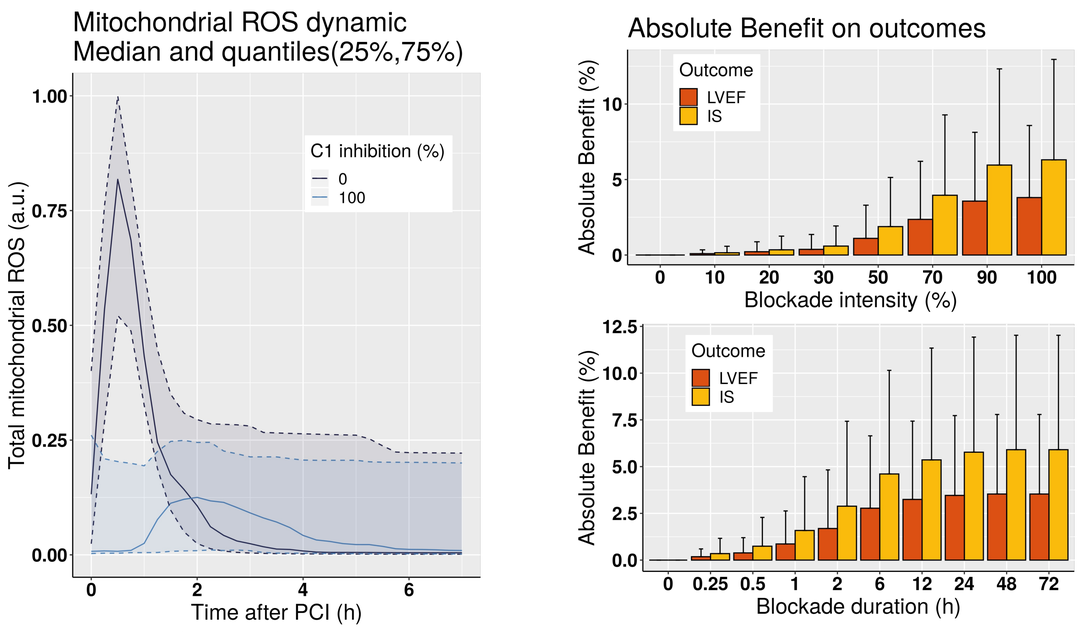


Figure 3: Left: Simulated Total mitochondrial ROS in arbitrary unit (a.u.) in the entire Virtual Population with C1 blockade (light blue, maximal intensity for 24 hours) and without (dark blue). Right: Comparison of mean Absolute Benefit across the Virtual Population in the different regimens that have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

Characterization of best responders

Using the Effect Model [3], **an optimal responder group characterized by a final TIMI flow grade above 3 and an occlusion location Mid or Proximal was found with an IS reduction over 10%** (Figure 4). Final TIMI flow grade above 3 was, by far, the best descriptor to characterize the responders: a successful reperfusion is necessary in order to benefit from the blockade of ROS production by C1. The consistency of this result is per se a validation of the model. **These results support a subgroup analysis with the results of a potential phase 3 clinical trial evaluating C1 blockade efficacy.**

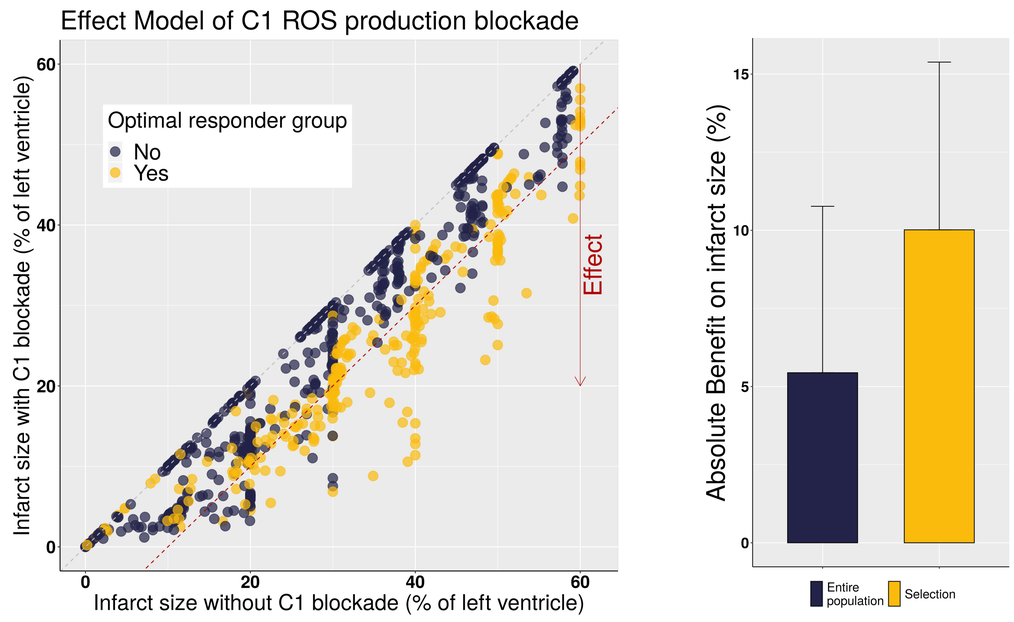


Figure 4: Left: Simulated Effect Model of the blocking of ROS production by C1. Patients are selected on the basis of the characterization of optimal responders (inclusion of final TIMI flow grade equals to 3 and lesion location Mid or Proximal). For each virtual patient (represented as a colored dot),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

DISCUSSION

We produced digital evidence that reduction of ROS burst through C1 modulation reduced reperfusion injury and improved cardiac function leading to a clinical benefit. This approach can be used to find new targets and optimize innovations. Identification of responders is crucial in developing therapeutic plans for patients selection and reduction of the sample size. In silico clinical trial is a powerful tool that can contribute to the go/no go decision for biopharma, clinical researchers and regulatory agencies.

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