



PAGE abstract

PAGE 2020	2
Author(s)	2
Affiliations	2
E-mail address(es) of corresponding author(s)	2
Title of contribution	2
Abstract	2
Background	2
Objectives	2
Methods	3
Model development	3
Effect model	3
Results	4
Discussion	4
Conclusion	5
References	5

PAGE 2020

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Title of contribution

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

Abstract

Objectives

Myocardial reperfusion injury (RI) **[1]**, is caused by increased oxygen supply after severe 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), will reduce the explosive damage of the overwhelming ROS production during the reperfusion and cause a relevant clinical benefit.

We ran an in silico clinical trial to test C1 blockade and evaluate the intensity and duration needed for a clinical benefit in ST-elevation myocardial infarction (STEMI) treated with percutaneous coronary intervention (PCI). In electrocardiography, the ST segment connects the QRS complex and the T wave.

Methods

Model development

We broke down into four sub-models the pathophysiology of myocardial RI in STEMI patients. The sub-models were: (1) mitochondria, (2) cardiomyocyte, (3) myocardium and (4) ventricular function bridging infarct size (IS) to left ventricular ejection fraction (LVEF).

For each sub-model, a Knowledge Model (KM) and a Computational Model (CM) were developed. We collected the biological entities and their functional relationships in a series of assertions. The KM was translated into ordinary differential equations (ODE). The model integrating all submodels had 496 parameters and 173 ODE. Then, the model was calibrated using various information extracted from scientific literature, pre-clinical and clinical data. Finally, the disease model was validated [2] in a Virtual Population (VP) representative of real patients on four outcomes: creatine phosphokinase (CPK), troponin I (Tnl), IS and LVEF with an independent dataset. Validation was done on two different metrics: (a) spearman rank correlation (evaluated through permutation testing) evaluated the model capacity to rank patients on the basis of their outcome severity. (b) ROC curve AUC evaluated the model capacity to identify patients with a severe outcome from others (A threshold of 0.7 was previously set to define acceptability).

Effect model

The Effect Model [3] describes the relationship between the rate of disease-related events with and without C1 blockade when beginning PCI. The difference between these rates gives the absolute benefit.

Results

1000 virtual patients (Table 1) were simulated during STEMI (1 to 12 hours ischemia) followed by PCI. Three days post-PCI the simulated mean ($\pm$ SD) IS was 31% ($SD \pm 15\%$) and the mean ($\pm$ SD) LVEF was 41% ($SD \pm 10\%$). A realistic behavior was observed on CPK and Tnl.

Table 1: Virtual Population descriptors

Parameters	Simulated dataset
Number of patients	1000
Sex	Female: 500, Male: 500
Age	Mean: 55.0 y.o, SD: 12.5
Weight	Mean: 63kg, SD: 11.2
Left ventricular mass	Mean : 114.4g, [63.2; 194.3]
Right dominance	Yes: 794, No: 206
Ischemia duration	Median: 6.5h [1; 12]
LAD lesion location	Distal: 335, Mid: 313, Proximal : 352
LAD diagonality	Small Or Absent: 329, Medium : 333, Large : 338
Thrombus burden grade	1 : 197, 2 : 202, 3 : 202, 4 : 202, 5 : 197
Initial TIMI flow grade	0 : 454, 1 : 432, 2 : 114
Final TIMI flow grade	0 : 31, 1 : 55, 2 : 473, 3 : 441
Rentrop grade	0 : 455, 1 : 447, 2 : 98
Chest pain previous 48h	Yes: 255, No: 745
SaO2	Mean: 97.5; SD: 0.92
Haematocrit	Mean: 0.45, SD: 0.005

200 virtual patients were simulated to study (a) the effect of an increasing C1 inhibition and (b) the duration of inhibition. The inhibition led to an IS reduction of 5% and a minimal inhibition duration of 10h was necessary. Using the Effect Model, an optimal responder group characterized by final TIMI flow grade and occlusion location was found with an IS reduction over 10%.

Conclusion

This in silico clinical trial produced digital evidence that blocking ROS production at C1 prevented the ROS burst and reduced RI leading to a clinical benefit.

Moreover, this approach can be used to find new targets and optimize innovations. Identification of responders is crucial in developing therapeutic plans for patient 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.

References

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