HPC simulations for in-silico drug testing in humans: therapeutic strategies in acute myocardial ischemia

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1. Introduction

Acute myocardial ischemia is a major cause of sudden cardiac death. Anti-arrhythmic treatments or side-effects associated with cancer therapies can produce cardiotoxic effects increasing the occurrence of adverse cardiac events especially in patients with coronary artery disease. In-vivo and in-vitro drug trials have associated complications regarding ethics and costs, whereas cardiotoxic evaluation in animal experiments is not necessarily translatable to humans.

2. Methods

A computational multiscale model of acute ischemic human ventricles embedded in a torso (Figure 1A) was developed and validated with extensive experimental and clinical data (Figure 1B). The model comprehends from ion channels in cardiomyocytes to whole organ function, allowing the simulation of the 12-leads ECG. Ischemia-induced arrhythmic risk was quantified by computing the vulnerability window (VW) for reentry, i.e. the set of coupling intervals in which an ectopic stimulus in the ischemic border zone triggers reentrant patterns (Figures 1C, D, E). The effects of pharmacological action were simulated by blocking sodium, potassium and calcium ionic currents.

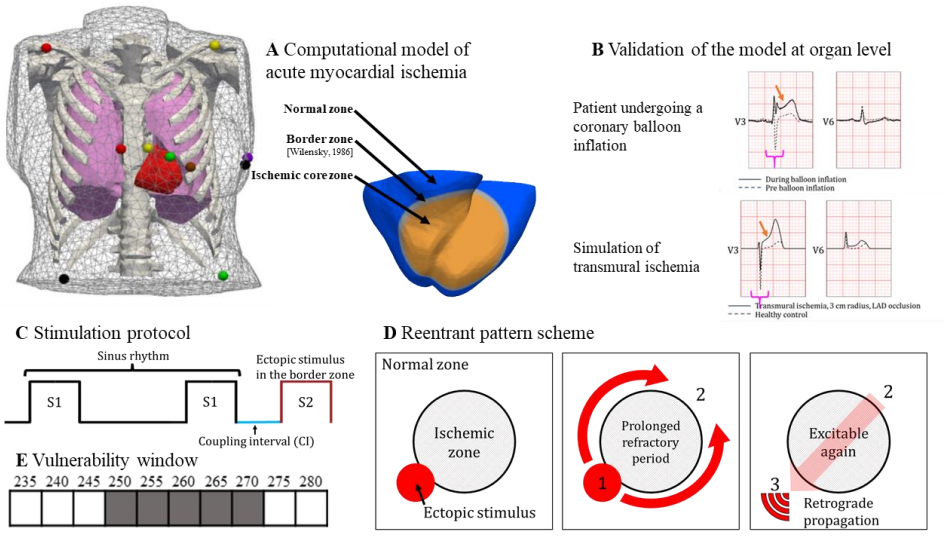

Figure 1 *A: Computational model of acute myocardial ischemia in human: torso with 12-leads ECG electrode positions (left) and ventricles (right). B: Validation of the model at organ level: ECG recording obtained from a patient undergoing a balloon coronary inflation in the LAD coronary artery (top) and simulation of ischemia in the same location (bottom) leading to consistent ECG abnormalities. C: Stimulation protocol based on sinus rhythm plus ectopic stimulus in the border zone for quantification of arrhythmogenesis. D: Schematic view of a reentry. E: Vulnerability window: grey cells represent those coupling intervals in which the ectopy leads to a reentry.*

3. Results & Discussion

The simulation of class I antiarrhythmic drugs (sodium blockers) increased arrhythmic risk, as shown in the vulnerability windows in Figure 2A. This is in agreement with the high mortality of patients under ischemic risk using flecainide/encainide, as observed in the CAST trial.[1] Higher risk in the scenario considering a 25% sodium block is based on two mechanisms of drug action: a lower conduction velocity in the myocardium and an increased dispersion of refractoriness between healthy and ischemic regions, both facilitating the formation of reentrant circuits (Figure 2A, bottom). The sodium block scenario yielded reentry based on the tissue heterogeneities produced by ischemia, despite showing very similar ECGs (Figure 2B).

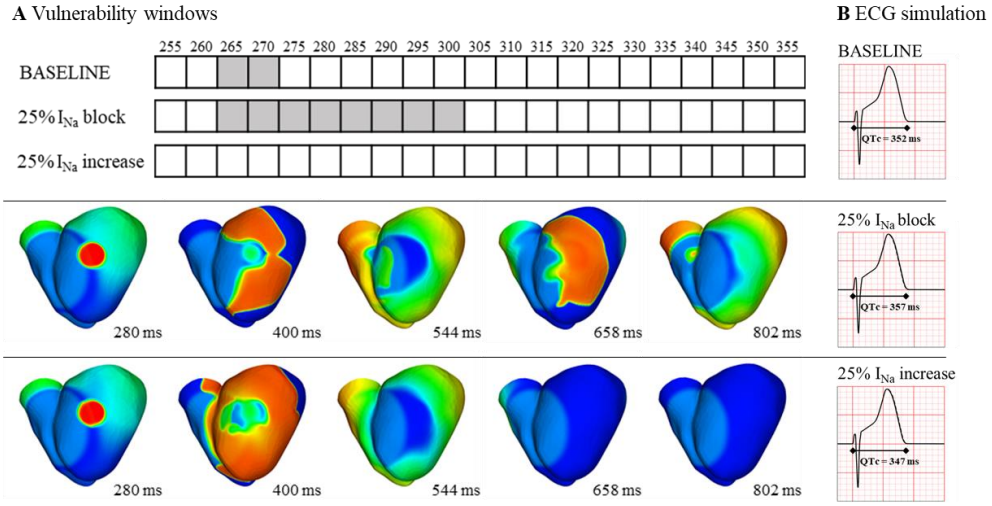

Figure 2 *Arrhythmogenic mechanisms triggered by sodium channel block. A: Vulnerability windows computed for ischemia with variable sodium channel availability, and propagation of ectopic stimulus for 25% sodium block/increase. B: Simulated ECG signals.*

Mild potassium block (class III antiarrhythmic drugs) reduced tissue heterogeneities and hence risk. Stronger block facilitated other pro-arrhythmic mechanisms by prolonging the QT interval (SWORD trial).[2] Additional moderate calcium block avoided the formation of these arrhythmogenic mechanisms, typically associated with long QT syndrome.

The relevance of QT prolongation is not limited to cardiotoxicity induced by anti-arrhythmic drugs but also to tyrosine-kinase inhibitors (TKI)[3], commonly used for treating leukaemia and tumours. Furthermore, some TKI agents, like nilotinib, have been identified as a potential precursor of vasospasms, which promote the occurrence of ischemic episodes in patients with no prior cardiac history. Our results identify QT prolongation and transient ischemia as key factors in pro-arrhythmic cardiotoxicity induced by cancer drugs, resulting often in lethal arrhythmias.

4. Conclusion

In this study, high performance computing simulations using human-based multiscale ventricular models provide mechanistic insights into the pro-arrhythmic effects associated to classic anti-arrhythmic drugs, such as flecainide and sotalol, or first-line cancer treatments. This technology can also point out new directions towards new anti-arrhythmic therapies.

5. References

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