



Influence of patient-specific acute myocardial ischemia maps on arrhythmogenesis: A computational study

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ABSTRACT

The early phase of acute myocardial ischemia is associated with an elevated risk of ventricular reentrant arrhythmias. After partial or total occlusion of a coronary artery, some regions of the heart experience a reduction in myocardial blood flow. This causes metabolic and cellular processes, such as hypoxia, hyperkalemia and acidosis, which lead to changes in the transmembrane ionic dynamics. The effect of such alterations may result in the formation of electrical loops and reentries.

In this context, computational approaches based on differential multiscale models may serve to predict patient-specific arrhythmic propensity in a given scenario. Specifically, they could assess the arrhythmic risk by simulating the generation of reentrant episodes, possibly persistent, triggered by ectopic beats and in presence of acute myocardial regions. Since quantitative information (extent, localization, ...) about acute ischemic regions are hardly available from medical imaging, to date, in computational models such regions are either arbitrarily drawn or inspired by chronic infarcted information. In both the cases, this does not represent a patient-specific condition of acute ischemia.

This work aims to overcome this limitation by introducing a novel patient-specific electrophysiological model, based on Myocardial Blood Flow (MBF) maps acquired during stress-CTP acquisitions of stable Coronary Artery Diseased (CAD) patients in hyperemic conditions. Indeed, during such an acquisition, CAD may destabilize and acute ischemic events may occur, allowing to obtain measured MBF maps representative of patient-specific acute ischemic regions.

First, we aim to numerically investigate the induction and sustainment of reentrant drivers in different patients, in order to assess their arrhythmic propensity. Secondly, we perform an intra-patient sensitivity analysis, where different levels of acute ischemia are virtually depicted for the most arrhythmogenic patient. Our results suggest that the amount of ischemic regions seems to have less influence on arrhythmogenesis rather than their pattern.

1. Introduction

Myocardial ischemia is defined as the localized reduction of blood flow and, consequently, oxygen in the cardiac tissue. Most of myocardial ischemia are due to Coronary Artery Disease (CAD) [1], which is caused by narrowed or completely blocked vessels that are no longer able to provide the physiological blood supply. Depending on how rapidly myocardial ischemia evolves over time, it can be defined in two ways: acute myocardial ischemia (AMI), which involves a sudden and significant reduction of blood flow, and chronic myocardial ischemia, which develops gradually, often causing persistent symptoms that may worsen over time [2,3].

Some hours (1.5–5) after the onset of AMI, the histological properties of the myocardium may change resulting in the formation of a

scar (myocardial infarct), which can lead to the generation of reentry loops [4]. Other clinically relevant consequences may occur just after the acute ischemic event (first 10 min) at the metabolic and ionic level [5,6]. Indeed, during this phase, hypoxia (reduced supply of oxygen) [7], hyperkalemia (increased extracellular potassium concentration) [8] and acidosis (reduced intracellular pH) [9] occur in the ischemic region. Each of these alterations originates downstream the coronary occlusion and then distributes heterogeneously within the myocardium. This subdivision of the myocardium into areas with different ionic and metabolic characteristics causes adverse effects on cardiac electrophysiology, such as heterogeneous action potential morphology

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and refractory periods: as the ischemic effects worsen, the electrophysiological properties of the tissue will progressively change. Thus, this heterogeneity, induced by acute ischemia, provides an important pro-arrhythmic substrate [6,10–13], possibly leading to sudden cardiac death [14]. Specifically, arrhythmias that take place during the first minutes of AMI depend mainly on reentrant mechanisms, contributing to the development of ventricular tachycardia and, possibly, to the degeneration in ventricular fibrillation [10].

The consequences that AMI has on cardiac electrophysiology have been a subject matter of research for many years. Due to the difficulty in measuring the processes underlying acute ischemia-induced arrhythmias in clinical settings, experimental studies have been performed on animals [15–17] reporting electrocardiographic measures during acute ischemia and the corresponding volumetric conduction speed changes. In this context, patient-specific computational models offer a versatile platform on which virtually explore potential pro-arrhythmic scenarios that are hardly measurable in the clinic [18–20]. Pioneering studies performed in 2D geometries allowed to obtain first insights about such processes [21]. First steps toward the computational analysis of the major effects of AMI in 3D geometries were made by studying simplified geometries [22] and animal ventricles with globally ischemic tissue [23], so to characterize the changes in vulnerability to electric shocks during the first phase of AMI. The gradual expansion of the ischemic effects following a coronary occlusion, and consequently the resulting spatial heterogeneity of a human left ventricle, was then introduced in [24–26]. Because of the difficulty in obtaining AMI data, it is not easy to accurately identify the location and the extent of the ischemic regions. For this reason, the majority of the studies portrayed the heterogeneities of the ionic functions due to AMI through an idealized representation of the ischemic and border zones [27–32]. More recent studies made the assumption of identifying the acute ischemia regions with infarcted areas reconstructed from imaging, even though it is known that in general they do not match one another [33]. While a relatively new area of research involves using imaging of impaired myocardial blood perfusion to inform spatial patterns of transient ischemia [34,35], these approaches, similar to previous work, have not yet explored patient-specific scenarios.

As a consequence, none of the previous studies, to the best of our knowledge, accounted for patient-specific regions characterizing the tissue heterogeneity resulting from AMI. Since the morphology and location of such regions are fundamental to determine arrhythmogenesis in a specific patient, we believe that the use of patient's AMI regions is necessary in view of predictive analyses.

The first goal of this work is to overcome the previous limitation, in order to evaluate the arrhythmogenic propensity in human patient-specific acute ischemic scenarios. To this aim, we develop an electrophysiological framework based on a modified version of the Ten Tusscher–Panfilov model [36] that accounts for the ionic variations induced during the early phase of AMI [37]. Specifically, we identify AMI regions, as well as border zones, from patient-specific perfusion Myocardial Blood Flow (MBF) maps of four patients suffering from stable CAD, where an acute and reversible ischemia has been pharmacologically induced during stress Computed Tomography Perfusion (stress-CTP) acquisitions [38]. Arrhythmogenic propensity is numerically studied by means of the S1 stimulation protocol applied to different points located in the border region, in order to simulate pathological conditions where ectopic beats randomly depolarize the tissue.

The second goal of the paper is to assess the influence of the shape and extent of the AMI region on arrhythmogenesis. To this aim, for one specific patient we build virtual scenarios corresponding to different levels of AMI. This allows us to numerically investigate the induction and sustainment of reentrant drivers as a function of realistic acute ischemic scenarios and to assess arrhythmic propensity for different ischemic configurations.

We subdivided the paper into two parts. In the first one we focus on the study of modeling electrophysiology assessing arrhythmogenesis induced by the patient-specific acute ischemia (Methods in Section 2 and Results in Section 3). In the second part we provide a parametric study based on assessing the influence of the dimension and pattern of AMI regions on arrhythmogenesis (Methods in Section 4 and Results in Section 5). Finally, in Section 6 we provide an overall discussion of the outcomes reported in both parts.

2. Methods Part I - Arrhythmogenesis in presence of patient-specific acute ischemia

2.1. Mathematical model of cardiac electrophysiology

The electrical activation of the heart is the result of two coupled multi-scale processes: at the microscopic scale, the generation of ionic currents through the cellular membrane producing a rapid change of the resting voltage, namely the action potential; at the macroscopic scale, the propagation in space of the electrical impulse from cell to cell.

The three-dimensional propagation of the electrical impulse along the cardiac fibers and through the myocardial muscle can be described by means of the monodomain equation, a diffusion–reaction partial differential equation in which an assumption of proportionality between the intracellular and extracellular domains is introduced. In this case, the use of the monodomain over more physiologically accurate models, such as the bidomain one [39], is preferred to reduce computational cost since in this work we do not consider external sources such as in defibrillation [40,41]. This PDE is suitably coupled with a system of ordinary differential equations describing the ionic species concentrations dynamics.

Being Ω the physical domain (i.e., a left ventricle) of the model (See Fig. 1, left, where we report as a representative case the geometry of patient M9), at each time $t > 0$ s the general form of the coupled problem is as follows:

Find $\mathbf{w} \in (0, T] \times \Omega \rightarrow \mathbb{R}^d$ and $u \in (0, T] \times \Omega \rightarrow \mathbb{R}$, such that:

$$\begin{cases} \frac{d\mathbf{w}}{dt} + \mathbf{g}(u, \mathbf{w}) = 0 & \text{in } \Omega, \\ \chi C_m \frac{\partial u}{\partial t} - \nabla \cdot (\Sigma \nabla u) + \chi I_{ion}(u, \mathbf{w}) = I_{app}(\mathbf{x}, t) & \text{in } \Omega, \\ (\Sigma \nabla u) \cdot \mathbf{n} = 0 & \text{on } \partial\Omega. \end{cases} \quad (1)$$

The first equation describes the variation over time of the gating variables and of the ionic concentrations $\mathbf{w}$, where u is the transmembrane potential and $\mathbf{g}$ is a suitable function depending on the ionic model. The second one is the monodomain equation, where χ is the surface area-to-volume ratio, C_m is the membrane capacitance, Σ is the anisotropic conductivity tensor, encoding the conduction properties along the three principal directions. It is in general expressed in terms of three scalar quantities σ_f , σ_s and σ_n representing the conductivities along the fiber direction $\mathbf{a}_f$, the direction $\mathbf{a}_s$ orthogonal to $\mathbf{a}_f$ and tangential to sheets, the direction $\mathbf{a}_n$ orthogonal to sheets:

$$\Sigma = \sigma_f \mathbf{a}_f \mathbf{a}_f^T + \sigma_s \mathbf{a}_s \mathbf{a}_s^T + \sigma_n \mathbf{a}_n \mathbf{a}_n^T. \quad (2)$$

I_{ion} models the sum of the ionic currents passing through the cell membrane, and I_{app} accounts for the applied physiological and ectopic impulses. Moreover, homogeneous Neumann conditions are prescribed at the borders of the volume ($\partial\Omega$) in order to impose electric insulation. Suitable initial conditions for $\mathbf{w}$ and u should be also prescribed to the system.

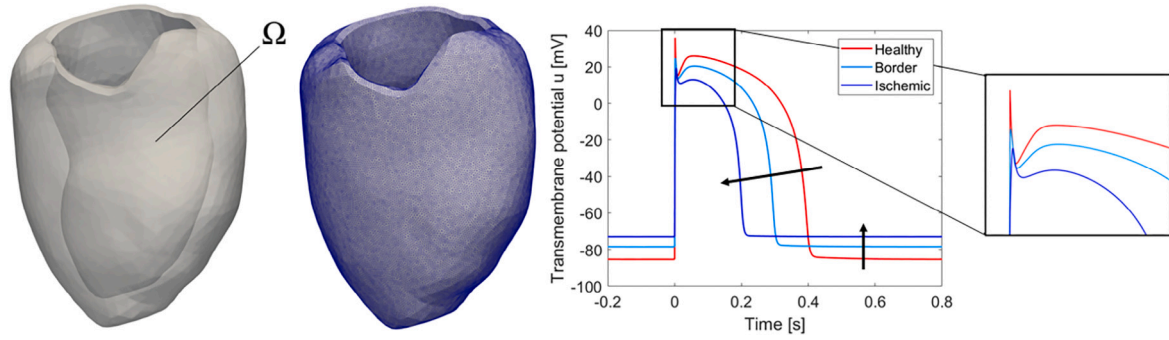


Fig. 1. Left: computational domain Ω ; Middle: computational mesh; Right: alterations of the action potential for increasing hypoxia, hyperkalemia and acidosis. In particular, notice both the reduction of the initial transmembrane potential spike and of the depolarization slope

2.2. Hypoxia, hyperkalemia and acidosis: the modified version of the Ten Tusscher–Panfilov model

When an acute ischemic event occurs, the imbalance between the oxygen demand and supply causes an alteration of the myocardial tissue function: the typical effects are cessation of contraction, alterations in membrane potential, and a variety of metabolic changes. In particular, the major consequences are the reduction of the initial transmembrane potential spike and of the depolarization slope (see the zoomed-in image in Fig. 1, right), the shortening of the Action Potential Duration (APD) [9,42] and the increment of the resting potential of the cell (see Fig. 1, right), which causes the elongation of the Effective Refractory Period (ERP), i.e. the longest interval between two electrical impulses that fails to depolarize the tissue [43]. At the macroscopic level, Conduction Velocity (CV) of the electrical impulse slows down and excitability is reduced [43,44].

These effects are caused by alterations at the ionic level, which could be summarized by means of the following processes:

- (i) the reduction of O_2 (hypoxia), which causes a slowdown in the process of ATP synthesis. This results in the opening of ATP-sensitive K^+ channels that induces potassium leakage outside the cell [7,42];
- (ii) the accumulation of the potassium ion in the extracellular domain $[K^+]_o$ (hyperkalemia), resulting in the increment of the resting (Nernst) potential E_K [8,45];
- (iii) the reduction of intracellular pH (acidosis), which decreases the influx of sodium and calcium currents through the cellular membrane [9,46].

Such ionic and metabolic effects are modeled in this work by starting from the Ten Tusscher–Panfilov model (TTP06) [36], which is one of the most used and exhaustive models for simulating ventricular electrophysiology for 3D numerical experiments. In order to be able to exploit the TTP06 model also in pathological scenarios of AMI, it is fundamental to add to the mathematical ionic model the ATP-sensitive K^+ current (see point (i) above). In recent years, several design of this additional current have been developed (see, e.g., [28,37,47–52]). Specifically, in this study we use the version proposed in [37]:

$$I_{K-ATP} = G_{K-ATP} f_{K-ATP} \left(\frac{[K^+]_o}{[K^+]_{o,n}} \right)^{0.24} (u - E_K). \quad (3)$$

The amplitude of the current depends on the ratio between the actual ($[K^+]_o$) and the physiological ($[K^+]_{o,n} = 5.4$ mmol/L) concentrations. It also depends on the Nernst potential of potassium E_K , which varies with $[K^+]_o$ according to the TTP06 ionic laws, and on the channel conductance $G_{K-ATP} = 0.05$ mS/ μ F [37]. f_{K-ATP} is used as scaling factor to vary the conductance in the model, depending on the tissue condition (healthy, transitional or ischemic).

Here, the new current I_{K-ATP} is added in two of the equations of the TTP06 model:

Table 1

List of physical parameters used in our study to model hypoxia, hyperkalemia and acidosis, together with their values and references.

Electrophysiology model parameters				References
G_{K-ATP}	0.05 mS/ μ F			[29]
	Healthy zone	Border zone	Ischemic zone	
f_{K-ATP}	0	0.1	0.2	[29]
$[K^+]_o$	5.4 mmol/L	7.2 mmol/L	9 mmol/L	[53]
G_{Na}	14.838 mS/ μ F	13.057 mS/ μ F	11.1285 mS/ μ F	[46]
G_{CaL}	0.0000398 mS/ μ F	0.000035 mS/ μ F	0.00002985 mS/ μ F	[46]

- in the potassium dynamics equation, described as the variation in time of the intracellular potassium concentration, calculated as the ratio of the sum of the potassium-dependent currents and $V_C F$, representing the product between the cytoplasmic volume and the Faraday constant;
- in the sum of the transmembrane ionic currents.

This modified version of the Ten Tusscher–Panfilov model is useful to represent the metabolic impairments that arise because of the reduced coronary flow [48,51].

In what follows, we report how the ionic parameters of the ionic TTP06 model are affected by hypoxia, hyperkalemia and acidosis, see [37] for further details. Specifically, the authors proposed to use for the ischemic region characteristic values corresponding to the state occurring ten minutes after the ischemic event, according to experimental cellular curves [43,53].

The effective choices to model hypoxia, hyperkalemia and acidosis are summarized as follows:

- (i) the new current conductance is varied through the scaling factor f_{K-ATP} as follows: $f_{K-ATP} = 0$ in the healthy zone (HZ) so to model the current being silent; $f_{K-ATP} = 0.1$ in the transitional region (border zone, BZ); $f_{K-ATP} = 0.2$ in the ischemic zone (IZ);
- (ii) the healthy value of the extracellular concentration of potassium is set $[K^+]_{o,n} = 5.4$ mmol/L, and it is increased to $[K^+]_o = 7.2$ mmol/L in the transitional zone BZ and to $[K^+]_o = 9$ mmol/L in the ischemic zone IZ (for completeness, we provide a comparison and analysis of hyperkalemia's effects on action potential morphology for the Tomek model versus this modified version of the TTP06 model in the Appendix, Appendix A.1);
- (iii) the reduction of intracellular pH that arises after ten minutes into an ischemic event corresponds to a decrease of the peak I_{Na} and I_{CaL} conductances of 25% in IZ. In BZ a reduction of 12% is applied.

In Table 1 we summarize the values of all the physical parameters related to the modified version of the Ten Tusscher–Panfilov model used in this work.

2.3. Numerical methods

The electrophysiological model (1) with the modified TTP06 ionic model accounting for (3) is discretized in time with the semi-implicit Backward Differentiation Formula of order 2 (BDF2) [54,55]. Specifically, the nonlinearities appearing in g and I_{ion} are treated by using second order extrapolations of the unknowns u and w . Because of the extremely high stiffness of cellular models, due to the significant variables variations over short timescales, a small value for the time-step Δt is required [39]. This also allows us to satisfy the milder absolute stability constraint due to the semi-implicit scheme.

As regards the discretization in space, the transmembrane potential in the left ventricle geometry is modeled by means of the Finite Elements (FE) method. In order to accurately capture the fast propagation of the electrical impulse, quadratic P^2 FE are employed together with a correspondingly small size of the computational mesh [56]. We use the Ionic Current Interpolation (ICI) approach to manage the ionic current I_{ion} , which builds an interpolation directly on the mesh nodes, allowing us to have a stable solution due to the introduction of a suitable numerical diffusion [57].

To provide suitable initial values for the unknowns u and w , we perform a pre-processing simulation where the modified TTP06 cellular OD models (one for each tissue condition, i.e. healthy, transitional, ischemic) are run for about 800 beats until cycle limit values are reached.

2.4. Construction of patient-specific configurations

The starting point is the construction of four patient-specific geometries of left ventricles of stable CAD patients (in what follows, referred to as M6, M7, M8, M9) acquired from CT scans, see [38]. Two diagnostic acquisitions have been performed for each patient: a coronary CT angiography (cCTA) at rest and a myocardial stress Computed Tomography Perfusion (stress-CTP) under stress due to adenosine-induced vasodilation. The latter acquisition allows to measure the flow reserve of the patient, i.e. the cardiac perfusion in possibly acute myocardial ischemia regions induced by the stress, which destabilize CAD. Specifically, a constant injection of 0.14 mg/kg/min of adenosine is performed over four minutes; after three minutes from the start of the injection, a stress-CTP acquisition is performed during free breathing.

From cCTA, three-dimensional geometries of the left ventricle myocardium are reconstructed and turned into a volumetric mesh by using VMTK, a collection of libraries and tools for 3D reconstruction, geometric analysis, mesh generation and surface data analysis for image-based modeling [58,59].

From stress-CTP, the evaluation of myocardial perfusion is achieved through the measurement of myocardial blood flow (MBF) under pharmacologically induced stress conditions. Notice that a perfusion defect in a specific region revealed by stress-CTP indicates that a localized acute ischemia induced by the stress is developing during the procedure. Specifically, for each patient, we have at disposal MBF maps in [ml/min/100 ml], representing the average value over the heartbeat normalized over 100 g of tissue (see Fig. 2, top). In order to cluster MBF maps into the three healthy, transitional and ischemic regions, we provide a manipulation of them by means of Paraview (open-source, multi-platform data analysis and visualization application based on Visualization Toolkit (VTK) [60]), see Fig. 2, bottom. In particular, we interpolate the scalar MBF maps acquired from stress-CTP, reported in Fig. 2, top, onto the computational meshes of the smoothed ventricle geometries segmented from the cCTA images, see Fig. 2, bottom. To do this, the filter PointDatasetInterpolator is exploited. Then, based on the interpolated MBF values, we create a clustering of the computational mesh based on three regions (healthy, border and ischemic), performed with the filter Calculator, through which we create specific volume labels used later in our simulations as input parameters, by imposing two thresholds on MBF values, see below. In accordance with clinical indications, healthy, border and ischemic zones in the myocardial tissue are determined as follows:

- Healthy zone (HZ): MBF values higher than 100 ml/min/100 ml [61,62] (red color in the figure);
- Border zone (BZ): in order to account for significant transitional regions [53], we identify the region with MBF values ranging between 70–100 ml/min/100 ml (light-blue color in the figure);
- Ischemic zone (IZ): MBF values lower than 70 ml/min/100 ml (blue color in the figure).

Notice that our patients come from the PERFECTION study [63] where one of the exclusion criteria was the presence of (as we read from the paper) “prior myocardial infarction”. Thus, when the MBF map shows an ischemic region, we can be sure that it corresponds to induced acute ischemia and not to a previously developed chronic ischemia.

We notice also that the ischemic zones appear to be in some cases fragmented. This is a well-known phenomenon described and studied in previous works [64,65]. Probably, this is due to a heterogeneous vascularization of the myocardium, in term of density of vessels per unit area, possibly determining fragmentation of the corresponding perfusion map.

According to the values discussed in Section 2.2, we assign to each of these three regions a different value for the variables f_{K-ATP} , $[K^+]_o$, G_{Na} , G_{CaL} .

In Table 2 we report the total volumes and the volume percentages of healthy, border and ischemic zones for each patient M6, M7, M8 and M9.

2.5. Stimulation procedure

In this work, we consider the following steps to identify the stimulation protocol S1:

- The sinus rhythm (SR). To simulate the propagation of the transmembrane potential from the atrioventricular node to the Purkinje network (not modeled in this work) terminations, three closely spaced in time spherical impulses are triggered at three different coordinates on the left ventricular endocardial surface. Specifically, we set the first impulse in the area high on the anterior-paraseptal wall just below the attachment of the mitral valve, the second impulse in the central area on the left surface of the interventricular septum, and the third impulse in the posterior paraseptal area at about one third of the distance from apex to base [66];
- The ectopic event (S1). In order to test the possible induction of arrhythmia, we set a fourth premature impulse (S1) that represents an ectopic event occurring in a vulnerable substrate because of abnormal automaticity or triggered activity [67]. Critical ectopic beats usually take place spontaneously on the epicardial surface along the border zone [68]: in some cases, this abnormal impulse is able to re-excite the tissue at the end of the refractory period of myocardial cells, leading to the formation of reentry mechanisms.

For each patient, we run several simulations applying the S1 stimulation protocol. Specifically, we randomly select twelve ectopic sites x_j that are equispatially distributed along the border zone (see Fig. 3) and which are activated at times $t_j > t^0$, where t^0 is the onset of SR. Among the latter, for each site j we look for the ectopic activation time $\tilde{t}_j$ associated to the Coupling Interval CI_j , i.e. the smallest distance from t^0 at which the impulse S1 is able to depolarize the tissue without encountering the repolarization front of SR: $CI_j = \tilde{t}_j - t^0$.

To this aim, we propose for each ectopic site x_j an iterative method where $t_j^{(k)}$ is suitably updated as in Algorithm 1.

After this procedure, we are able to associate a CI_j to each ectopic site x_j for each patient. By looking at the outcomes obtained from the final simulation, we count the number of reentry loops that the ectopic impulse is able to generate, so to analyze for each patient the intra-individual arrhythmogenic propensity of the tissue.

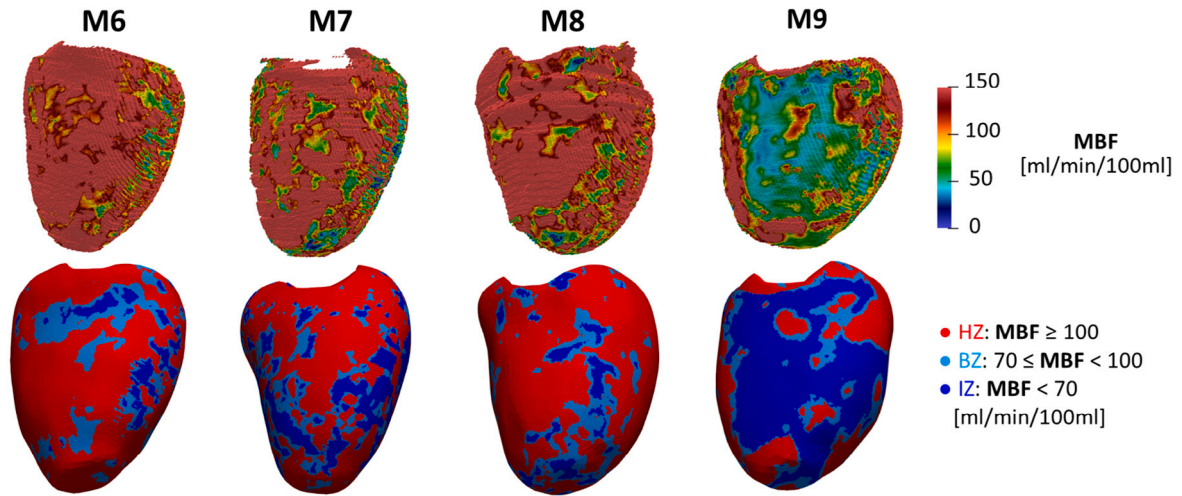


Fig. 2. Measurements of Myocardial Blood Flow (MBF) maps from stress-CTP (top) and their interpolation onto the computational meshes of the geometries reconstructed from cCTA (bottom). Patients M6, M7, M8, M9 from [38]. Epicardial views. Part I.

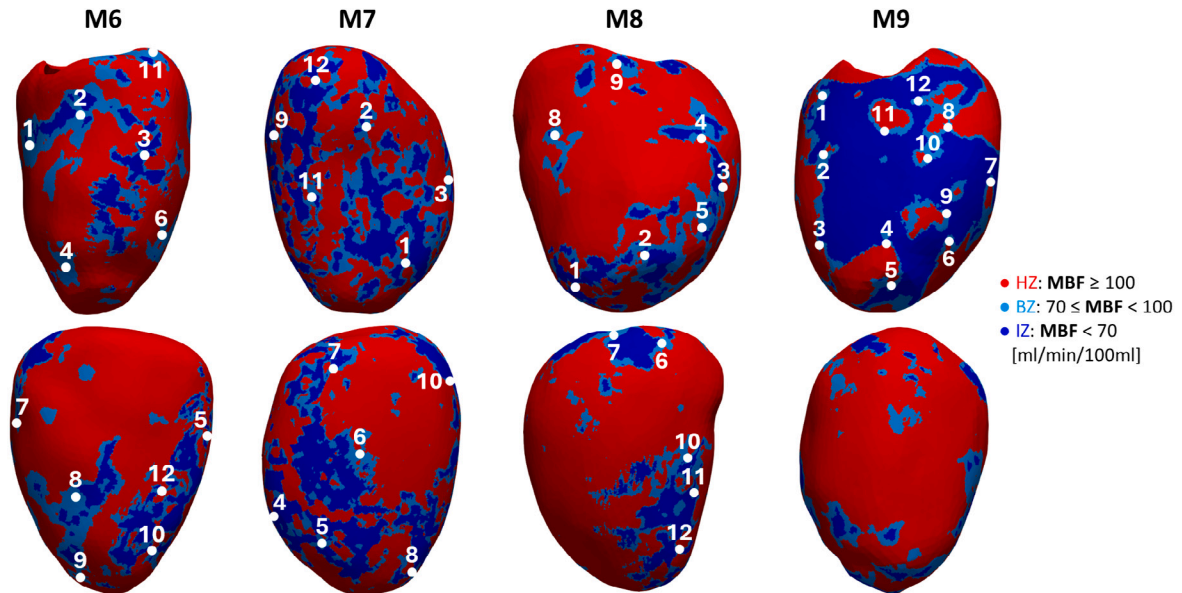


Fig. 3. Stimulation sites for the 12 ectopic impulses set for patients M6, M7, M8, M9 from [38]. The two rows depict two different epicardial views of the ventricle. In red the healthy zone (HZ), in light-blue the border zone (BZ), in blue the ischemic zone (IZ). Part I.

Table 2

Total myocardial volume and corresponding volume percentages of healthy, border and ischemic zones for each patient M6, M7, M8, M9. Part I.

	M6	M7	M8	M9
Total volume [cm ³]	117.6	179.6	214.0	126.2
% volume HZ	79.0%	56.0%	73.8%	63.2%
% volume BZ	16.3%	21.7%	13.8%	19.5%
% volume IZ	4.7%	22.3%	12.4%	17.3%

2.6. Set-up of the numerical experiments

All the numerical experiments are run using *life^x* [69], an open-source C++ library for the simulation of the heart functions, developed at MOX, Dipartimento di Matematica, in collaboration with LaBS, Dipartimento di Chimica, Materiali e Ingegneria Chimica “Giulio Natta” (Politecnico di Milano), in particular the repository *life^x-ep* [70]. The *life^x* library has been successfully validated for a normal propagation without reentries, see [71–73].

In this study, a volumetric tetrahedral mesh, with an average edge length $h = 0.7$ mm [74] (see Fig. 1, middle, where we report as a representative case the computational mesh of patient M9), and a value of the time discretization parameter $\Delta t = 5 \cdot 10^{-5}$ s [75] are used for each patient. Notice that the value of h is larger than the usual one used with linear $\mathbb{P}^1$ FE [39], since in this work we are employing quadratic $\mathbb{P}^2$ FE, for which the value of h could be doubled with equal accuracy [76,77]. To provide further confidence, we perform an analysis on the choice of the mesh size and of the Finite Element polynomial degree in the Appendix, Appendix A.2.

In our simulations we apply spherical impulses for the stimulation conditions, where each impulse has an amplitude of 34.28 V/s, a duration of $3 \cdot 10^{-3}$ s and a radius of 6 mm, values tuned to generate the propagating action potential. As regards the stimulation procedure used to determine CI, we consider in Algorithm 1 $k_{max} = 40$.

As regards the complex fibers-sheets architecture that characterizes the myocardium, we employ a Laplace–Dirichlet rule-based numerical reconstruction based on the Bayer–Trayanova (BT) model [78,79]. In order to simulate the traveling impulse in a left ventricle geometry, the

Algorithm 1 Stimulation procedure to determine CI for the j - th impulse

```

1: Set  $k = 0$ ;
2: Set  $M = 200$  ms;
3: Run a first simulation with sinus rhythm starting at  $t^0 = 0$  and
   ectopic impulse located in  $x_j$  at  $t_j^{(0)} = 400$  ms;
4: if  $(u(x, t_j^{(0)} + M) \leq -70$  mV  $\forall x)$  then
5:   while  $(u(x, t_j^{(k)} + M) \leq -70$  mV  $\forall x)$  &  $(k < k_{max})$  do
6:      $t_j^{(k+1)} = t_j^{(k)} + 10$  ms;
7:     Run a new simulation with  $t_j^{(k+1)}$ ;
8:      $k = k + 1$ ;
9:   end while
10:   $\tilde{t}_j = t_j^{(k)}$ ;
11: else
12:  while  $(u(x, t_j^{(k)} + M) > -70$  mV  $\forall x)$  &  $(k < k_{max})$  do
13:     $t_j^{(k+1)} = t_j^{(k)} - 10$  ms;
14:    Run a new simulation with  $t_j^{(k+1)}$ ;
15:     $k = k + 1$ ;
16:  end while
17:   $\tilde{t}_j = t_j^{(k-1)}$ ;
18: end if

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monodomain conductivities are calibrated so to obtain a longitudinal conduction velocity equal to 60 cm/s ($\sigma_f = 0.9247$ cm²/s, see (2)) and transversal and normal velocities equal to 40 cm/s ($\sigma_s = \sigma_n = 0.3644$ cm²/s, see (2)) [80].

Because of the absence of the scarring tissue, no changes of the monodomain conductivities are introduced to model the ischemic scenarios. Indeed, during the early phase of AMI, the reduction of the conduction velocities in the three main directions is only due to the metabolic and ionic heterogeneities that arise in the border and ischemic regions and not to a change of the conductivities σ_f , σ_s and σ_n , whose values in the early stage are very similar to the healthy case since gap junctions still communicate one another, see [11,12,81–83] for further details.

Simulations of 1.5 s of electrical activity are executed on two nodes with 48 processors per node on a high-performance computing resource of the Mathematics Department at Politecnico di Milano.¹ The computational time and the total degrees of freedom of the simulations are, for each patient, the following: 348 min - 10,417,794 DoF for M6; 532 min - 16,011,263 DoF for M7; 594 min - 19,072,106 DoF for M8; 376 min - 11,673,863 DoF for M9.

3. Results Part I - Arrhythmogenesis in presence of patient-specific acute ischemia

In Table 3 we report for all the patients the number of reentry loops R_j that the impulse S1, applied in each ectopic site x_j , is able to generate at time $\tilde{t}_j = CI_j + t_0$ ($t_0 = 0$), found by means of the proposed Algorithm 1.

As regards patient M6, the ectopic impulses do not generate reentrant activity: after finding CI_j for each ectopic site x_j , we observe that for this patient the impulse, after its onset, is able to propagate and depolarize the myocardial tissue again, but then it decays without forming any reentry loop. We can notice that patient M9 has the highest numbers of reentry loop formation. Indeed, for this patient, S1 is able to generate at least one loop in each ectopic site. Moreover, in points x_8 and x_9 the ectopic impulse finds the optimal triggering and electrical remodeling conditions that allow the formation of four reentry loops.

¹ The simulations discussed in this work were, in part, performed on the HPC Cluster of the Department of Mathematics of Politecnico di Milano which was funded by MUR grant Dipartimento di Eccellenza 2023–2027.

Table 3

Number of reentry loops (R_j) that are generated after the onset of the ectopic impulse S1 at times founded with 1 for patients M6, M7, M8, M9. Part I.

j	M6		M7		M8		M9	
	CI [ms]	R	CI [ms]	R	CI [ms]	R	CI [ms]	R
1	370	0	350	0	370	0	380	1
2	420	0	340	0	420	0	370	1
3	410	0	420	0	430	0	350	1
4	390	0	380	0	410	0	370	1
5	400	0	410	1	420	1	370	1
6	420	0	400	0	380	0	410	1
7	390	0	410	0	420	0	390	1
8	390	0	410	0	390	1	420	4
9	460	0	410	0	400	1	400	4
10	370	0	380	0	380	0	410	1
11	420	0	410	0	380	1	390	1
12	390	0	400	0	370	0	420	1

By contrast, in patient M7 S1 causes the formation of only one reentry loop in one ectopic sites over twelve, whereas in patient M8 S1 causes the formation of only one loop in four ectopic sites. Consequently, from our results, patient M9 appear to be the most prone to generate sustained reentrant drivers.

In Fig. 4 we report the progression of the first three reentry loops originated in the most arrhythmogenic case M9 for the ectopic impulse located in site x_8 (identified with a pink circle in row S1) for $CI_8 = 420$ ms. For selected time instants, we show the epicardial view on the left and the endocardial view in the middle, in order to evidence the depolarization maps that arise along the two ventricular surfaces. Moreover, we report a further view of a ventricle's section on the right, so to highlight the transmural depolarization front. In rows Reentry loop I, Reentry loop II and Reentry loop III, the curved white arrows indicate the formation of reentries at times $t = 700, 1000, 1350$ ms, respectively. At times $t = 550, 900, 1000, 1100, 1350, 1500$ ms we can notice that the reentrant activity is able to sustain itself because of the propagation in specific regions which occurs only at the endocardium (see the white arrows) and not at the epicardium (see the white circles), since the wavefront is spreading out along the transmural direction. This heterogeneous electrical activation creates the suitable conditions that allow the reentry loop to form.

In Fig. 5, we show for the three least arrhythmogenic cases M6, M7, M8 selected numerical results of maps of the electrical wavefront. Specifically, we report cases M6- x_2 and M7- x_3 (which do not induce any reentry loop), and M8- x_5 (which induces one reentry loop). In these patients, the ectopic impulses (identified with a pink circle in row S1) are able to depolarize the tissue after being set at time $\tilde{t}_j = CI_j + t_0 = 420$ ms, propagating in the directions indicated by white straight arrows. In the three patients, at time $t = 550$ ms we can notice a uniform depolarization of the ventricle both at the endocardium and at the epicardium. While in patient M6 and M7 S1 decays without forming any reentry loop, as we can see at time $t = 800$ ms, in patient M8 one reentry loop (indicated with white curved arrows) is generated at time $t = 700$ ms (row Reentry loop I) at the epicardium, depolarizing the ventricle for the second time.

Referring to Table 2 and considering the outcomes obtained from the simulations just discussed, it is interesting to notice the differences arising between patient M9 and the others. Indeed, although it is the most arrhythmogenic one (see Table 3), this patient turns out not to be the one with larger pathological (border and ischemic) region volumes (see Table 2), which is patient M7.

To conclude this results section, we report an analysis about conduction velocities found by our numerical experiments in the different regions, in order to give a quantitative evaluation of the influence of cellular changes on the propagation of the electrical impulse. To this aim, we provide an estimation of the conduction velocities along the principal direction of the electrical propagation through the healthy

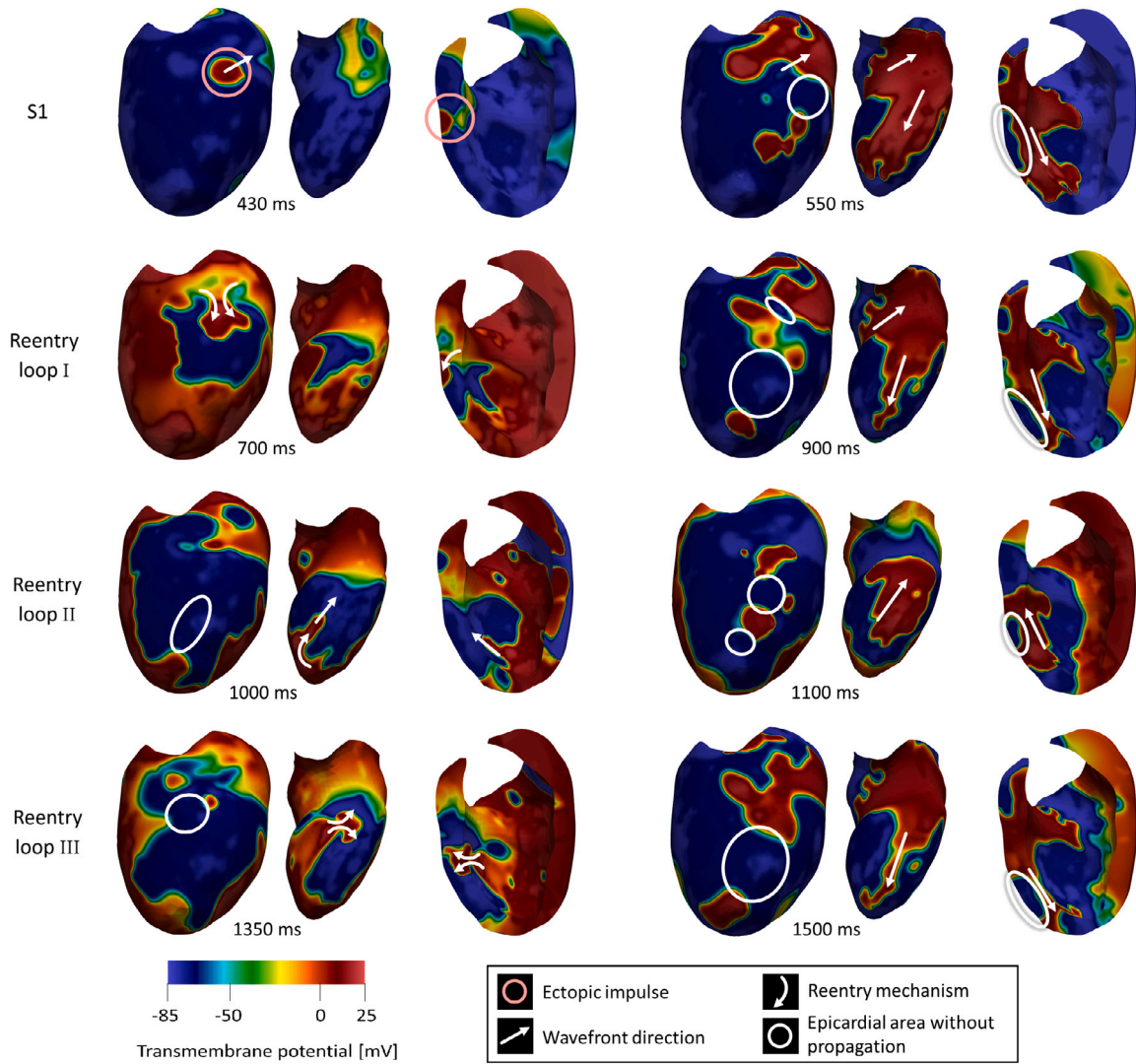


Fig. 4. Evolution of reentry loops generated by the ectopic impulse set in site x_8 at time $\tilde{t}_8 = CI_8 + t_0 = 420$ ms for patient M9. For selected time instants, we report the propagation of the transmembrane potential on the epicardium (left), on the endocardium (middle), and we report a sectional view of the ventricle in which the transmural propagation is visible (right). The first row (S1) represents the propagation just after the ectopic impulse (identified with a pink circle), whereas the other three rows represent the sequence of reentry loops. White straight arrows indicate the direction of the wavefront; white curved arrows indicate part of the reentry circuits; white circles identify the epicardial areas where the wavefront propagation is not allowed. Part I.

and ischemic zones of patient M9. Specifically, we perform five different measurements of the Euclidean distance between two points on the endocardium in the healthy zone and five in the ischemic zone, and we divided them by the time the electrical impulse needs to do these paths. Subsequently, we calculate the mean value of such estimates, finding 62.04 ± 4.08 cm/s for the healthy zone and 26.43 ± 2.00 cm/s for the ischemic zone. This finding is coherent with the literature [16], in particular with [37] which highlighted a conduction velocity decrease of about 60% in the ischemic region.

For completeness, in the Appendix, Appendix A.3, we report an analysis where different depolarizations are considered.

4. Methods Part II - Sensitivity analysis of acute ischemic regions

In order to evaluate how the extension and the volume of an AMI region can influence the generation of reentrant mechanisms in pathological left ventricles, we create two virtual scenarios of AMI for patient M9, the one that showed the highest arrhythmic propensity. The same mathematical and numerical methods explained in Sections 2.1, 2.2, 2.3 are used to run the simulations in *lifeX*. Starting from the

patient-specific geometry of patient M9 (Section 2.4), together with the clinical range (reported in the bullet points in Section 2.4 and, in what follows, referred to as severe, SEV), we consider two further ranges of MBF to describe two smaller ischemic and border zones (see Fig. 6):

- Scenario intermediate (INT):
 - HZ: MBF values higher than 80 ml/min/100 ml (red color in Fig. 6);
 - BZ: MBF values ranging between 60–80 ml/min/100 ml (light-blue color);
 - IZ: MBF values lower than 60 ml/min/100 ml (blue color).
- Scenario modest (MOD):
 - HZ: MBF values higher than 60 ml/min/100 ml (red color);
 - BZ: MBF values ranging between 50–60 ml/min/100 ml (light-blue color);
 - IZ: MBF values lower than 50 ml/min/100 ml (blue color).

These scenarios can further highlight how the extent and the distribution of the pathological regions influence the formation of reentries.

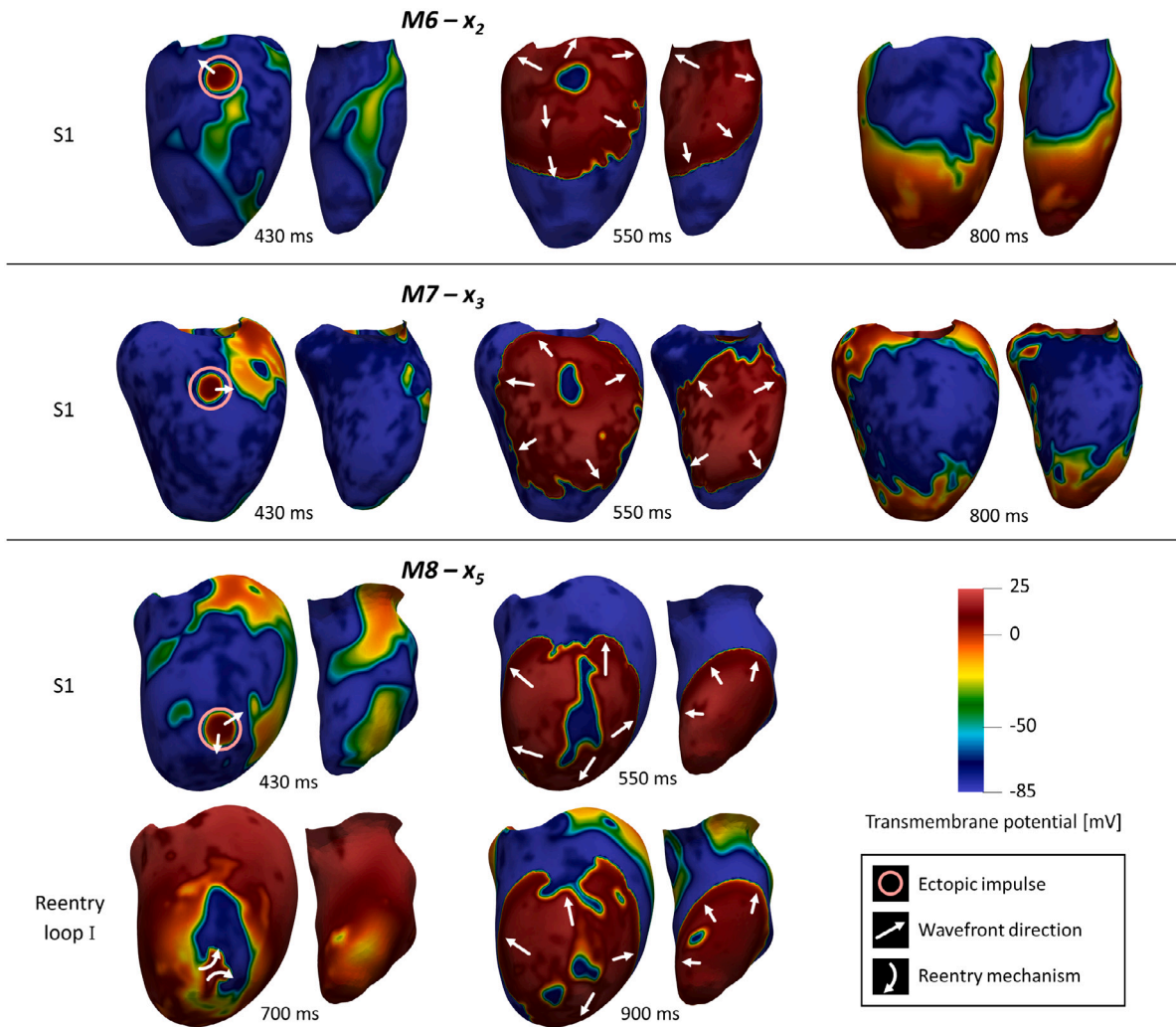


Fig. 5. Wavefront progression generated by the ectopic impulses set at time $\tilde{t}_j = CI_j + t_0 = 420$ ms in sites x_2 for patient M6, x_3 for patient M7, and x_5 for patient M8. For selected time instants, we report the propagation of the transmembrane potential on the epicardium (left) and on the endocardium (right). Rows S1 represent the propagation just after the ectopic impulse (identified with a pink circle). Notice the standard repolarization characterizing M6 and M7. On the contrary, row Reentry loop I in patient M8 represents the formation of a reentry loop. White straight arrows indicate the direction of the wavefront; white curved arrows indicate part of the reentry circuits. Part I.

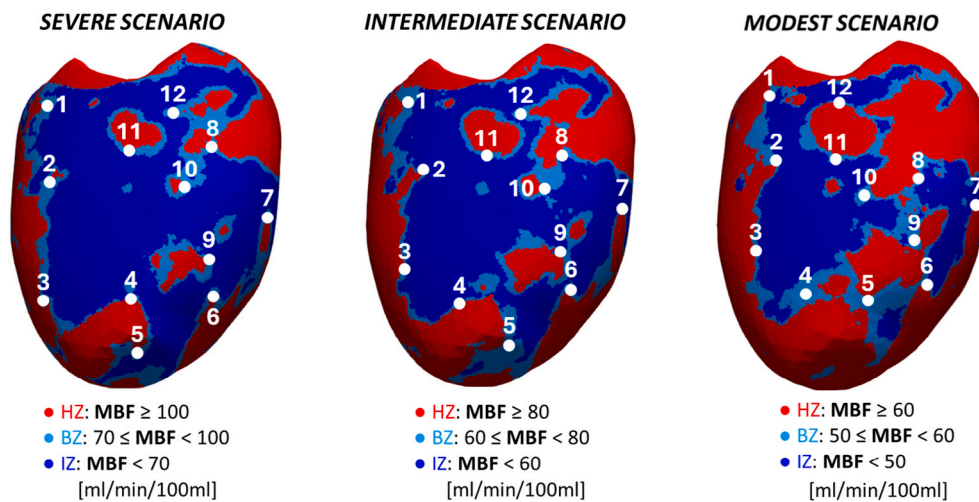


Fig. 6. Stimulation sites for the 12 ectopic impulses set for patient M9 (left, severe scenario (SEV)) and for the two virtual scenarios (center, intermediate scenario (INT); right, modest scenario (MOD)). In red the healthy zone (HZ), in light-blue the border zone (BZ), in blue the ischemic zone (IZ). Part II.

Table 4

Volume percentages of healthy, border and ischemic zones for severe (SEV), intermediate (INT), and modest (MOD) scenarios of M9. Part II.

	SEV	INT	MOD
% volume HZ	63.2%	76.4%	87.5%
% volume BZ	19.5%	11.1%	4.5%
% volume IZ	17.3%	12.5%	8.0%

Table 5

Number of reentry loops (R_j) that are generated after the onset of the ectopic impulse S1 at times founded with 1 for severe (SEV), intermediate (INT) and modest (MOD) scenarios. Part II.

j	SEV		INT		MOD	
	CI [ms]	R	CI [ms]	R	CI [ms]	R
1	380	1	380	1	390	1
2	370	1	360	1	370	1
3	350	1	350	0	340	0
4	370	1	380	1	370	1
5	370	1	380	1	390	0
6	410	1	380	1	410	1
7	390	1	390	0	400	0
8	420	4	420	2	410	0
9	400	4	400	1	400	1
10	410	1	400	1	400	0
11	390	1	400	0	400	1
12	420	1	420	0	410	0

In Table 4 we report the volume percentages of healthy, border and ischemic zones for the three scenarios considered for M9.

In order to simulate a possible case of spontaneous ectopic impulse, we use again the protocol described in Section 2.5 and the same set-up presented in Section 2.6. The twelve new ectopic sites x_j in the two virtual scenarios are also distributed along the border region as close as possible to the points chosen for the SEV case, in order to eliminate from the analysis the confounding factor given by the influence of the locations of the ectopic impulse on arrhythmogenesis.

5. Results Part II - Sensitivity analysis of acute ischemic regions

In Table 5 we report for severe (SEV), intermediate (INT) and modest (MOD) scenarios of patient M9 the number of reentry loops R_j that the impulse S1, applied in each ectopic site x_j , is able to generate at time $t_j = CI_j + t_0$ ($t_0 = 0$), found by means of the proposed Algorithm 1.

We can notice that the SEV scenario is able to generate at least one reentry loop for each ectopic impulse. Instead, for INT and MOD scenarios, one reentry loop occurs in seven and six ectopic sites, respectively, whereas two loops only in one case for INT. Consequently, as expected, our results highlight that the SEV scenario is more arrhythmogenic than INT and MOD.

To emphasize the different propagation patterns occurred in the three scenarios, we focus our analysis on the case of the ectopic impulse activated in site x_8 . By looking at Fig. 4 for SEV and at Fig. 7 for INT and MOD, where with the pink circle we indicate the location of the ectopic impulse, it is possible to see that, in the first instants after the onset of the impulse ($t \leq 550$ ms, row S1), the depolarization fronts of all the three scenarios are very similar and propagate along the same direction (identified by white straight arrows).

Going further in the analysis of the simulations' results, for $700 \text{ ms} \leq t \leq 900 \text{ ms}$ we observe different behaviors of the three scenarios. Specifically, for MOD the ectopic impulse decays without generating any reentry mechanisms; instead, for INT and SEV we observe a very similar propagating wavefront (see row Reentry loop I): in a similar way to that explained in Section 3, also for INT a first reentry loop is generated (see $t = 700$ ms) and endocardial pathways allow the sustainment of the propagation of the wavefront (see $t = 900$ ms).

Instead, by looking at what happens for $1000 \text{ ms} \leq t \leq 1100 \text{ ms}$, we can observe that both INT and SEV generate a second reentry loop, however with very different mechanisms and patterns. Specifically, unlike the SEV case, for INT such reentry loop is present both at endocardium and epicardium (see $t = 1100$ ms) and thus throughout the entire thickness of the myocardial region (see the sectional view reported on the right at time $t = 1100$ ms). This does not create the heterogeneous electrical condition which would allow a further (third) reentrant loop. Indeed, after the second reentry loop, the tissue repolarizes.

6. Discussion

6.1. On the novelties of the work

In this work, we report (at the best of our knowledge) the first computational study which includes patient-specific information on AMI regions, to assess the influence of Acute Myocardial Ischemia (AMI) on arrhythmogenesis. The use of patient-specific information on AMI distributions is fundamental to accurately assess the risk of arrhythmia formation in the specific patient. Indeed, the use of scar distribution as a surrogate of AMI zones [33] may not be very informative, since changes occurring at the ionic level during the early acute ischemic phase do not necessarily evolve into an infarct.

Accordingly, the main novelty of this work is to employ Myocardial Blood Flow (MBF) maps, coming from stress-CTP exams, to generate patient-specific acute ischemic regions in four patients. Indeed, during this type of acquisition, a sudden and reversible acute ischemia is pharmacologically induced. We notice that, to have at disposal acute ischemia maps due to coronary disease (and not induced as in our case) is quite impossible, since either the patient is suddenly treated (e.g. by implanting a defibrillator), or more than 10 min pass (thus going outside the acute regime). This is the reason why no computational study in the literature has ever exploited the use of patient-specific acute myocardial ischemic maps.

To overcome this limitation, our idea is to consider induced acute ischemia events of stable CAD cases due to the destabilization of CAD provoked by the pharmacological stress state, whose perfusion maps are revealed by stress-CTP; indeed, the major effects of an induced AMI, leading to hypoxia, hyperkalemia, acidosis, are the same of the spontaneous AMI case.

Notice that our computational study aims to assess the arrhythmogenic risk in presence of possible AMI in the worst possible scenario of the patient. Indeed, it is important to stress that the MBF maps used in our simulations are measured after 3 min from the start of adenosine injection, when the patients reach their maximal hyperemic condition. Thus, no further vasodilation is possible and AMI regions are at their maximal extension.

6.2. Propensity of arrhythmogenesis: inter- and intra-patients analyses

We first discuss the results obtained from the comparison among patients performed in Section 3. Our method is based on selecting multiple ectopic sites on the border regions covering a wide portion of the epicardium, unlike previous studies where only a single ectopic stimulus is often considered [28,33]. This allows us to explore throughout the entire ventricular myocardium the tendency of the patients to be arrhythmogenic.

Moreover, the inter-individual analysis allows us to examine the impact of the volume and of the distribution of border zone (BZ) and ischemic zone (IZ) on arrhythmogenesis. Indeed, MBF maps acquired from four patients with different severity and types of stenosis show heterogeneous pathological areas, characterizing the left ventricles with very dissimilar ischemic regions. It is noticeable in Fig. 3 that patient M9 presents a more confined ischemic area with respect to the other three, which show a scattered ischemic configuration. Also, by

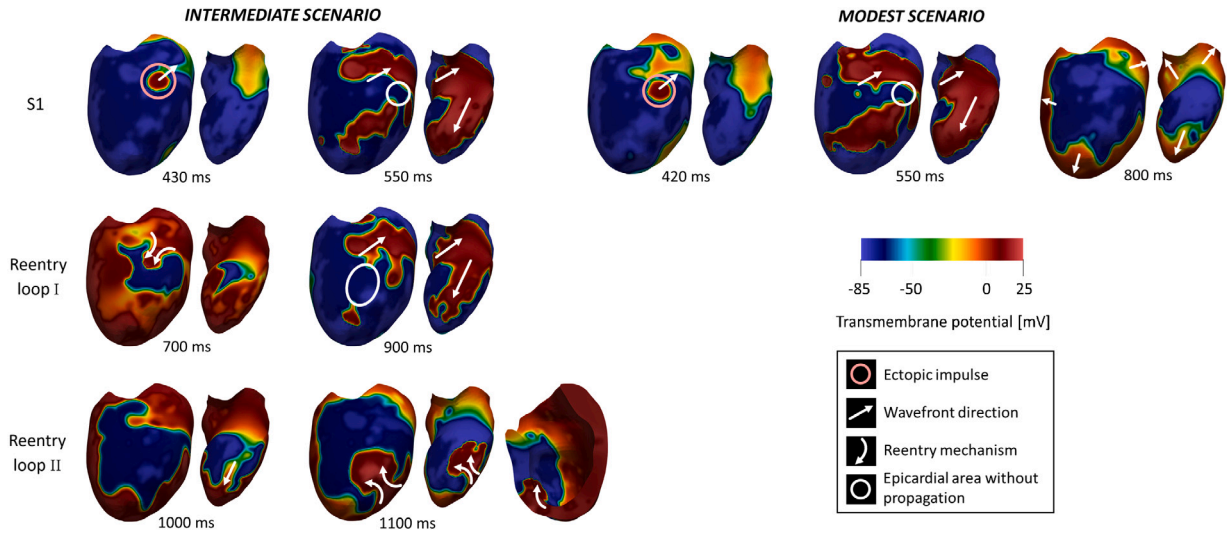


Fig. 7. Evolution of reentry loops generated by the ectopic impulse set in sites x_8 at time $\tilde{t}_8 = CI + t_0 = 420$ ms for intermediate (INT) scenario and at time $\tilde{t}_8 = CI + t_0 = 410$ ms for modest (MOD) scenario of patient M9. For selected time instants, we report the propagation of the transmembrane potential on the epicardium (left) and on the endocardium (right); moreover, for INT we report a sectional view of the ventricle in which the transmural propagation is visible at time $t = 1100$ ms. The first row (S1) represents the propagation just after the ectopic impulse (identified with a pink circle), whereas the other two rows represent the sequence of reentry loops. White straight arrows indicate the direction of the wavefront; white curved arrows indicate part of the reentry circuits; white circles identify the epicardial areas in which the wavefront propagation is not allowed. Part II.

performing an analysis on the volume percentages of the regions, as reported in Table 2, it is interesting to notice that the patient with bigger BZ and IZ is M7, followed by M9, M8 and finally M6. Moreover, from the outcomes presented in Section 3, we found that patient M9 appears to be the most prone to generate sustained reentrant drivers. This allows us to infer that the electrical substrate of this patient is more prone to develop arrhythmic events in the form of reentry loops compared to the other three patients, at least for what concern arrhythmic events induced by reentrant circuits/loops. Consequently, we can suggest that the property of the ischemic region that has major influence on arrhythmogenesis is not only its volume, but also its heterogeneous distribution throughout the myocardium; in particular, the greater the concentration of ischemic tissue in a specific region (as happens in M9), the greater the arrhythmogenic propensity.

A crucial aspect of patient M9 is that its arrhythmic propensity is accentuated by the presence of transmural and endocardial healthy pathways that allow the propagation of the impulse, as we can see in Fig. 4. This is due to an heterogeneous distribution of ischemia along the myocardial thickness. Owing to this epi-endocardial heterogeneity, the depolarization front is able to pass under epicardial regions that are still in their refractory state, thus reaching areas that can be depolarized and thus enabling the sustainment of the reentrant activity. This transmural heterogeneity could be due to the presence of a wash-out zone in the endocardium, which results from the interaction between the endocardial surface and the ventricular cavity. Indeed, thanks to this connection, oxygen and nutrients are able to diffuse from the cavity to the tissue, ensuring higher perfusion levels in the endocardium with respect to the epicardium. This condition is known to be arrhythmogenic during the first minutes of ischemia [84].

The second part of this study is devoted to a parametric study to assess the influence of the dimension of AMI regions on arrhythmogenesis, whose results are reported in Section 5. To this aim, we study the arrhythmic tendency of two virtual scenarios (intermediate — INT and modest — MOD) of patient M9 which are healthier than the original one (identified here as severe — SEV). We select this patient because it shows the highest number of reentry loops in most ectopic sites.

What we observed is that, with respect to SEV case, INT and MOD scenarios are less prone to generate arrhythmias, as highlighted in Table 5. Specifically, the pro-arrhythmic propensity able to sustain the

reentries decreases when BZ and IZ volumes (Table 4) decrease: in such a condition the ectopic impulse propagates with a higher conduction velocity, fastly depolarizing the tissue and hence encountering earlier the refractory state of the pathological regions, which blocks the wavefront.

It is interesting to correlate the values of volume percentages, reported in Tables 2 and 4, with the corresponding number of reentries, reported in Tables 3 and 5. We can notice that the regions' volumes of INT scenario are comparable with those of patient M8, and that MOD scenario has the most extended healthy zone among all scenarios/patients. However, patient M8 is less arrhythmogenic than INT: in M8 the impulse is able to generate one reentry loop only in four ectopic sites over twelve; by contrast, in INT the impulse is able to generate at least one reentry loop in eight ectopic sites over twelve. This observation is also confirmed by comparing M6 and MOD: even though M6 has a less extended healthy zone with respect to MOD, is less arrhythmogenic. This outcome confirms that the volume percentage of AMI regions seems to have less influence on arrhythmogenesis rather than their distribution inside the ventricle.

6.3. Clinical outcomes and perspectives

When a patient with stable CAD undergoes stress-CTP to evaluate the hemodynamic answer in stress conditions, possibly inducing an acute ischemic event, it may happen that ventricular tachycardia or even fibrillation starts during the acquisition. Since the patient is at the hospital, there is the possibility for the cardiologist to suddenly intervene. For such critical patients (for our convenience here, referred to as group A in what follows), a special clinical treatment is performed, in terms of revascularization by angioplasty or even implanted defibrillator.

On the other side, in the case of no arrhythmic event experienced during the stress-CTP acquisition, it is not possible to exclude that future arrhythmic event could happen as a consequence of the development of AMI. Indeed, ectopic beats that could generate the persistent loop are randomly activated and might not occur during the exam.

For all these reasons, quantifying the arrhythmogenic propensity of a patient who did not experience any arrhythmic event during stress-CTP (referred to as group B in what follows) would provide an

important clinical indication. Indeed, if the cardiologists knew that a patient of group B has a great risk of developing an arrhythmic event under AMI, they would probably enroll such a patient in a preventive/monitoring care plan, probably the same as group A.

In conclusion, this work represents a first step toward mechanistic understanding of the patient-specific impact of the distribution of poorly perfused regions within different left ventricles affected by acute ischemia on the onset of arrhythmias. Our novel approach based on personalized myocardial blood flow maps of induced acute ischemia is able to generate patient-specific numerical results of electrophysiology activity, capable of predicting the ventricle's arrhythmic response to ectopic events during acute ischemic conditions. This in-silico estimation represents a reliable predictive model useful to assess the arrhythmic risk of patients undergone stress-CTP if, during their day-to-day life, they experience acute ischemia event. Thus, we believe that the computational model we developed, if suitably validated, could be of great interest for the clinical practice, since it could allow the cardiologists to enlarge the group of critical CAD patients undergoing stress-CTP, who deserves a personalized clinical care. For such reasons, our computational model could be in a near future integrated in a specific digital twin, updated over a time-course, as part of the machine and able to reproduce electrophysiology of patients undergoing stress-CTP. To do this, the digital twin shall acquire suitable tracked health and lifestyle parameters (such as daily ECGs), allowing intelligent automation and adjustment of the predictive computational model.

6.4. Limitations and future developments

This work presents some limitations:

- First, the model does not include the His-Purkinje system (HPS). This is important to obtain an accurate conduction of the impulse with the correct sites and times of activation inside the ventricle [85]. Moreover, it is established in the literature that HPS contributes to cardiac arrhythmogenesis by increasing the likelihood of reentry formation [86,87]. For this reason, including the HPS may slightly change the obtained results by increasing the arrhythmic propensity of each patient. However, in view of our comparisons, we believe that our results could provide useful preliminary indications in patient-specific studies of arrhythmogenesis induced by AMI. Future studies on the inclusion of HPS will be however mandatory to follow up on what has been done so far;
- The transitional values of the electrophysiological parameters set in the border zone are kept constant and equal to an intermediate value between the values in the healthy and the ischemic zones. This does not reflect what is shown from experiments [53], that is a (continuous) non-constant variation from healthy to ischemic zones. The major effect of this choice is the abrupt ERP change through the border zone, as a consequence of the step variation of the ionic parameters. Specifically, ERP suddenly reduces when passing from the healthy to the border zone and suddenly increases when entering in the ischemic zone [43]. In contrast, a (for example) linear variation of ionic parameters within the border zone would smooth these transitions, resulting in a continuous profile of ERP through the border zone, with a minimum in the center. This has the potential effect to improve arrhythmogenesis: indeed, if an ectopic impulse originates in the border zone, the propagating frontwave would meet refractoriness even in such a region. In any case, this topic deserves specific future investigations;
- The mathematical model for the ionic current is composed by uniform properties along the thickness of the cardiac muscle. In particular, we use the parameters which usually characterize the myocardium, where instead one should differentiate between the properties in the endocardium, in the epicardium and in the myocardium (three-compartments model). Thus, there is no transmural and apex-to-base heterogeneity in the action potential duration [26,88]. The consequences of our choice is that, in presence of ischemic regions located in the epicardium and/or endocardium, refractory period in such regions may change with respect to the three-compartments model, due to an enlargement of APD. Further analyses should be conducted on such points in order to investigate their influence on arrhythmogenesis;
- The use of more complex stimulation protocols should be considered. Indeed, in real cases of ischemic ventricles, the activation of a single ectopic impulse hardly sustains an arrhythmic event: several ectopic impulses can originate at high frequencies one after the other in a single activation site mostly due to enhanced automaticity in HPS or focal reexcitation in the heart tissue [68,89]. Thus, the consequence of our choice is an underestimation of the arrhythmogenic propensity, which should be instead facilitated by a train of ectopic impulses;
- The absence of right ventricles. Because the ventricles operate as a unified syncytium, it is true that, to have a correct description of transmembrane potential propagation and, in particular, of reentry formation in the left ventricle, it is important to simulate also the right one. In particular, given our findings of Section 6.2 about heterogeneity of ischemic regions, we may expect such results can be extended also to the biventricle case. In this study, we limit ourselves to the left ventricle due to the lack of geometric and MBF data for the right part. However, in view of a clinical application of our tool (see Section 6.3) it will be mandatory to include the right ventricle together with its MBF;
- The lack of validation of our results. To address this, future research could involve collecting information on patients' possible arrhythmic events recorded just after stress-CTP. This would allow to validate the ability of our tool to reproduce arrhythmic events in presence of acute ischemic substrate.

Finally, we notice that a possible future alternative to MBF maps to detect patient-specific acute myocardial regions relies on electrical data measured during the ischemic event (see e.g. [15] for the case of animals), once such data could be measured in humans e.g. by means of implantable diagnostic devices.

CRedit authorship contribution statement

Alessandra Corda: Writing – original draft, Visualization, Software, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Stefano Pagani:** Writing – review & editing, Supervision, Methodology, Investigation, Formal analysis, Conceptualization. **Christian Vergara:** Writing – original draft, Supervision, Resources, Project administration, Funding acquisition, Formal analysis, Conceptualization.

Ethical approval

Ethical Review Board approval was obtained (R250/15-CCM 262). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent

Written informed consent was obtained from all subjects (patients) in this study.

Declaration of competing interest

None declared.

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Appendix A

A.1. Comparison between the Tomek model and the modified version of the Ten Tusscher–Panfilov model in terms of hyperkalemia

In this section we report a comparison between the Tomek model [90] and the TTP06 modified model used within this work in terms of hyperkalemia. For this purpose, we perform a group of simulations on a 3D slab model of $40 \times 40 \times 0.2$ mm that enable us to study the transmembrane propagation in the hyperkalemic conditions arising in the border zone ($[K^+]_o = 7.2$ mmol/L) and in the ischemic zone ($[K^+]_o = 9$ mmol/L). From our results, we find that the following characteristics are caught by two models:

- Both reduce the resting membrane potential (see Fig. 8, left);
- Tomek model captures a reduction in the action potential duration;
- Unlike the Tomek model which significantly prolongs the effective refractory period with increasing hyperkalemia, the modified TTP06 model shows a more modest increase (see Fig. 8, right).

We notice that one of the difference between the two models lies in the increment of the ERP values when passing from the healthy condition to the most hyperkalemic one: the TTP06 model does not result in a marked increase of ERP at high concentrations of potassium, contrary to what was found using the Tomek model. In presence of AMI (hypoxia, hyperkalemia and acidosis), our model is in accordance with clinical [91,92] and computational studies [21,93].

A.2. On the choice of the mesh size and of the Finite Element polynomial degree

In this section we report an analysis on how different mesh sizes (h) and Finite Element polynomial degrees ($\mathbb{P}$) influence conduction velocities. The aim is twofold:

- To conduct a mesh sensitivity analysis by keeping $\mathbb{P}^2$ constant, starting with h equal to 1.2 mm and progressively refining it to 0.7 mm and then to 0.35 mm;
- To demonstrate that our chosen parameters of $h = 0.7$ mm and $\mathbb{P}^2$ represent a good selection by quantifying the errors in conduction velocity with respect to a reference scenario ($h = 0.1$ mm and $\mathbb{P}^1$) [94].

We design a 3D cable geometry ($0.6 \times 0.6 \times 35$ mm) composed of regular tetrahedral elements. This specific geometric and meshing strategy ensures that we avoid artifacts typically associated with complex 3D geometries or irregular meshes, thereby allowing us to isolate and study the propagation characteristics in a way similar to a true 1D cable. For each pair of h and $\mathbb{P}$, we construct six scenarios: one for each of the three ionic configurations where the cable is considered homogeneous (fully healthy, fully border or fully ischemic), and for each of these we perform two simulations, one where the cable is aligned with the longitudinal fiber direction and another aligned with the transversal fiber direction. To initiate the electrical impulse propagation along the cable, we set a planar impulse to one of the cable's terminal cross-sections. Throughout these simulations, we keep constant the values of conductivities ($\sigma_f = 0.9247$ cm²/s, $\sigma_s = \sigma_n = 0.3644$ cm²/s) and time step ($\Delta t = 5 \cdot 10^{-5}$ s). To determine the conduction velocities (CV), we measure the Euclidean distance between two specific points on the cable and divide this by the time taken for the electrical impulse to traverse that path.

Then, we quantify the absolute percentage error in conduction velocities with respect to the optimal reference scenario ($h = 0.1$ mm, $\mathbb{P}^1$) using the following formula:

$$\text{Err \%} = \left| \frac{CV^{h,\mathbb{P}} - CV^{0.1 \text{ mm}, \mathbb{P}^1}}{CV^{0.1 \text{ mm}, \mathbb{P}^1}} \right| \times 100\% \quad (4)$$

and we calculate the mean error for the four remaining pairs of h and $\mathbb{P}$. In Table 6 we report for each pair of h and $\mathbb{P}$ the respective DoF, CV results and errors computed with respect to the optimal reference case. In the first three rows we report the mesh sensitivity analysis for $\mathbb{P}^2$ Finite Elements, from which we can observe clear convergence of conduction velocities as the mesh is refined for all the scenarios. Indeed, the relative error for $h = 0.7$ mm, $\mathbb{P}^2$ is less than or equal to 2.5% in any case a part from Healthy Transversal, which is however less than 5.5%. Thus, the $h = 0.7$ mm, $\mathbb{P}^2$ scenario proves to be sufficiently accurate.

A.3. Arrhythmogenesis with more drastic changes to the depolarization peak

In this section, for the sake of completeness, we perform an explorative analysis on the influence of more drastic changes to the depolarization peak. In particular, we implement a more pronounced reduction in the peak I_{Na} conductance (G_{Na}), a current known to play a crucial role in the rapid depolarization phase of the cell membrane. Specifically, we reduce G_{Na} by 90% in the ischemic zone (case NEW Ischemic) and by 45% in the border zone (case NEW Border). These new alterations affect the action potential morphology by reducing the initial transmembrane potential spike and the depolarization slope, as visible in Fig. 9.

To assess the effect on reentry formation, we start the analysis by selecting two ectopic stimulation sites, x_1 and x_8 , from patient M9. These sites are chosen because they previously demonstrated reentry activity, generating 1 and 4 reentry loops respectively (as reported in

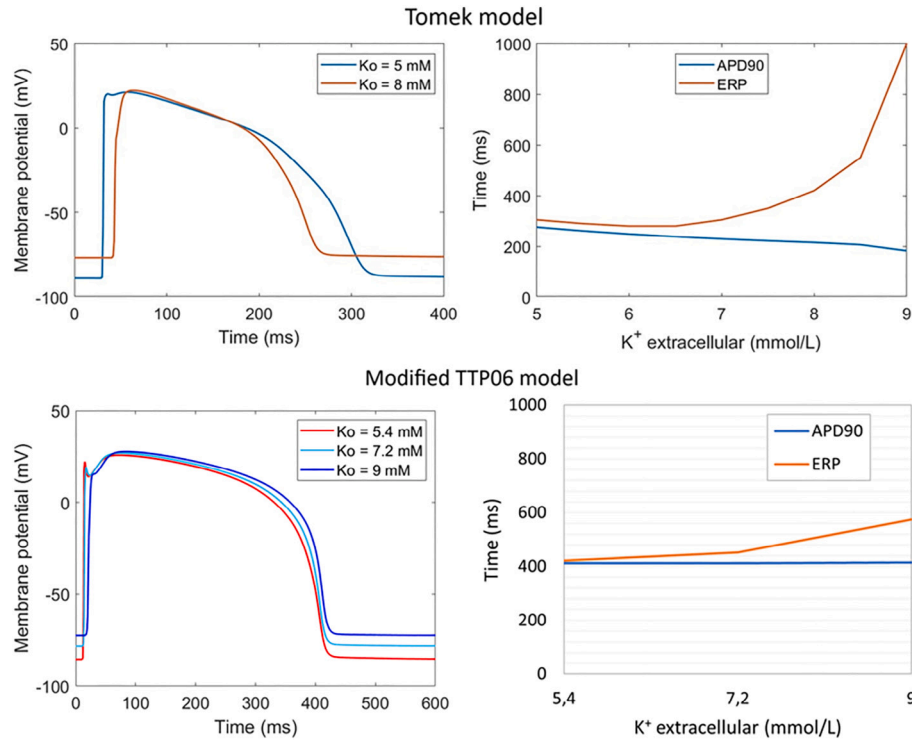


Fig. 8. The effect of hyperkalemia on action potential morphology (left) and on the action potential duration (APD90) and the effective refractory period (ERP) (right). Top: Tomek model, taken from [90]; Bottom: modified TTP06 model, obtained from our simulations.

Table 6

Conduction Velocities (CV) along the longitudinal (L) and transversal (T) directions in the three ionic configurations (healthy, border, ischemic) for each pair of h and $\mathbb{P}$ with respective DoF. The errors are computed with respect to the case $h = 0.1$ mm, $\mathbb{P}^1$.

h [mm]	$\mathbb{P}$	DoF	Conduction velocities [cm/s]						Mean err %
			Healthy		Border		Ischemic		
			L	T	L	T	L	T	
1.2	2	725	57.2 3.9%	30.1 23.1%	46.9 2.1%	26.1 16.0%	26.2 1.7%	14.6 15.2%	10.3%
0.7	2	2287	60.6 1.7%	37.1 5.4%	48.5 1.3%	30.3 2.5%	26.6 0.2%	16.9 1.5%	2.1%
0.35	2	11 395	60.1 1.0%	40.4 3.1%	48.0 0.2%	31.7 1.8%	26.6 0.2%	17.2 0.4%	1.1%
0.1	1	20,850	59.5	39.2	48.0	31.7	26.6	17.2	

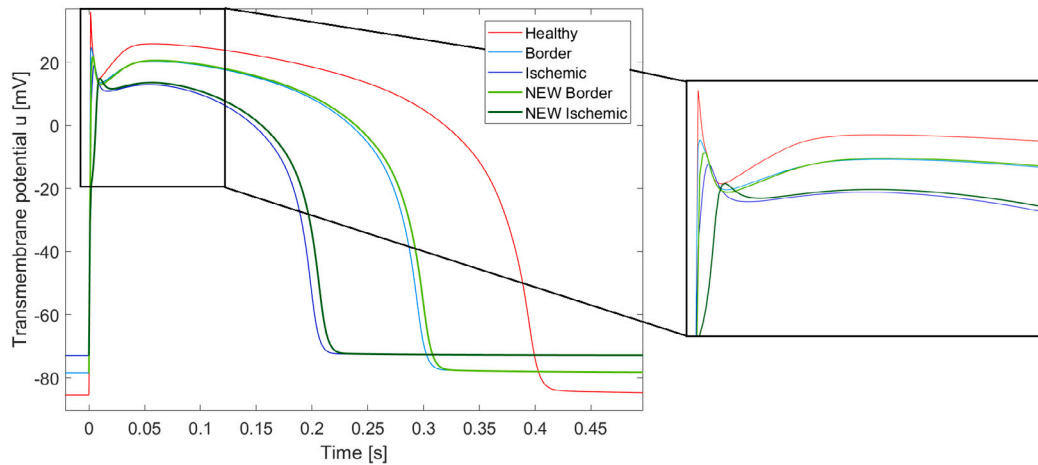


Fig. 9. Comparison between the action potentials reported in Fig. 1 of the manuscript (Healthy in red, Border in light-blue and Ischemic in dark-blue) and the new action potentials obtained after the changes to the depolarization peak (NEW Border in light-green and NEW Ischemic in dark-green).

Table 3 of the manuscript, with corresponding Coupling Intervals (CI) of 380 ms for x_1 and 420 ms for x_8 , with the original I_{Na} conductance reductions (25% in ischemic, 12% in border zone). We then re-conduct the simulations at these same ectopic sites using the newly imposed drastic I_{Na} conductance reductions, following the analysis procedure outlined in Algorithm 1 of the manuscript.

The outcomes of these new simulations are as follows:

- For ectopic site x_1 , the new Coupling Interval (CI) is 400 ms. The number of reentry loops generated after the onset of the ectopic impulse is 0;
- For ectopic site x_8 , the new Coupling Interval (CI) is 440 ms. The number of reentry loops generated after the onset of the ectopic impulse is also 0.

The results from simulations with more pronounced reduced I_{Na} conductance (90% in ischemic, 45% in border zone) reveal a complete suppression of reentry events at both previously arrhythmogenic ectopic sites. This suppression derives from the reduction in the action potential's excitability and upstroke velocity, which provoke increased refractoriness in the border regions and a complete conduction block in the ischemic regions. Specifically, a longer Coupling Interval (CI) is required for the ectopic impulse to be captured (e.g., CI increases to 400 ms for x_1 and 440 ms for x_8). This longer CI directly reflects the need for more time to activate the ectopic impulse, given the reduced strength of the depolarization spike. Moreover, the total unexcitability of the ischemic zone prevents any reentries to form, as the ectopic impulse, once initiated, can only propagate around such region never managing to enter it.

These findings indicate that arrhythmogenesis is not simply proportional to tissue damage. Instead, moderate depolarization alterations may create conditions for reentry, whereas excessively severe changes result in an unexcitable tissue, decreasing the possibility for reentries to form. This highlights a complex interplay between the degree of tissue property alteration and the propensity for arrhythmias.

Appendix B. Supplementary data

Supplementary material related to this article can be found online at <https://doi.org/10.1016/j.combiomed.2025.110975>.

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