In Silico Cardiac Model to Evaluate Myocardial Ischemia effect on Hemodynamic Parameters

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***Abstract*—Myocardial ischemia is one of the leading cause of sudden cardiac death, often due to narrowing of Coronary artery resulting in poor oxygen supply (ischemic effect) in cardiac muscles. This disease has a high variable manifestation due to difference in location and extent of damaged area, thus hampering the understanding of disease progression and stratification. In this paper, we propose a multimodal simulation of cardiac ischemia to understand the disease progression with change in ischemic size and myocardial electrical propagation and to observe changes in hemodynamic parameters with change in disease severity. The in-silico cardiac model binds electrophysiological characteristics with hemodynamic parameters, thus giving a broader understanding of the effect of disease progression on various parameters like ejection fraction, contractility, blood pressure, etc, to assess ischemic manifestation leading to heart failure. Three different cases of ischemia have been simulated to study the effect of disease and its progression. The developed in silico cardiac model can be used to simulate and study the holistic effect of any such cardiac conduction disorder along with its effect and manifestation over hemodynamic parameters.**

***Index Terms*—Electrophysiology, Hemodynamics, Myocardial Ischemia, Compliance, Transmembrane Potential**

I. Introduction

Myocardial ischemia, often resulting from Coronary artery diseases is a major precursor for sudden cardiac death [1]. This disease though high in prevalence, faces clinical challenges in management due to its high variable manifestation. Patient with ischemia reports different pathological findings based on difference in ischemic region in the myocardium, extent and severiety of scar tissue and other prevailing disease condition like diabetes [2]. Ischemic effect is exhibited by marked ECG abnormalities, specifically changes in ST segment in some patients, whereas for some patients, this pathological marking in ECG may be almost unnoticeable [3].

There has been numerous research to unravel the progression and manifestation of acute ischemia, but the complexity of ischemia-induced changes have hampered evaluation and understanding of alteration of cardiac properties with progression of the disease [4]. The conventional method to study the electrophysiological changes associated with myocardial ischemic are through animal models of clinical pathophysiology. In recent years, computer simulations and mathematical models have provided substantial insight into ischemic abnormalities in cardiac electrophysiological behavior. Computer simulation and modeling not only pertains understanding of the disease and its progression mechanism, lately this models are also used for clinical applications [5]. Although substantial research exists on modeling mechanisms related to hemodynamics, electrophysiology, computational fluid dynamics, biomechanics, etc. [6]- [7], researchers are now focusing on multiscale mathematical framework to simulate the cardiac function at the whole-organ scale.

In the domain of computer modeling for myocardial ischemia, mathematical models provide certain understanding and applicability in drug testing [8], however, such models lack the ability to efficiently deal with large numbers of mixed scenarios that include confounding factors. There are several open source platforms to model ischemic progression, like SCIRun problem solving environment [9]. However, the major drawback of these platforms remains in the fact that they process only the underlying electrophysiology, neglecting the effect of ischemia on cardiac hemodynamics. Ischemia affects contractility of the heart muscle resulting in pump inefficiency and thus hampering the hemodynamic equilibrium. As such, any computer modeling trying to understand and predict ischemic progression must comprise the dual effect of change in electrophysiology and hemodynamics as the disease manifests.

In this paper, we propose an in silico cardiac model, coupling the effect of electrophysiology (EP) and hemodynamics to assess the progression of myocardial ischemia from its inception to its pressing effect on the pumping function of heart, expressed by change in ejection fraction. We simulate various grades of ischemia, varying the size of the ischemic region in a cardiac EP framework for computing 'Forward EP'. Body surface potential (BSP) are generated for different ischemic episodes and single lead ECG configuration is derived to analyse the effect of ischemia from changes in ECG morphology, typically during the ST segment which characterizes ventricular repolarization. The simulated BSP from the electrophysiology framework is used to drive the hemodynamic model, which have been modeled as a 4 chambered heart with pulmonic and lumped systemic circulation. Developed integrated in-silico model takes into account cellular to organ level manifestation of ischemia, and have been used to simulate healthy heart dynamics and three specific cases of ischemia. For all the cases, ECG, blood pressure, left

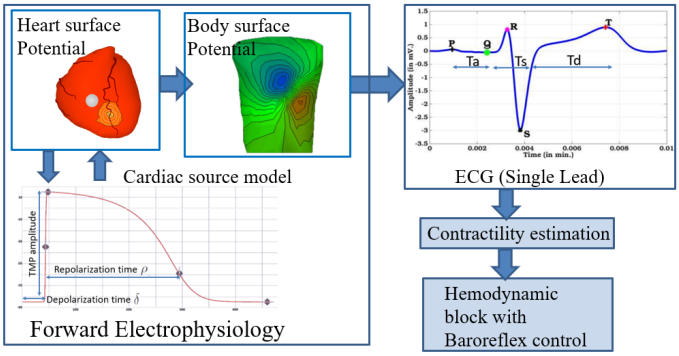


Fig. 1: Schematic of the in-silico cardiac model integrating electrophysiology and hemodynamics

ventricle dynamics, ejection fraction and Photoplethesmogram (PPG) signal have been generated which closely matches with medical observations. A schematic of the developed model is depicted in Fig.1.

II. Methodology

In silico cardiac model comprises of two separate modules, naming EP and hemodynamics, coupled together. Ischemic effect is simulated on EP module and its effect is visualized in hemodynamic module.

A. Electrophysiology model

EP model largely comprises of solving the forward problem, i.e, calculating body surface potential from a known heart potential [10]. Conventionally, the heart potential is described either using myocyte model defining cardiac action potential or a mathematical equivalent approximating the transmembrane action potential (TMP). To calculate body surface potential, the cardiac TMP are fed through cardiac propagation model like monodomain or bidomain equations and boundary conditions are defined through proper heart torso coupling. These extensive field equations are solved using numerical techniques like Finite element method (FEM) for volume integration or Boundary element method (BEM) for surface integration. Solution of the field equations results in generating the body surface potential (BSP).

In this work ECGsim [11], an open source educational software have been used to compute the 'Forward EP pipeline'. ECGsim is based on a biophysical model that connects transmembrane action potential of representative myocytes on heart surface to electrocardigram (ECG) signal on the surface of body. Geometrical parameters related to atria, ventricle and torso are reconstructed from magnetic resonance imaging.

Cardiac source model is expressed as an equivalent double layer (EDL) of sources on the closed surface of the atria and ventricles and is analogous to an equivalent source of the currents generated at the cell membrane during depolarization of a myocyte, referred to as transmembrane potential (TMP) [12]. The cardiac surface is divided in to a triangular mesh of 1500 elements or nodes, each such node poses an equivalent source which is proportional to TMP of the nearest myocyte. Time course of strength of the EDL are defined as an analytical function, mostly, by a Sigmoid curve, expressed as product of three logistic functions involving markers for the timing of local depolarization and repolarization, thus approximating TMP [12]. Source matrix (S) at node 'n' at time instant 't' is defined as:

$$S(t;\delta,\rho) = D(t;\delta)R(t;\rho) \tag{1}$$

where, D is the depolarization phase, R is the repolarization phase. The timing of local depolarization at node 'n' is denoted as δ, timing of local repolarisation at node 'n' is defined as ρ (Fig.1). The interval $\alpha = \rho - \delta$ is taken as a measure of the local action potential duration. Such timing parameters and TMP amplitudes can be varied to induce different EP conditions.

Based on the EDL source description, local strength at position 'x' on the surface of the myocardium (Sv) can be mapped to potential ϕ generated at location 'y' on the body surface as:

$$\phi(t,y) = \int B(y,x)V_m(t,x)d\omega(y,x) \tag{2}$$

where, $B(y,x)$ is the transfer function expressing the volume conductor model, considering geometry and conductivity in the chest cavity, V_m is the local transmembrane potential at heart surface and $d\omega(y,x)$ is the solid angle subtended at y by the surface element $dS(x)$ of the myocardial node Sv. Volume conductor model as expressed in (2) cannot be solved analytically due to complex assymetrical shape of individual compartments, rather, it is solved numerically, using a specialized Boundary element method (BEM) algorithm. Potential at discretized body surface consisting of 'l' lead position are expressed as:

$$\phi(t,l) = \sum_n B(l,n)S(t;\delta,\rho) \tag{3}$$

where B is a transfer matrix, incorporating the solid angles subtended by source elements as viewed from the nodes of the triangulated surface. Elements of matrix B express the source strengths of all 'n'(n=1500) nodes on the heart as potentials at 'l'(l=256) lead positions on the torso surface. The resulting matrix 'ϕ 'generates the body surface potential, a subset of which is the standard 12 lead ECG and single lead ECG configuration. The generated single lead ECG (Fig.1) serves as the driving signal to the hemodynamic block.

B. Hemodynamic model with baroreflex control

Hemodynamic model consists of a four chambered heart with systemic and pulmonic circulation along baroreflex autoregulation as shown in Fig.2. The pumping of the heart is triggered through an autonomous contractility function, derived from the EP block. Heart chambers have been modeled as compliant vessels. Vasculature of major vessels have been modeled as a combination of resistive and capacitive tube. All the major heart valves have been modeled to work in synchronized manner corresponding to depolarizatrion and repolarization of the heart chambers, thereby bringing the pulsatile effect with pressure gradient generation and volumetric

change in blood flow. Detail description of this model can be found in [13].

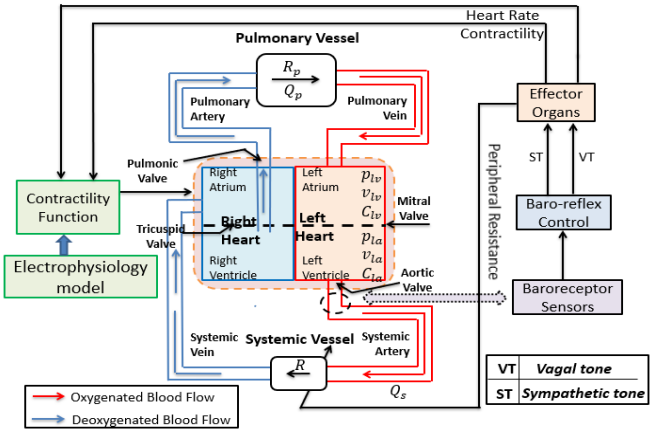


Fig. 2: Schematic of the hemodynamic module

Coupling of EP and hemodynamics block is through a contractility function, which in turn determines the compliance of auricles and ventricle and bring about the pumping action of the heart. Single lead ECG is decomposed to its characteristic constituents like PQ (auricular depolarization), QRS (ventricular depolarization) and ST duration (ventricular repolarization), ST morphology and R-R interval (Fig.1). Ischemic effect is largely defined by morphological changes in ST segments. These changes are encoded to modulate compliance function and timing information to control synchronized operation of four heart chambers. Compliance function for auricle is modeled as:

$$C_{la}(t) = C_{min,la} + 0.5(C_{max,la} - C_{max,la})A_{la}(t - D) \quad (4)$$

where $C_{min,la}$, $C_{max,la}$ are the minimum and maximum compliances in the left-atrium, D is the time-delay in firing between auricle and ventricle and A_{la} is the activation function for the left-atrium, defined as [14]:

$$A_{la} = \begin{cases} 0 & 0 \le t < T_a \\ 1 - \cos\left(2\pi \frac{t - T_a}{T - T_a}\right) & T_a \le t < T \end{cases} \quad (5)$$

where, T_a is the activation time for the left-atrium (analogous to PQ interval) and T defines the duration of a cardiac cycle.

Compliance function of the left-ventricle:

$$C_{lv}(t) = C_{es,lv} \times A_{lv}(t) \quad (6)$$

where $C_{es,lv}$ is the end-systolic compliance and A_{lv} is the activation function for the left-ventricle defined as:

$$A_{lv} = \begin{cases} \frac{1-\cos((t/T_s)\pi}{2} & 0 \le t < T_s \\ \frac{1-\cos((t-T_s)/(T_d-T_s)\pi}{2} & T_s \le t < T_d \\ 0 & T_d \le t < T \end{cases} \quad (7)$$

T_s, T_d are the systolic and diastolic time duration of a cardiac cycle analogous to QRS and ST duration in ECG template.

Cardiovascular system dynamics can be modeled mainly through variables like pressure variation in systemic artery (p_{sa}), left heart ventricle (p_{lv}) and right heart ventricle (p_{rv}) and are expressed as follows:

$$\dot{p}_{sa} = \frac{1}{c_{sa}} \left[\frac{p_{lv} - p_{sa}}{R_{Ao}} - \frac{p_{sa} - p_{sv}}{R} \right] \quad (8)$$

$$\dot{p}_{lv} = -\frac{\dot{C}_{lv}(t)}{C_{lv}(t)} p_{lv} + \frac{1}{C_{lv}(t)} \left[\frac{p_{pv} - p_{lv}}{R_{Mi}} - \frac{p_{lv} - p_{sa}}{R_{Ao}} \right] \quad (9)$$

$$\dot{p}_{rv} = -\frac{\dot{C}_{rv}(t)}{C_{rv}(t)} p_{rv} + \frac{1}{C_{rv}(t)} \left[\frac{p_{sv} - p_{rv}}{R_{Tr}} - \frac{p_{rv} - p_{pa}}{R_{Pu}} \right] \quad (10)$$

where, c_{sa} is the compliance of systemic artery, $C_{lv}(t)$, $C_{rv}(t)$ are left and right heart chamber compliance, R is the resistances in the systemic vessels, R_{Ao}, R_{Mi}, R_{Tr}, R_{Pu} are the aortic, mitral, tricuspid and pulmonary valve resistance.

From the hemodynamic model, parameters like arterial blood pressure, complete dynamics of left ventricle, like end systolic and diastolic volume (ESV, EDV), ejection fraction (EF), cardiac output (CO), stroke volume (SV), end systolic and end diastolic pressure volume ratio (ESPVR, EDPVR) can be calculated which reveals concise information related to the state of heart and cardiovascular system [15]. Apart from the common hemodynamic variables, photoplethesmogram (PPG) signal is also estimated through mathematical modeling on arterial pressure signal.

C. Simulating Ischemia

Cases of transmural myocardial ischemia have been simulated as an occlusion in the left anterior descending artery (LAD), effecting apical anterior and anterio-septal area of heart. Cellular etiology of ischemia suggests variational effects in ionic concentration at cell level which manifests itself in the form of action potential or TMP on the cardiac surface [16]. Specifically, the pathophysiology of ischemic effect can be simulated by inducing the following conditions:

- Reduction of action potential amplitude corresponding to reduction in strength of effected area of myocardium
- Reduction in repolarization time, linked to imbalance in Ca++ pump due to excessive extracellular K+ion
- Decrease in propagation velocity in the effected tissue due to scar formation

These changes were incorporated in the EP block, by changing specific parameters of TMP, like changing the repolarization time, maximum amplitude, depolarization time etc. in and around the area of LAD. Effected ischemic regions were modeled as 'scar tissues', dimension of these scar tissue were varied with disease progression. Healthy condition (no scar tissue, normal BSP and ECG) was simulated along with three cases of ischemia, naming 'moderate', 'severe' and 'silent'. Moderate ischemia case has been simulated as a scar tissue of 30 mm size with velocity reduction of 50% in the effected area, with 20% reduction in TMP amplitude and repolarization time. Severe case has been modeled as a scar tissue of 40 mm size with velocity reduction of 50% in the effected area and 35% reduction in TMP amplitude and repolarization time.

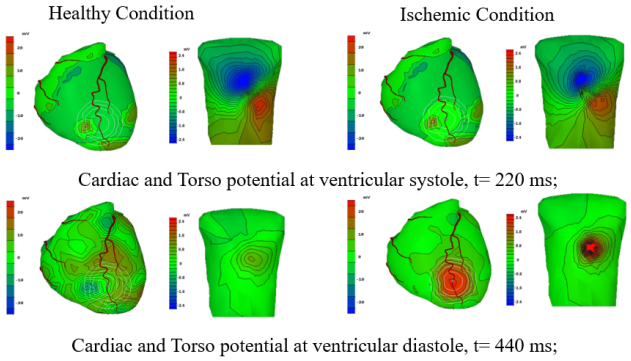


Fig. 3: Cardiac and BSP for healthy and ischemic heart at ventricular systole and diastole

The term 'moderate' and 'severe' are representative cases to understand the ischemic behaviour, these terms itself are not calibrated with medical definition and standard. Silent ischemia is a special case where pathological manifestation happens only during stress or exercise conditions. Modeling includes scar tissue of 15 mm size with velocity reduction of 50% in the effected area and 12% reduction in TMP amplitude and repolarization time.

Forward EP pipeline computes ECG template for all the cases under consideration and thereafter fed to hemodynamic platform to generate the hemodynamic parameters. Fig.3 shows healthy vs. ischemic cardiac potential and BSP as simulated in the electrophysiology module. Two seperate instances representing ventricular depolarization (at 220 ms, roughly during the time of QRS complex generation) and repolarization (at 440 ms, during ST segment of ECG). As indicated from the figure, ischemic BSP varies significantly during the repolarization phase which gets reflected in the ECG [17].

III. Result and Discussion

A. Ischemic behavior reflection in simulated ECG and Hemodynamic Parameters

Simulated ECG for healthy, moderate and severe ischemia are shown in Fig.4a. As evident from the figure, simulated ECG captures large changes in the ST segment, correlated with ventricular repolarization phase. It is well accepted in medical literature that transmural ischemia results in elevated ST segments, often with 'Q' wave inversion [3]. Change in ST segment refers to a generic weakness in the myocardium around the effected area and the effect magnifies with increase in size of scar tissue. This weakness in turn effects the pump function, resulting in altered left ventricle pressure-volume (PV) dynamics as shown in Fig.4b. The PV loop of the moderate and severe ischemia in comparison to healthy PV, shows reduction in cardiac output and ejection fraction and a general trend of systolic dysfunction, commonly related with ischemia. Simulated PPG, shown in Fig.4c also reveals interesting insights on ischemic property. There is a reduction in PPG signal amplitude in both systolic and diastolic phases, related with the decreasing stroke volume of heart as ischemia progresses. This is particularly interesting because PPG sensors are noninvasive sensors implemented in many smart phones and commercially available wearbles. Morphological changes seen in this signals, correlated with ischemic behavior can aid in early screening of ischemic cases.

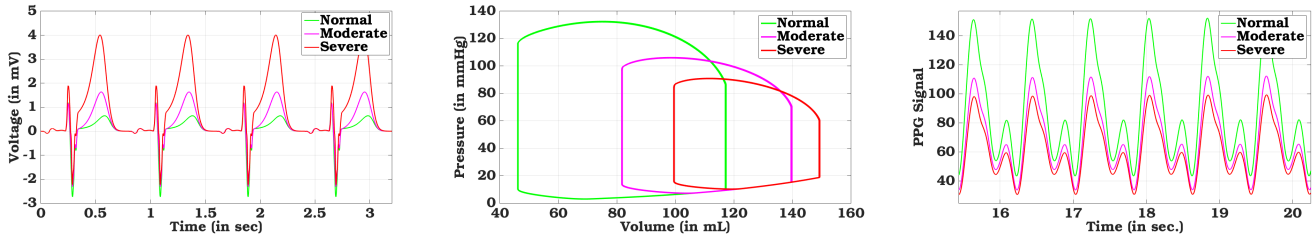
B. Silent ischemia

Ischemia is generally associated with chest pain and pathological changes in ST segment in ECG, which are easy symptoms for diagnosis. However, ischemic episodes are asymptomatic or silent in as many as 80% of cases [18], where there are no associated symptom manifestation in during daily ambulatory activity, but results in maximum cases of sudden cardiac death due to lack of manifestation at diagnosis. Silent ischemia can only be detected under stress testing, where the hidden disease conditions gets reflected in the ECG morphology. Fig.5a shows the simulated ischemic ECG under normal (unstressed) and stress testing. Stress scenario is simulated with an increased heart rate, as evident during exercise or stress condition. As seen from the figure, ECG during normal condition is similar to the healthy template, irrespective of small scar area simulation. As the heart rate is increased, ECG morphology changes from normal to pathological. Similar observations are made in PV loop dynamics and PPG generation (Fig.5 b,c), where unstressed condition replicates normal behavior, whereas under stress, EF decreases significantly.

Table 1 tabulates different simulated cases with the derived hemodynamic parameters. As evident from the table, as ischemic behavior magnifies, there are detectable changes in EF, SV, CO, ESPVR which correlates with ventricular muscle stiffness and EDPVR correlating with contractility [19]. Healthy, moderate, severe and silent ischemic condition (unstressed) are simulated at heart rate of 75 beats/min. For silent ischemia stressed condition, ECG was simulated at heart rate of 92 beats/min. Blood pressure of the silent ischemia case under stressed condition reveals a lower diastolic range compared to unstressed, which is another indication of electrical conduction disorder in myocardium.

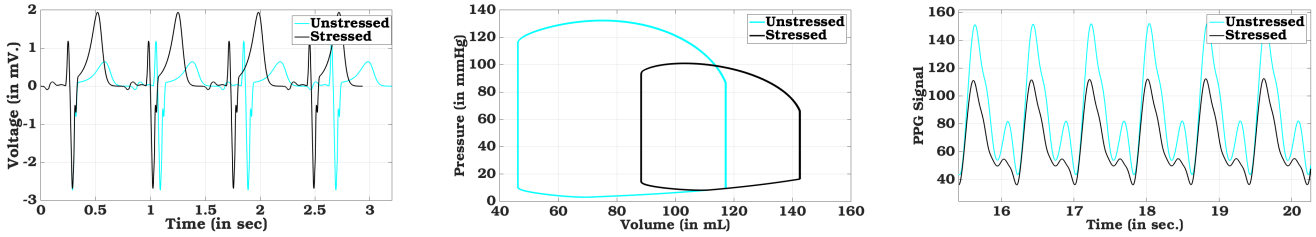
IV. Conclusion

In this paper, we propose an in-silico cardiac model to capture EP changes that occur in heart dynamics during myocardial ischemia. Underlying EP changes are coupled with a hemodynamic model of cardiovascular system to get a complete understanding of the disease progression and its manifestation not only at the electric conduction level but also at the mechanical functioning of heart. Developed in silico model can be used to understand the disease etymology and can help in computing 'what if analysis' that could aid as an educational guide. Reflection of changes in electric parameters over hemodynamic variables like ejection fraction aids in a holistic understanding of the disease progression and analysis. Developed in-silico platform to understand and replicate the effect of ischemia can also be used for applications like



(a) (b) (c)

Fig. 4: Healthy, moderate and severe template a) Simulated ECG; b) Left ventricle PV loop, c) Simulated PPG



(a) (b) (c)

Fig. 5: Silent ischemia simulation under unstressed and stressed condition a) Simulated ECG; b) Left ventricle PV loop, c) Simulated PPG

TABLE I: Cardiac parameters for various simulated cases

Condition	Heart rate (beats/min)	BP (mm of Hg)	ESV (ml)	EDV (ml)	ESPVR	EDPVR	EF	SV(ml)	CO (l/min)
Healthy	75	125/85	46.13	117.1	2.52	0.16	0.606	70.97	5.25
Moderate Ischemia	75	105/70	81.72	139.6	1.20	0.26	0.414	57.88	4.34
Severe Ischemia	75	90/60	99.49	149.3	0.86	0.36	0.33	49.81	3.73
Silent Ischemia (unstressed)	75	125/85	46.2	117.3	2.52	0.15	0.606	71.1	5.73
Silent Ischemia (stressed)	92	100/65	88.37	142.6	1.07	0.29	0.38	54.23	4.96

synthetic data generation (ECG and PPG) for disease classification, pertaining to Coronary artery disease and improving machine learning algorithm, generate personalized model for patient care continuum or as a guidance platform to plan defibrillator placement and predict outcome of such procedures.

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