Computational Analysis of the effect V241F KCNQ1 Mutation on Cardiac Ventricular Mechanical Responses: Simulation Method.

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Abstract
Several studies have found genetic mutations, which affect characteristics of specific ion channels and cause cardiac arrhythmia such as atrial and ventricular fibrillation [1]. Study about understanding the genetic predisposition, modeling cardiac tissue to apply on simulation study, and how genetic mutation influence the Atrial and Ventricular Fibrillation challenge the researcher to solve it. To construct a computational model of a cardiovascular system, we used 3D finite element model of a failing human ventricle, combined with a lumped model of the circulatory system [12]. In a 3D cardiac tissue CAD electromechanical model, we analyze the propagation wave in 2 conditions, normal sinus rhythm and reentry. During normal sinus pacing, the electrical stimulation applied from Purkinje fibers tissue. In our research, we investigate the effect of V241F mutation in canine ventricular in failure state using the computational method. This is the first study to implement a finite element of an image based on the electromechanical model for the heart, to investigate cardiac electrophysiology and mechanics for *V241F* mutation. The mutation V241F effected the mechanical behavior according to electrical as an input. In a single cell, V241F with pure mutation shortened the ventricular APD around 67% and 33% for intermediate variant mutation.

Keywords: Finite Element Model (FEM), Mechanical simulation, Cardiovascular

1. Introduction

Several studies have found genetic mutations, which affect characteristics of specific ion channels and cause cardiac arrhythmia such as atrial and ventricular fibrillation [1]). Study about understanding the genetic predisposition, modeling cardiac tissue into Computer Aided Engineering (CAE) to apply on simulation study, and how genetic mutation influence the Atrial and Ventricular Fibrillation challenge the researcher to solve it. The recent study that has the important role for the cause of atrial and ventricular fibrillation is the mutation in the KCNQ1 potassium channel. KCNQ1 is the α-subunit of the voltage-gated potassium channel, encoded by the KCNQ1[2]. In the cardiac cell, KCNQ1 assembles with KCNE1 (β-subunit) and forms a channel complex constituting the delayed rectifier potassium current (I_{ks}) [3]. I_{ks} plays an important role in repolarization and termination of a cardiac action potential (AP). Mutation in KCNQ1 can lead to dysfunction of I_{ks} channel in the cardiac cell. Mutation can be classified as their impact on protect function, a gain of function and loss of function[4].

There are several gain function of I_{ks} in KCNQ1 were found and associated with AF, such as S140G, V141M, S209P, 147R, R231C, and R231H [5]. Even many mutations of KCNQ1 correlated with AF. The mechanism of mutation itself still poorly understood. There is a study from [6] with the KCNQ1 mutation that has a correlation with AF was found. V241F is the study that gains of function mutation in the S4 transmembrane domain of KCNQ1 and becomes important voltage sensor for I_{ks} channel. [6] determined that V241F KCNQ1 mutation makes increment I_{ks} with experimental study.

The purpose of this study is to predict and design the electrical and mechanical behavior under V241F mutation using computational methods and Computer Aided Design (CAD) modeling. This study simulated the heart model in form of single cell tissue and 3D CAD by using advanced electromechanical model. We analyze two phenomena of electrical activation. First, the mutation during normal sinus rhythm, and second during reentrant condition that makes scroll wave in 3D ventricular failing heart model. We identified the electromechanical behavior including the action potential duration (APD), the wavelength of reentrant scroll wave, ATP consumption rate, stroke volume (SV), stroke work (SW), left ventricular (LV) pressure, and ejection fraction (EF) under those two conditions.

2. Research Methodology

2.1 Description of Cardiac 3D tissue CAD modeling

To construct a computational model of a cardiovascular system, we used an existing 3D finite element model of a failing human ventricle, developed in earlier studies [8-11], combined with a lumped model of the circulatory system [12]. The electromechanical model consists of two components, electrical and mechanical, into which the membrane kinetics are incorporated. The model is reconstructed by ventricular geometry based on magnetic resonance (MR) and diffusion tensor magnetic resonance (DTMR) imaging of the heart [11]. displays the whole schematic electromechanical model of both the electrical and mechanical components, as well as their coupling.

2.1. Description of Electrical Mechanical Model

eIn this study, we used failed canine ventricles electromechanical model with limited element combined with the lumped-parameter model. The electromechanical model in here consists of electrical and mechanical properties that coupled by intracellular calcium *(Ca^{2+})* transient. The cell model we incorporated in our model was following [6] model human ventricle tissue. The cell membrane is represented as a capacitor that connected with the resistances which mean the cell model itself. The electrophysiological behavior of this action can be described as this following differential equation from [7]:

$$C_m \frac{dV_m}{dt} = -(I_{stim} + I_{ion})$$

Where V is voltage, t is time, I_{ion} is the sum of all transmembrane ionic currents, I_{stim} is current external stimulus, and C_m is the cell capacitance per unit surface area. The total ionic current I_{ion} was represented by :

$$I_{ion} = I_{Na} + I_{K1} + I_{to} + I_{Kr} + I_{Ks} + I_{CaL} + I_{NaCa} + I_{NaK} + I_{pCa} + I_{Na} + I_{pK} + I_{bCa} + I_{bNa}$$

Where in this equation I_{NaCa} is Na^+-Ca^{2+} exchanger current, I_{NaK} is Na^+-K^+ pump current, I_{pCa} is Ca^{2+} pump current, I_{bNa} and I_{bCa} are background Ca^{2+} and Na^+ current. According to our model with the 3D spatial model, to represent the electrical propagation phenomenon can be described with this partial differential equation:

$$\frac{dV}{dt} = -\frac{I_{ion}+I_{stim}}{C_m} + \frac{1}{\rho xSxCm}\frac{\partial^2 V}{\partial x^2} + \frac{1}{\rho ySyCm}\frac{\partial^2 V}{\partial y^2} + \frac{1}{\rho zSzCm}\frac{\partial^2 V}{\partial z^2}$$

where V is the voltage difference, t is time, I is current, I_{ion} is the ionic current and I_{stim} is stimulus current, C_m is capacitance per unit of surface area, ρ is the cellular resistivity with respect to the x, y, and z directions, and S is surface to volume ratio with respect to the x, y, and z directions.

2.3. Simulation Protocol

In this study, we used to fail canine heart ventricle homogenous (endocardium cell) and heterogeneous (contain endocardium, M-cell, and epicardium). For single cell simulation, we used a standard of S1-S2 protocol. Single cell action potential (AP) was computed by applied condition the cell model 30 times at 1s of basic cycle length (BCL). After 30 stimulations were applied at this BCL, we try to obtain the APD_{90} from the last AP. APD_{90} was defined as the time duration between the AP upstroke and 90% repolarization.

In a 3D cardiac tissue CAD electromechanical model, we analyze the propagation wave in 2 conditions, normal sinus rhythm and reentry. During normal sinus pacing, the electrical stimulation applied from Purkinje fibers tissue. The Purkinje fibers integrated with endocardial of a ventricle. In our study, we set the parameter of sinus pacing condition with normal conduction velocity (CV) for wild type (WT) and V241F mutation. Even though the parameter set in the same CV, we can see the effect of V241F mutation to the time of propagation wave electrical result.

According to the electrical simulation result of sinus pacing, we obtained the electrical activation time (EAT), electrical de-activation time (EDT), and calcium information of sinus pacing. From the result of EDT, we can see which condition from WT and V241F mutation that depolarization faster. In the mechanical simulation, we put the calcium information as input in order to see the mechanical responses of pumping ventricle that induced by calcium. After that, we can see overall electromechanical result during WT and V241F mutation.

After we got the result from the electrical simulation of sinus pacing, we take the 10s Ca^{2+} transient data as the input of mechanical simulation. For sinus pacing case, we took only the last cycle to see the mechanical behavior of the ventricular. We can measure the stroke work (SV), stroke work (SW), Ejection Fraction (EF), and the ATP consumption rate of the heart ventricle.

Beside the sinus pacing case, there is reentry case with a different process. First, we set the parameter of three cases WT, V241F intermediate mutation and pure mutation with the same d-scale and same Conduction Velocity (CV). The CV of these cases is 61 cm/s. Even though the CV set with the same parameter, the electrical of each condition cannot be the same. During reentry condition, the electrical triggered from the apex on the bottom of the ventricle. Reentry wave in the electrical 3D model was initiated using the S1-S2 protocol to induce the reentry. First, the S1 stimulus was applied producing planar wave-front propagating in one direction. When the refractory tail of wave cross through the middle of ventricle epicardium wall, a second S2 stimulus was applied in the middle of the

medium, parallel with the S11 wave but only over three-quarters of the medium to produce a spiral wave. After that to make the condition instability reentry, half of the depolarized domain reset to the initial condition.

Next, from the result of an electrical simulation, we take the last 10 second of Ca^{2+} transient data when reentry condition steady appeared. We used Ca^{2+} as the input for the mechanical simulation. After we got the mechanical simulation result, we can analyze the ventricular mechanical responses during reentries such as pressure, volume, and contractile of ATP consumption rate.

3. Discussion

In our research, we investigate the effect of *KCNQ1* V241F mutation in canine ventricular in failure state using the computational method. This is the first study to implement a finite element of an image based on the electromechanical model for the heart, to investigate cardiac electrophysiology and mechanics for *KCNQ1 V241F* mutation. The major findings of our research are as follows:

1. In single cell simulation that applied to 3 types of cellular model (endo, M-cell, epi), KCNQ1 V241F mutation increased the I_{ks} density. While the APD shortened when mutation of V241F applied. Especially the pure mutation has the shortest APD restitution curves compared to intermediate V241F and WT condition.
2. According to 3D ventricular model, during sinus pacing of V241F pure mutation accelerate repolarization fastest compare to intermediate mutation and WT. While the EAT in the same time because the depolarization of variant mutations have no different. The EDT of pure mutation shortest compares to other mutation because the repolarization of pure mutation ends fast.
3. During reentry case, pure mutation of V241F condition generates the shortest wavelength of membrane potential propagation compare to intermediate mutation and WT.
4. Pure mutation o*KCNQ1* V241F has the lowest performance of stroke volume, stroke work, and ejection fraction. That makes the mechanical behavior during reentry have the low pressure of LV, low ATP consumption rate, and make the blood volume inside LV still high.

In our research, *KCNQ1* V241F pure mutation induced the highest increment of $I_{ks.}$ I_{ks} plays an important role in repolarization and termination of Action Potential. The increment of I_{ks} generates early repolarization of AP that make shortened APD. Short APD in V241F KCNQ1 mutation is thought as the cause of short wavelength and persistent spiral wave in the limited size of 3D tissue model. For 3D failure canine ventricular tissue during sinus pacing, the fastest repolarization happened during V241F pure mutation condition. The faster repolarization applied to heart ventricle, it makes the ventricle have less strength to contraction.

During reentry condition, the shortened APD can make the wave length shorter and frequent of Action Potential increase. The APD during V241F mutation shorter then WT. Especially the pure mutation of V241F has the shortest APD. It aligned with the snapshot of electrical simulation wave length that pure mutation of V41F has the shortest wavelength.

To predict the mechanical behavior of KCNQ1 V241F mutation, we computed the hemodynamics responses to see the pressure waveform of the ventricle, volume waveform, Pressure-Volume (PV) curve, SV, EF, SW and ATP consumption rate. Our result shows that the V241F mutation effect decreased the LV pressure and the ATP consumption rate during reentry. Because the pressure of LV to low it makes the ventricle doesn't have much strength to pump the blood out of the ventricle. This condition makes the volume of blood inside ventricle still much exist. V241F pure mutation has the highest value of blood volume because of the pressure of LV the weakest one. The relation of pressure and volume wave form of LV can be seen with PV curve, pure mutation of V241F produced the smallest loop during reentry condition. This indicates the ventricle contractility was decreased with the mutation. Because of that, the ventricle cannot pump enough blood and make the ATP consumption rate of pure mutation has the lowest value. The results are aligned with sinus pacing condition. As the result, the SV, SW, EF and ATP consumption rate during sinus pacing of Pure mutation V241F has the lowest value.

4. Conclusion

For the conclusion of our study, by using a computational model of the canine heart failure 3D CAD model, the mutation in subdomain KCNQ1 with two variant mutations of V241F intermediate and pure effected the mechanical behavior according to electrical as an input. In a single cell, V241F with pure mutation shortened the ventricular

Action Potential Duration around 67% and 33% for intermediate variant mutation. In mechanical responses, V241F mutation decreased the ejection fraction, stroke volume, and stroke work. Because of that, the ATP consumption rate for mutation condition needs to be increased for contraction of the ventricular model.

References:

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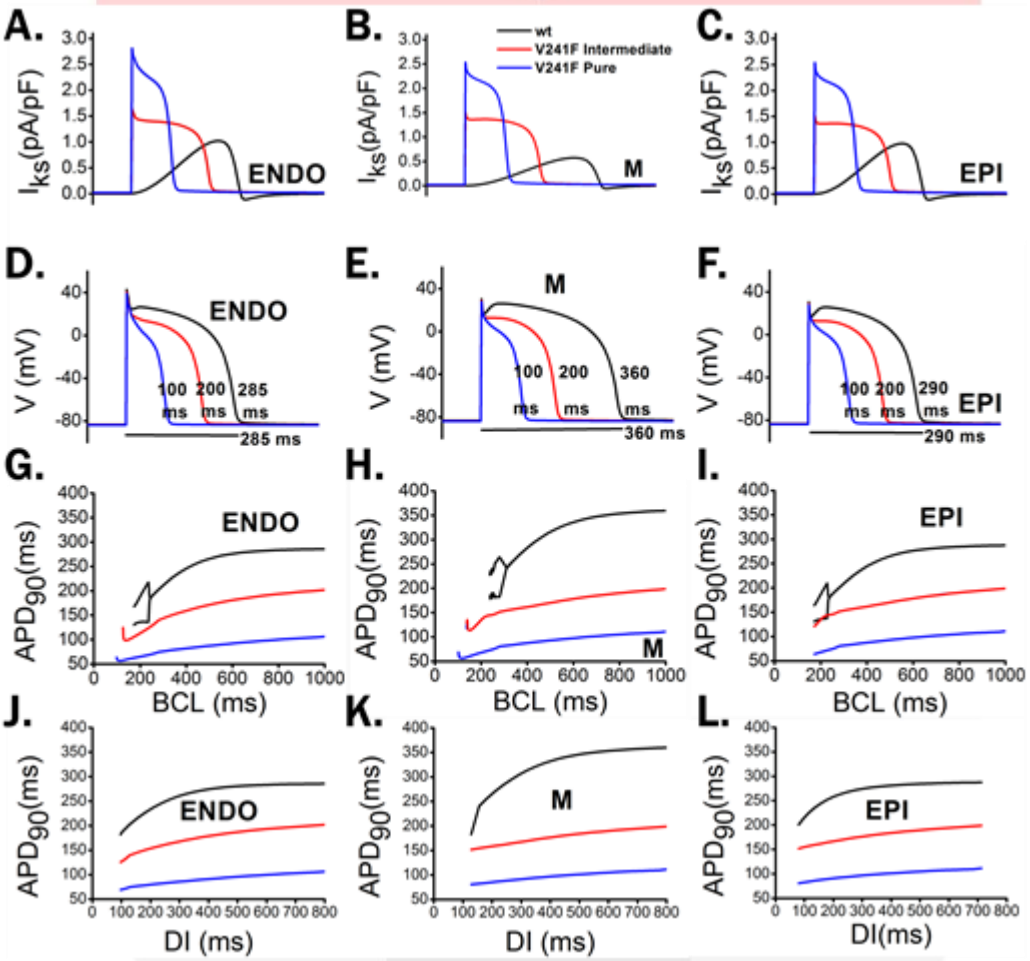
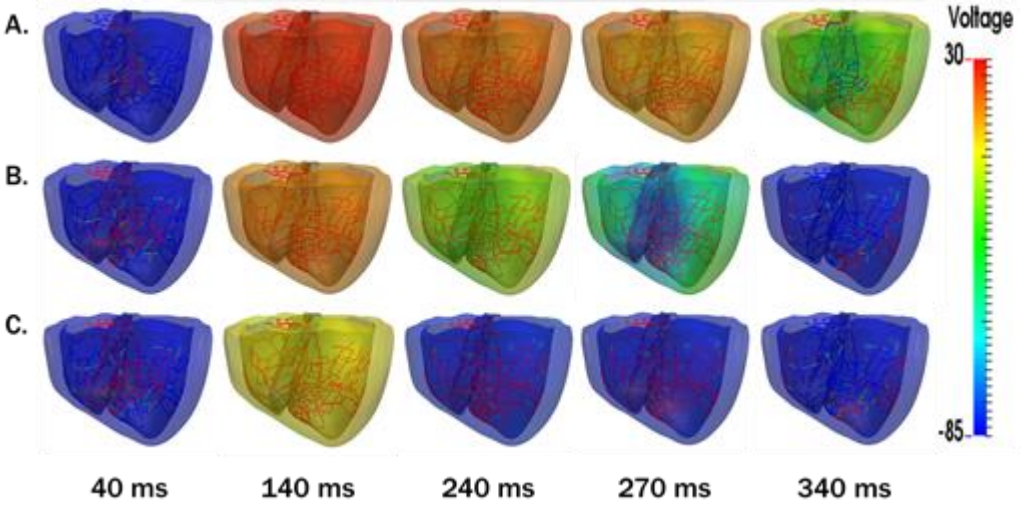
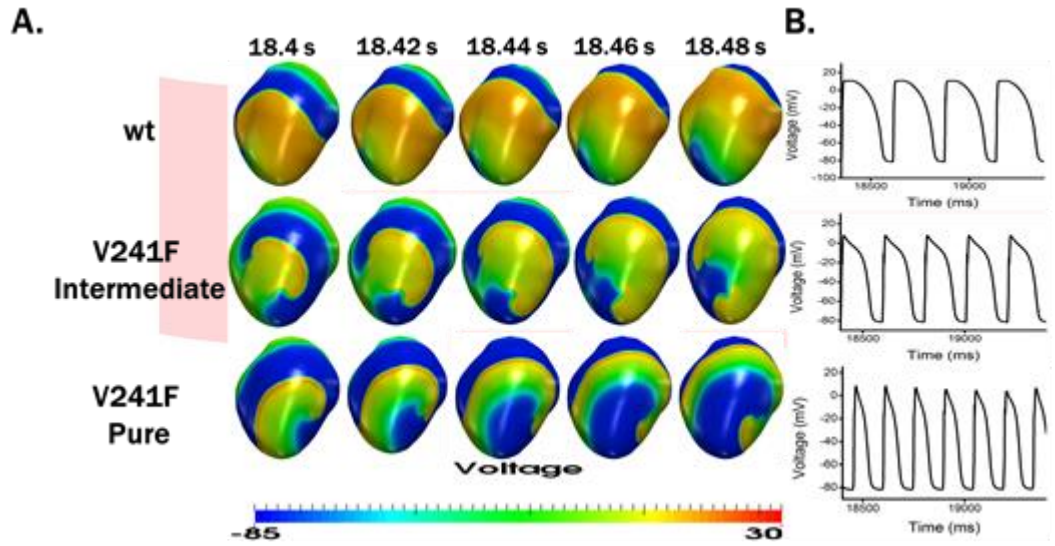
Appendix A
[Electro Mechanical Result]

1) Single Cell Result

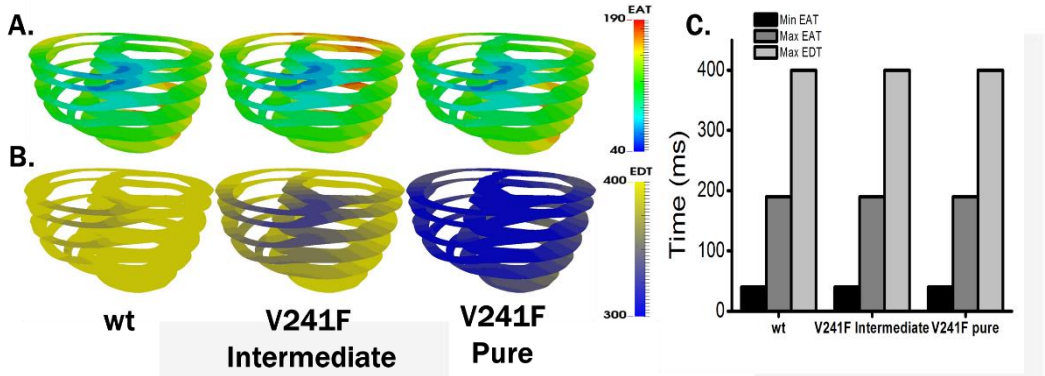


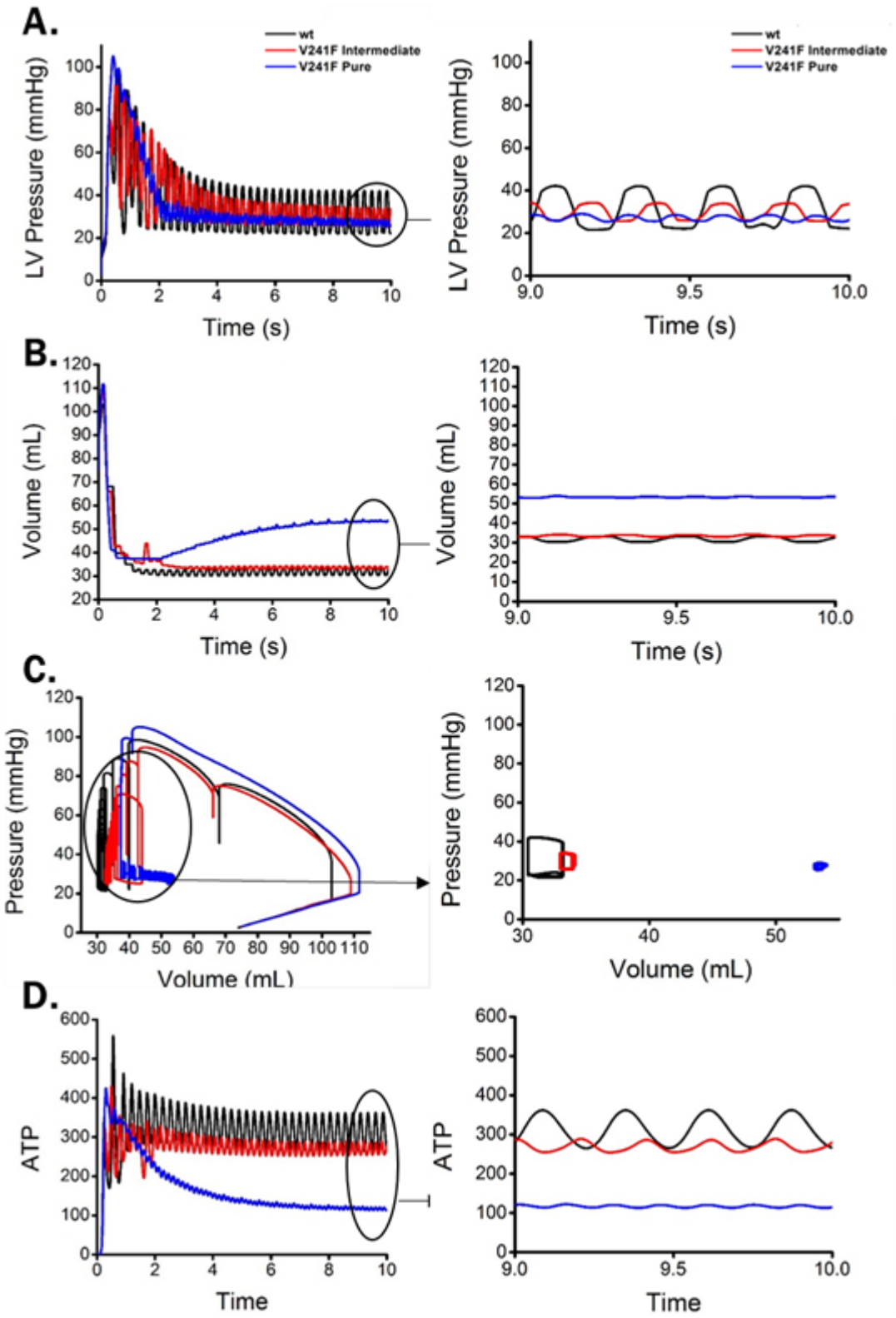
2) 3D Electromechanical result




A.
18.4 s
18.42 s
18.44 s
18.46 s
18.48 s
wt
V241F Intermediate
V241F Pure
Voltage
-85
30
B.
Voltage (mV)
Time (ms)

SS


A.
B.
EAT
190
40
EDT
400
300
wt
V241F Intermediate
V241F Pure
C.
Min EAT
Max EAT
Max EDT
Time (ms)
400
300
200
100
0
wt
V241F Intermediate
V241F pure



Variant Type	Stroke Volume (mL)	Stroke Work (mmHg ml)	Ejection Fraction (%)	ATP consumption rate (s^{-1})
wt	50.69	44.95601	60.5%	168.7896

V241F Intermediate	28.52	28.68837 X 10^{-2}	27.78%	168.7531
V241F Pure	28.4722	28.66935 X 10^{-2}	27.73%	130.95055

v