International Journal of Engineering

Journal Homepage: www.ije.ir

In Silico Analysis of Stem Cells Mechanical Stimulations for Mechnoregulation Toward Cardiomyocytes

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PAPER INFO

Paper history:
Received 10 January 2022
Received in revised form 03 August 2022
Accepted 01 September 2022

Keywords:
Cardiac Tissue Engineering
Pulsatile Flow
Cyclic Strain
Stress Phase Angle
Shear Stress

ABSTRACT

Because of the ability of stem cells to self-renew and differentiate into cardiomyocytes, they are optimal cell sources for cardiac tissue engineering. Since heart cells experience cyclic strain and pulsatile flow in vivo, these mechanical stimuli are essential factors for stem cell differentiation. This study aimed to investigate the effect of a combination of pulsatile flow and cyclic strain on the shear stress created on the embryonic stem cell layer with a elastic property in a perfusion bioreactor by using the fluid-solid interaction (FSI) method. In this study, the frequency and stress phase angle had been assumed as a variable. The results show that the maximum shear stress at frequencies of 0.33, and 1 Hz and with frequency differences in cyclic strain (0.33 Hz) and pulsatile flow (1 Hz) are 0.00562, 0.02, and 0.01 dyn/cm², respectively. Moreover, in the stress phase angles 0, $\pi/4$, and $\pi/2$, the maximum shear stress are equal to 0.00562, 0.009, and 0.014 dyn/cm², respectively. The results of this study can be an effective step in developing cardiac tissue engineering and a better understanding of the effects of mechanical stimuli on stem cell differentiation.

***doi**: 10.5829/ije.2022.35.11b.18*

1. INTRODUCTION

Heart failure is the leading cause of mortality globally, and the methods of diagnosing this disease still have many shortcomings [1]. When blood flow to the heart muscle is abruptly interrupted, a heart attack occurs that leads to causes immutable myocardial ischemia, formation of a non-contractile scar, and loss of cardiac muscle cells (cardiomyocytes). Currently, surgical interventions for the treatment of heart disease have limitations such as heart donor shortage, the need to take immunosuppressant drugs after transplantation, and limited strength of transplanted organs [2]. Also, since adult mammalian heart muscle cell proliferation rapidly ceases after birth, this tissue has a limited ability to regenerate itself [3]. Therefore, cardiac tissue engineering offers new solutions to overcome these limitations using combinations of cells with regenerative capacity, scaffolds, growth factors, and mechanical and/or electrical stimuli [4]. In general, different types of stem cells are used in regenerative medicine for cardiovascular diseases including Bone marrow-derived mononuclear cells (MNCs), Mesenchymal stromal/stem cells (MSCs), Cardiac Stem Cells (CSCs), Embryonic stem cells (ESCs), and Induced pluripotent stem cells (iPSCs) [5]. Scaffolds or membranes used in cardiac tissue engineering are suitable substrates for controlled secretion of growth factors and replacement for some damaged extracellular matrices after myocardial infarction. [6]. To have successful cardiac tissue engineering, the use of bioreactors to mimic the native microenvironment of cardiomyocytes, accompanied by electrical and mechanical stimuli such as strain, pressure, and fluid flow, can be beneficial [7]. Cells sense a mechanical environment primarily through the integrin-mediated focal adhesion and actin cytoskeleton tension, which interact with external biophysical stimuli to evoke downstream signaling (mechanotransductive signaling) [8]. It has been demonstrated that fluid shear stress plays an essential role in embryonic development and organogenesis [9]. Cardiomyocytes or contractile cells are under cyclic strain and pulsatile flow due to the heart

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Please cite this article as: M. Ebad, B. Vahidi, In Silico Analysis of Stem Cells Mechanical Stimulations for Mechnoregulation Toward Cardiomyocytes, ***International Journal of Engineering, Transactions B: Applications***, Vol. 35, No. 11, (2022) 2229-2237

being full and empty in-vivo [10]. These mechanical stimuli play a key role in differentiating stem cells, regulating cardiac tissue function, increasing gene expression, and homeostasis [2]. Therefore, it would be of great value to evaluate the effects of different mechanical stimuli on the differentiation of stem cells into cardiomyocytes. In the study by Mihic et al., by applying a single-axis cyclic stretch at a frequency of 1.25 Hz for 72h to embryonic stem cells, the length of cell and gap junction expression was increased [11]. In 2011, Tulloch et al. [12] stated that cells that are exposed to uniform cyclic stretching at 1 Hz for four days experienced an increase in cardiomyocyte elongation with sarcomere alignment. In another study, when the neonatal cardiac cellular constructs were exposed to pulsatile flow in a perfusion bioreactor for 24h, it significantly synthesized high levels of contractile protein and cell-cell adhesion [13]. In the study of Shen et al. [14] embryonic stem cells underwent a 1.48 mL/minute pulsatile flow rate and a 5% cyclic strain at the frequency of 0.33 Hz differentiated into cardiac cells at a shear stress of 5.6×10^{-3} dyn/cm². Since most of the investigations performed on this subject have been studied experimentally [10, 15], we decided to study the effect of the frequency and stress phase angle (the phase difference between stress and strain) of mechanical stimuli (cyclic strain and pulsatile flow) on the maximum shear stress created on embryonic stem cell layer using finite element method.

2. MATERIALS AND METHODS

Finite element method was used in this study to simulate the problem. This method has various applications in different fields [16-18], as it can help us evaluate the effects of different parameters simultaneously and reduce the cost and time of our engineering investigations. In this computational analysis, the geometry of the problem is a 3D model of a cell-bioreactor complex that consists of a cell layer, membrane, silicon layer, and bioreactor (Figure 1). Using the two-way FSI analysis in COMSOL software, the combination of mechanical parameters of 1.48 mL/minute pulsatile flow and 5% cyclic strain was considered [14]. The inlet boundary conditions on the left and bottom of the bioreactor are 1.48 mL/minute pulsatile flow rate (water) and 5% cyclic strain (air), respectively. The fluid (water) was considered Newtonian, viscous, and incompressible with a viscosity of 8.1e-4 (Pa.s), and a density of 1000 kg/m^3. Also, Air pressure, Dynamic viscosity, and density of air were 1.35 atm, 2e-5 (Pa.s), and 1.225 kg/m^3, respectively [14, 19]. Moreover, the pressure of 0 Pa was considered as the outlet boundary condition [20]. The non-slip condition was applied to all the walls. It is assumed that all boundaries were fixed. The mechanical properties considered for the solid models are summarized in Table 1 [14].

The frequency and stress phase angle had been assumed as a variable. The amount of frequency in this study was

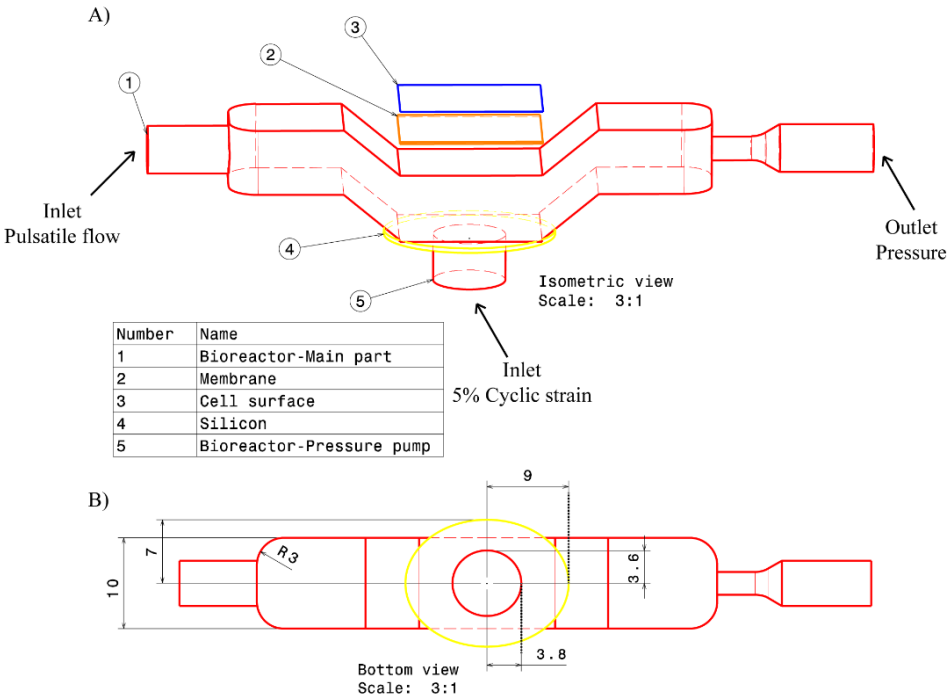

Figure 1. Geometry of bioreactor- stem cell layer complex A) isometric and B) bottom view [14]

TABLE 1. Mechanical properties of solid domain

Solid domain	Elastic modulus (MPa)	Poisson's ratio	Density (kg/m³)
Embryonic stem cell	0.01 [21]	0.45 [21]	1060 [22]
Cell-seeded membrane	0.6 [23]	0.44 [24]	1400 [24]
Silicon membrane	150 [25]	0.49 [25]	1030 [26]

considered 0.33 Hz and 1Hz which are in the physiological range of the body [14, 27]. Besides, To analyze the effect of the stress phase angle, three phases 0, $\pi/4$ and $\pi/2$ were considered (Figure 2a) [28]. Navier–Stokes, pulsatile flow, and cyclic strain equations were used as the governing equations in the problem was noted in equations 1-3, respectively [29-32]:

$$\frac{\partial \rho \boldsymbol{V}}{\partial t} + \nabla \cdot (\rho \boldsymbol{V}\boldsymbol{V} - \tau) = \boldsymbol{f}^{B} \quad (1)$$

$$Q_{(t)} = Q_0 + Q_0 \sin(\omega t + \varphi) \quad \omega = 2 \times \pi \times f \quad (2)$$

$$\varepsilon_{(t)} = \varepsilon_0 \sin(\omega t) \quad (3)$$

wherein Equation (1), ρ is the density, $\boldsymbol{V}$ is the velocity vector, τ is the stress tensor, and $\boldsymbol{f}^{B}$ is the body force vector of the fluid medium. In Equation (3), Q is the flow rate, t is the time, ω is the angular velocity, Q_0 is the flow rate at t =0 which is equal to 1.48 mL/minute, φ is the phase angle, and f is the frequency. In Equation (4), ε_0 is the maximum amplitude of the strain is equal to 5%. Besides, kinematic equilibrium equation and traction equilibrium along the fluid–structure interfaces can be written as follows (Equations (4)-(5)) [33]:

$$\mathbf{u}_{fluid} = \mathbf{u}_w \cdot \mathbf{u}_w = \frac{\partial \boldsymbol{d}_{solid}}{\partial t} \quad (4)$$

$$\sigma.\mathbf{n} = \Gamma.\mathbf{n}\,, \quad \Gamma = [-\mathbf{P}\mathbf{I} + \mu\left(\nabla \mathbf{u}_{fluid} + \left(\nabla \mathbf{u}_{fluid}\right)^{T}\right) - {}^{2}/_{3}\,\mu(\nabla.\mathbf{u}_{fluid})\mathbf{I}] \quad (5)$$

According to Equation (4), this part is related to the coupling of fluid and solid velocities (which is the result of its deformation due to the flow) at the interface between these two domains, and equation 5 is related to the transfer of stress from fluid flow to the solid domain. In applying no-slip boundary conditions at the wall, the coupling conditions at the fluid-solid interface, $\boldsymbol{d}_{solid}$ is the solid displacement, μ is the dynamic viscosity, and $\nabla\ \mathbf{u}_w$ and $\mathbf{u}_{fluid}$ are the wall and fluid velocity, respectively. For this (FSI) physics, to create a computational mesh in the desired model tetrahedral elements were used (Figure 2(b)). To ensure the mesh independence of the solution, the geometry was discretized in five models with different element numbers (116157, 277892, 399663, 532159, and 678932), and the changes in shear stress magnitude were analyzed. However, there was no sensible change in the magnitude of the maximum shear stress with the number of elements beyond 399663. Therefore, this number of elements was used for the five models of this study (Figure 2(c)).

3. RESULTS

In this study, for the first time, using computational simulation, the effect of different mechanical parameters on the shear stress created on the embryonic stem cell layer was investigated. As a result, two parameters of frequency, and stress phase angle were analyzed.

3. 1. Frequency In the first study, the effect of frequency was investigated for three different models. In the first and second models, both pulsatile flow and cyclic strain had an equal frequency of 0.33 Hz, and 1Hz, respectively. Also, for the third model, the pulsatile flow and cyclic strain had a frequency equal to 0.33 Hz and 1 Hz, respectively. The air-fluid pressure fields for the model with different frequencies can be seen in Figure 3a. The maximum shear stress for the first group is 0.00562 (Figure 3(b)), which is very close to the shear stress obtained in the Shen et al. [14] study (0.0056 dyn/cm²). This shear stress is also evenly distributed on the surface of the cell layer during the period [0.65, 0.75, and 0.85 s] (Figure 4(a)) that the center of the cell layer experiences the maximum value of shear stress. When both mechanical stimuli, pulsatile flow, and cyclic strain, are performed at a frequency of 1 Hz, the amount of shear stress on the cell layer roses remarkably to 0.02 dyn/cm² Within the specified time (1.15, 1.25, and 1.35 s), but this magnitude shear stress is not uniformly spread on the surface of the stem cell layer (Figure 4b). In the third model, the difference between the frequencies of the mechanical parameters led to an increase in the maximum shear stress from 0.0056 dyn/cm² to 0.01 dyn/cm² at the specified time (1.15, 1.25, and 1.35 s). However, the maximum shear stress occurs on the left side of the embryonic stem cell layer, where the pulsatile flow was applied (Figure 4(c)).

3. 2. Stress Phase Angle For the second model, Since the effect of the stress phase angle parameter on cardiomyocytes has not been studied to date, in this study, the effect of this parameter on shear stress created on the cell layer was investigated. In the model where there was no phase difference between the mechanical parameters ($\varphi = 0$), the shear stress is equal to 0.00562 dyn/cm², and the whole cell surface was subjected to

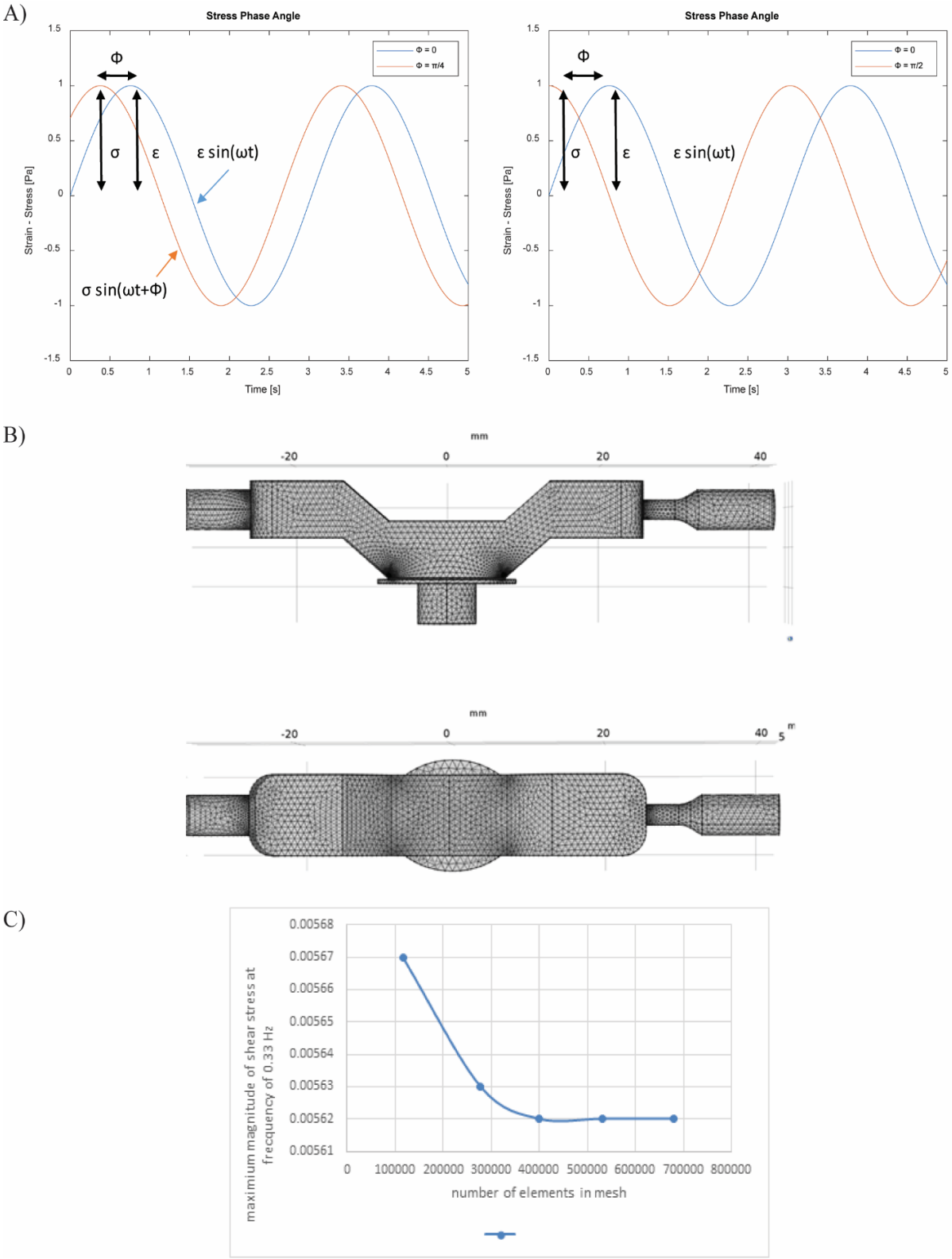

Figure 2. A) Schematic of stress phase angle (left) $\pi/4$ and (right$\pi/2$, B) Tetrahedral mesh of the geometry, C) Plot of mesh independency of the solution

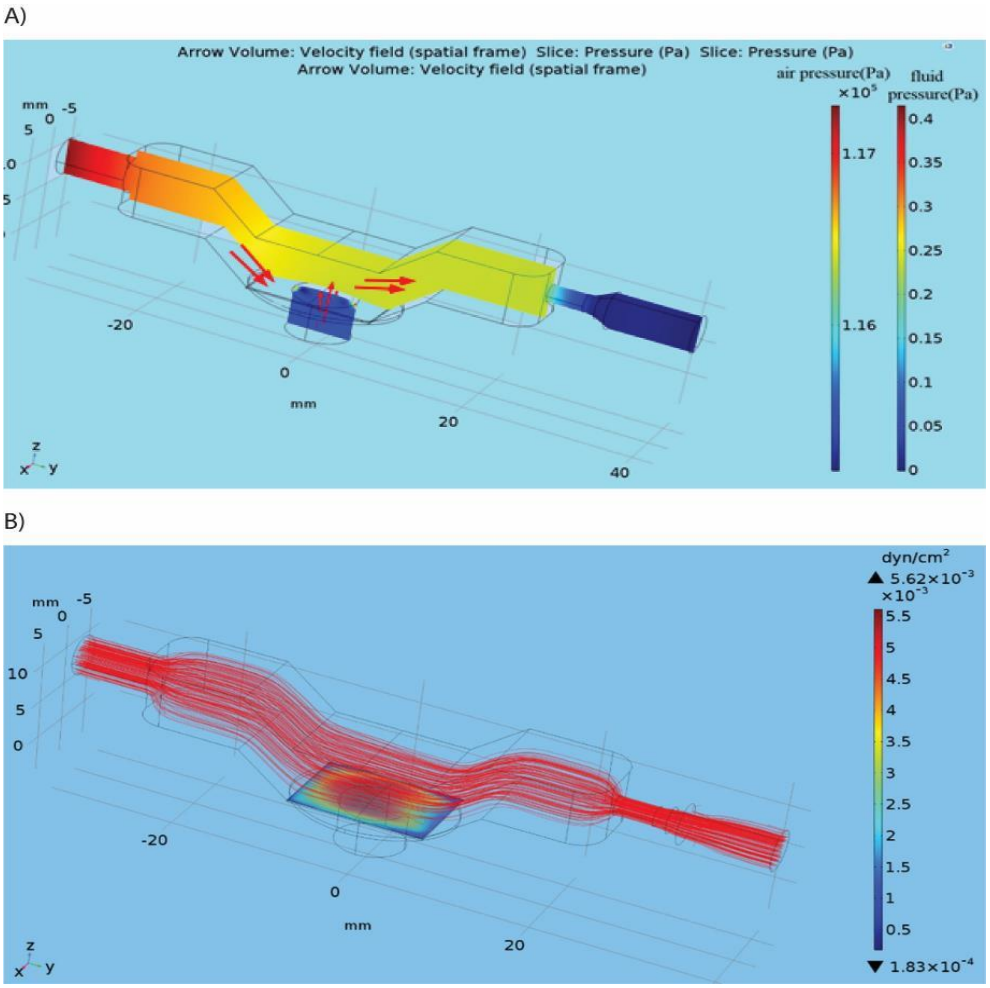

Figure 3. Pressure and shear stress contours in the model; A) Air- fluid pressure fields for the model with different frequencies (third model). (Red arrows indicate the direction of air-fluid movement.), B) The maximum magnitude of shear stress created on the stem cell layer with frequency of 0.33 Hz (Red stream lines indicate laminar flow)

uniform shear stress (Figure 4a). In the fourth model, where the stress phase angle between the mechanical parameters is $\pi/4$, the surface of the cell layer was unevenly subjected to 0.009 dyn/cm² during the period (3.3, 3.4, and 3.5 s) (Figure 4d). In the last model, where the phase angle is $\pi/2$, the maximum stress created on the cell layer is 0.014 dyn/cm² at the specified time (2.9, 3, and 3.1 s) (Figure 4e). As can be seen, this stress has the highest value in the position where the pulsatile flow is applied, and the right side of the cell layer experiences the least amount of stress. As shown in Figure 4(d-e), the phase $\pi/2$ has more value for the maximum magnitude of shear stress than the phase $\pi/4$, but both phases have a more non-uniform distribution than phase 0. In the following, a comparison of the effect of frequency and stress phase angle on the maximum magnitude of shear stress created on the surface of embryonic stem cells can be seen in Table 2.

4. DISCUSSION

As a result, it can be mentioned that both frequency and phase angle stress parameters have considerable effects on the distribution and amount of shear stress. By Increasing the frequency from 0.33 Hz to 1 Hz, the maximum shear stress increased. Besides, the frequency difference between the cyclic strain and the pulsatile flow also increases the maximum shear stress. At frequencies of 0.33, 1 Hz, and in the condition of different frequencies for each of the stimulations, shear stresses are equal to 0.00562, 0.02, and 0.01 dyn/cm², respectively. At frequencies of 0.33 Hz, 1 Hz, and the frequency difference between the mechanical parameters, the best shear stress distribution on the embryonic stem cell layer occurs at times 0.75s, 1.25s, and 1.25s, respectively (Figures 4(a2), 4(b2), and 4(c2)). However, in the third group, part of the surface of the cell layer experiences less shear stress, which poses

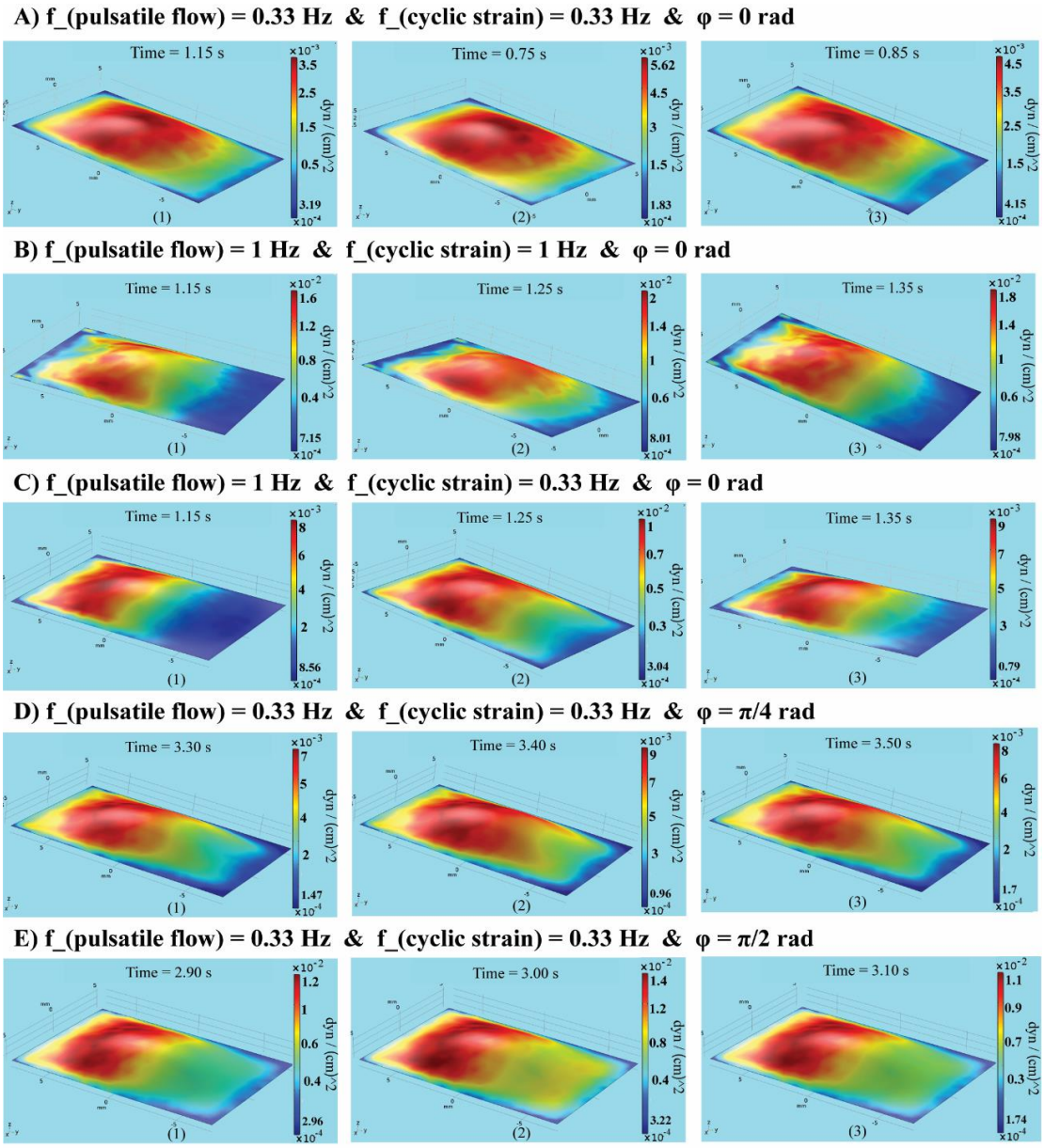

Figure 4. The maximum magnitude of shear stress created on the embryonic stem cell layer with frequency A) 0.33 Hz, B) 1 Hz C) different frequency between pulsatile flow and cyclic strain, and stress phase angle D) $^{\pi}/_{4}$, E) $^{\pi}/_{2}$

TABLE 2. Comparison of shear stress in the fifth models

Models	Frequency at cyclic strain (Hz)	Frequency at Pulsatile flow (Hz)	Stress phase angle	Maximum nagnitude of shea stress (dyn/cm²)
1	0.33	0.33	0	0.00562
2	1	1	0	0.02
3	0.33	1	0	0.01
4	0.33	0.33	$^{\pi}/_{4}$	0.009
5	0.33	0.33	$^{\pi}/_{2}$	0.014

challenges to ensure cell differentiation. Also, the existence of a phase difference between the pulsatile flow and cyclic strain leads to an increase in shear stress heterogeneously. The maximum shear stress in the stress phase angle $^{\pi}/_{4}$, and $^{\pi}/_{2}$ is equal to 0.009 dyn/cm² and 0.014 dyn/cm², which occurs in time 3s and 3.4s, respectively (Figure. 4(d2) and 4(e2)). The stress phase angle has also a significant effect on the distribution of shear stress created on the embryonic stem cell layer. Moreover, it was showed in a previous study [34] that at shear stress greater than 2.4 dyn/cm² cardiomyocytes

undergo apoptosis, whereas in our five models, the shear stress was below this critical point, from 0.00562 to 0.014 dyn/cm², which indicated that cell death did not occur. Another important point is that at low shear stress and low average velocity, beneficial effects occur in many tissue engineering systems [34]. Therefore, it can be stated that all the presented shear stress is in the appropriate range that cardiac cell differentiation occurs by activating cardiac proteins and genes [13, 14, 35]. According to the proposed models, we can conclude that the best condition for differentiating stem cells into heart cells occurs in the first model in which the frequency of mechanical parameters and stress phase angle are 0.33 Hz and 0, respectively. In this condition, the cells are exposed to a suitable and uniform range of shear stress, so that more cells are distinguished into cardiomyocytes.

5. LIMITATION AND FUTUR WORKS

In this study, a cell layer was considered to simplify and achieve a reliable computational model of cells cultured on the membrane. Also, the inability to simulate biochemical phenomena in computational software and the high computational costs of FSI analysis is the limitation of this study. For future studies, the effect of substrate surface nanotopography, as well as oscillatory flow, may be valuable to be analyzed. Besides, for investigating responses of the subcellular elements to mechanical stimuli, considering several cells with subcellular components instead of the cell layer can be worthwhile [10, 36, 37]. The assumption of viscoelastic and hyperelastic properties for embryonic stem seems to be closer to reality and is recommended for future studies.

6. CONCLUSION

Because of the physiological function of the heart, this tissue is subject to pulsatile flow and cyclic strain in vivo. Therefore, these mechanical parameters play an important role in differentiating stem cells to cardiomyocytes. In the present study, using fluid-solid interaction modeling and the combination of cyclic strain and pulsatile flow, the effect of frequency and stress phase angle parameters on the maximum shear stress applied to the embryonic stem cell layer in a perfusion bioreactor for mechanical modulation of the cells toward differentiating into cardiac cells, was investigated. For the first study, the three frequencies of 0.33 Hz, 1 Hz, and the frequency difference between the mechanical parameters were considered. Besides, the effect of stress phase angle $\pi/4$, and $\pi/2$ on shear stress was considered in the second study. It can be stated that the stress phase angle, the increase, and the existence of frequency differences between the two distinct mechanical stimuli (pulsatile flow and cyclic strain) led to an increase in the maximum magnitude of shear stress on the embryonic stem cell layer. In the first model, the distribution of maximum shear stress created on the surface of the stem cell layer at a given time was more homogeneous than in other models. In general, according to the simulations, the optimal state of the bioreactor is at the frequency of 0.33 Hz, and the stress phase angle is 0 because the shear stress distribution is more uniform, which brings better differentiation.

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Persian Abstract

چکیده

به دلیل توانایی سلول های بنیادی برای خود تجدید و تمایز به قلب، آنها منابع سلولی بهینه برای مهندسی بافت قلب هستند. از آنجایی که سلول های قلب کرنش سیکلی و جریان پالسی را در داخل بدن تجربه می کنند، این محرک های مکانیکی عوامل ضروری برای تمایز سلول های بنیادی هستند. این مطالعه با هدف بررسی اثر ترکیبی از جریان پالسی و کرنش سیکلی بر تنش برشی ایجاد شده بر روی لایه سلول‌های بنیادی جنینی با خاصیت ارتجاعی در یک بیورآکتور پرفیوژن با استفاده از روش برهمکنش سیال–جامد (FSI) اتجام شد. در این تحقیق، فرکانس و زاویه فاز تنش به عنوان یک متغیر در نظر گرفته شده است. نتایج نشان می دهند که حداکثر تنش برشی در فرکانس های ۰.۳۳ و ۱ هرتز و با اختلاف فرکانس در کرنش سیکلی(۰.۳۳ هرتز) و جریان پالسی (۱ هرتز) به ترتیب dyn/cm^2 ۰.۰۰۵۶۲، ۰.۰۲ و ۰.۰۱ می باشد. همچنین زاویه فاز تنش ۰، $\pi/4$ و $\pi/2$، حداکثر تنش برشی به ترتیب برابر با dyn/cm^2 ۰.۰۰۵۶۲، ۰.۰۰۹ و ۰.۰۱٤ است. نتایج این مطالعه می تواند گامی موثر در توسعه مهندسی بافت قلب و درک بهتر اثرات محرک های مکانیکی بر تمایز سلول های بنیادی می باشد.