PORTRAYING THE EFFECT OF SOURCE INFLUX ON INTERDEPENDENT CALCIUM AND INOSITOL 1,4,5−TRISPHOSPHATE DYNAMICS IN CARDIAC MYOCYTE

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Abstract. Calcium governs the most versatile and universal signaling mechanism in living systems which includes contraction of the cardiac tissues, information processing in the brain, release of digestive enzymes by the liver etc. High blood calcium leads to various diseases and problems like chronic fatigue and tiredness, poor memory, atherosclerosis, muscle aches and cramps, bone pain, poor sex drive, osteoporosis and broken bones, kidney stones and heart rhythm problems such as atrial fibrillation. Various investigators have been made on study of calcium signaling in cardiac myocyte to understand its mechanisms. But most of existing investigators have mainly focused on study of calcium signaling in cardiac myocyte without paying attention on interdependence of calcium signaling and inositol−1;4;5 trisphosphate (IP3) signaling. In the present work, we have studied a mathematical model to understand the impact of source influx of calcium and maximum rate of production of IP3 on these coupled signaling processes. This study suggests that maximum rate of production of IP3 plays a more significant role in these coupled dynamics. Also, calcium and IP3 shows a beautiful coordination with each other, which explains the role of IP3 in calcium signaling in cardiac myocyte. Such studies will provide the better understanding of various factors involved in calcium signaling in cardiac myocyte, which as a result will be of great use to biomedical scientists for making protocols for various heart diseases.

Keywords: calcium signaling; coupling; IP3; maximum rate of IP3 production; source influx.

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1. **Introduction**

Heart failure is a dynamic and diligent sickness, portrayed by diminished capacity of the heart to pump blood [1]. Heart failure remains a genuine medical problem all through the world. Nowadays the issue of heart failure is also common in young age people as well. Patients with heart failure experience the ill effects of the major problem and the accessible medications are frequently lacking. The exact components which prompt heart failure are yet not surely known. It is basic to comprehend the capacity of heart to manage heart related illnesses. The heart is in charge of the course of blood in the human body. Blood conveys supplements which are essential for the capacity and life of various organs. Additionally, blood retains the waste produced in the body [2]. Hence, legitimate blood circulation is important for keeping up structure and elements of various organs. The blood circulation is directed by systematic and rhythmic expansion and contraction of heart.

![Figure 1](image-url)  
**Figure 1.** The mechanism of calcium ($Ca^{2+}$) and $IP_3$ dynamics in a cardiac myocyte including $IP_3$ receptor ($IP_3R$), SERCA pump and leak. The position $x = 0 \mu m$ represents the position of the source influx of $Ca^{2+}$ and $x = 4 \mu m$ represents the position of $IP_3$ influx.
Cardiac myocytes are the cells present in the heart which are in charge of expansion and contraction of heart by a complex procedure which does the pumping of blood from heart to the circulatory framework. It is subsequently vital to comprehend the extension and compression system of cardiac myocytes. The centralization of calcium particles inside heart muscle cells assume a basic job in fortifying the constriction of heart amid the heartbeat. Intracellular $Ca^{2+}$ dynamics which happens in cardiac myocyte for accomplishing the basic functions of heart is a complex process [3]. This particular intracellular $Ca^{2+}$ dynamics is accomplished by different biophysical processes like diffusion, influx, rate of maximum production, source, leak and so on which occur in cardiac myocyte. Additionally, calcium is lethal to the cells consequently its overabundance can be destructive to the cell. The calcium regulation in the cell, happens through different biological processes which governs transition of the calcium. Subsequently, it is exceptionally important to understand how the intracellular calcium focus is overseen by different biological parameters and procedures [4].

A wealth of experimental data is available detailing elementary $Ca^{2+}$ release events [5] and functional properties of the $IP_3$ receptors. Experiments are limited by protocol and therefore computational studies, across different spatial and temporal scales, are a significant and indispensable tool. Various attempts for the study of calcium regulation in other cells [6, 7, 8, 9, 10, 11, 12, 13, 14] are reported in the literature. Pathak et al. [15] have developed mathematical models to understand independent $Ca^{2+}$ signaling process in cardiac myocyte. But they have not considered the impact of $IP_3$ dynamics in their model. But some experimental studies [16, 17, 18] as well as theoretical investigations [19, 20, 21] have shown the importance of other ions on calcium dynamics in cell. Also, Li and Rinzel [22] have reduced the nine-variable De Young-Keizer model [23] for $Ca^{2+}$ dynamics mediated by $IP_3$ receptor ($IP_3R$) in endoplasmic reticulum (ER) membrane to a two-variable system. Myocytes can distinguish simultaneous local and global $Ca^{2+}$ signals involved in contractile activation from those targeting gene expression [24]. Hohendanner et al. [25] have discussed the state of knowledge regarding the origin and the physiological implications of $Ca^{2+}$ transients in different cardiac cell types (adult atrial and ventricular myocytes) as well as experimental and mathematical approaches to study $Ca^{2+}$ and $IP_3$ dynamics in the cytosol. In the present work a systematic effort has been
made to study a mathematical model to understand the dependence of $Ca^{2+}$ and $IP_3$ dynamics on each other and also, the effect of source of $Ca^{2+}$ and maximum rate of production of $IP_3$ on cell signaling process. The present model is used to explain intracellular calcium signaling in cardiac myocyte including $IP_3$ dynamics. A successful model should be able to predict and explain functional properties involved in the process of calcium signaling [26].

2. Main results

2.1. Calcium and $IP_3$ dynamics model. The underlying mechanism of coupled $Ca^{2+}$ and $IP_3$ dynamics in a cardiac myocyte as shown in FIGURE 1 leads to a $Ca^{2+}$ and $IP_3$ dynamic mathematical model. FIGURE 1 illustrates all the influxes and outfluxes of this mechanism. The arrows in FIGURE 1 demonstrates the pathway of $Ca^{2+}$ and $IP_3$ flow in cytosol of cardiac myocyte. Due to the leak attached to the ER membrane, free $Ca^{2+}$ ions leaks in the cytosol from ER which breaks phosphatidylinositol 4,5-bisphosphate($PIP_2$) to release $IP_3$ which then gets bind with $IP_3$ receptor ($IP_3R$) and opens the receptor gate to facilitate diffusion of free $Ca^{2+}$ ions from ER to cytosol. Now, when the concentration of free $Ca^{2+}$ ions increase in cytosol then $SERCA$ pump comes into picture. It flush out the excess $Ca^{2+}$ ions from cytosol to ER to maintain the background concentration of $Ca^{2+}$ in cytosol. Again the whole process takes place and so on. The cyclic and dynamic process leads to few reaction-diffusion equations. The reaction-diffusion equations for $Ca^{2+}$ and $IP_3$ are given by [27],

\[
\frac{\partial [Ca^{2+}]}{\partial t} = D_c \nabla^2 [Ca^{2+}] + \frac{J_{IPR} - J_{SERCA} + J_{Leak}}{F_c},
\]

where $[Ca^{2+}]$ is the concentrations of $Ca^{2+}$ in the cytosol, $D_c$ is the diffusion coefficient of cytosolic calcium and various flux terms are given by [27],

\[
J_{IPR} = V_{IPR}m^3h^3([Ca^{2+}]_e - [Ca^{2+}]),
\]

\[
J_{Leak} = V_{Leak}([Ca^{2+}]_e - [Ca^{2+}]),
\]
Portraying the effect of source influx on interdependent $Ca^{2+}$ and $IP_3$ dynamics

\[ J_{SERCA} = V_{SERCA} \frac{[Ca^{2+}]^2}{K^2_{SERCA} + [Ca^{2+}]^2}, \]

where $J_{IPR}$, $J_{Leak}$ and $J_{SERCA}$ are the flux terms for $IP_3R$, leak and SERCA pump respectively. Also, $[Ca^{2+}]_e$ is the concentrations of $Ca^{2+}$ in the ER. $V_{IPR}$ and $V_{Leak}$ are flux rate constants of $IP_3$ receptor and leak respectively. Whereas, $V_{SERCA}$ is the maximum SERCA pump rate. Here, Michaelis constant for SERCA pump is denoted by $K_{SERCA}$. In this formulation, $F_c$ and $F_e$ are the volume fractions, relative to total cell volume, of the cytosol and ER, respectively (with $F_c + F_e = 1$). The Li-Rinzel model [22], however, utilizes time scale arguments to eliminate two of the three binding reactions, replacing them with the equilibrium equation [27],

\[ m = \frac{[IP_3]}{[IP_3] + K_{IP_3} + [Ca^{2+}] + K_A}, \]

where $[IP_3]$ is the concentration of $IP_3$ in cytosol. The variable $h$ represents the fraction of subunits not yet inactivated by $Ca^{2+}$ is given by [27],

\[ h = \frac{K_{Inh}}{K_{Inh} + [Ca^{2+}]}, \]

Here, activating $IP_3$ binding site dissociation constant, activating $Ca^{2+}$ binding site dissociation constant and inhibiting $Ca^{2+}$ binding site dissociation constant are denoted by $K_{IP_3}$, $K_A$ and $K_{Inh}$ respectively. Also, shown in FIGURE 1 are $IP_3$ production and degradation pathways. The reaction-diffusion equation for the cytosolic $IP_3$ concentration ($[IP_3]$) is given by [27],

\[ \frac{\partial [IP_3]}{\partial t} = D_i \nabla^2 [IP_3] + \frac{J_{Production} - \lambda (J_{Kinase} + J_{Phosphatase})}{F_c}, \]

where $D_i$ is the diffusion coefficient of $IP_3$. All the flux terms involved in $IP_3$ dynamics are given by [27],

\[ J_{Production} = V_{Production} \frac{[Ca^{2+}]^2}{[Ca^{2+}]^2 + K^2_{Production}}, \]
\( J_{\text{Kinase}} = (1 - \theta)V_1 \frac{[IP_3]}{[IP_3] + 2.5} + \theta V_2 \frac{[IP_3]}{[IP_3] + 0.5}, \)

\( J_{\text{Phosphatase}} = V_3 \frac{[IP_3]}{[IP_3] + 30}, \)

Here, \( J_{\text{Production}}, J_{\text{Kinase}} \) and \( J_{\text{Phosphatase}} \) are fluxes for \( IP_3 \) production, Kinase and Phosphatase respectively. Also, \( V_{\text{Production}} \) is maximum \( IP_3 \) production and \( K_{\text{Production}} \) is Michaelis constant for \( Ca^{2+} \) activation. Whereas, \( V_1 \) denotes maximum rate constant at low \( Ca^{2+} \), \( V_2 \) is maximum rate constant at high \( Ca^{2+} \) and \( V_3 \) is maximum rate constant of phosphatase. The parameter values used in these equations are taken from Xenopus oocytes [28], but because the overall rate was found to be too slow, we have scaled the entire degradation rate by an adjustable parameter, \( \lambda \) which is scaling factor. The \( Ca^{2+} \) dependence of the 3-kinase degradation pathway is described by a Hill function [27],

\( \theta = \frac{[Ca^{2+}]}{[Ca^{2+}] + 0.39}, \)

The analysis of the complete model is not possible using basic phase plane techniques. However, in a whole-cell model (i.e. where the diffusion terms are eliminated), the \([Ca^{2+}]_e\) equation can be eliminated using the conservation relation for the total cellular \( Ca^{2+} \) concentration \(([Ca^{2+}]_T) [27],\)

\( [Ca^{2+}]_T = F_c[Ca^{2+}] + F_e[Ca^{2+}]_e, \)

This allows the model to be reduced to the three variables \([Ca^{2+}], [IP_3]\), and \( h \) [29]. Here, it is assumed that all the calcium buffers are fast, immobile and unsaturated [30, 31]. Thus, the calcium buffering is included implicitly in this model by treating all calcium fluxes as explicit fluxes. Now, this model is formulated to study \( Ca^{2+} \) and \( IP_3 \) dynamics and role of source influx on these dynamics in one dimensional unsteady state case in the next section.
2.2. One dimensional model to study $Ca^{2+}$ and $IP_3$ dynamics. The calcium diffusion in cardiac myocyte in the presence of $IP_3$ dynamics for one dimensional unsteady state case is given by [27],

$$
\frac{\partial [Ca^{2+}]}{\partial t} = D_c \frac{\partial^2 [Ca^{2+}]}{\partial x^2} + \frac{J_{IPR} - J_{SERCA} + J_{Leak}}{F_c},
$$

And $IP_3$ diffusion in cardiac myocyte in the presence of $Ca^{2+}$ dynamics for one dimensional unsteady state case is given by [27],

$$
\frac{\partial [IP_3]}{\partial t} = D_i \frac{\partial^2 [IP_3]}{\partial x^2} + \frac{J_{Production} - \lambda (J_{Kinase} + J_{Phosphatase})}{F_c},
$$

The initial and boundary conditions governing the $Ca^{2+}$ and $IP_3$ diffusion process are given by [32, 33, 34],

(i) Initial condition

$$
[Ca^{2+}]_{t=0} = 0.1 \mu M,
$$

(ii) Boundary condition

$$
\lim_{x \to 0} \left( -D_c \frac{\partial [Ca^{2+}]}{\partial x} \right) = \sigma,
$$

$$
\lim_{x \to 4} [Ca^{2+}] = [Ca^{2+}]_{\infty} = 0.1 \mu M,
$$

Also, the boundary conditions governing $IP_3$ dynamics in this model are derived from Brown et al. [32]. They have experimentally derived 3 – $D$ geometry displayed time-dependent behavior of the $IP_3$, therefore following boundary condition used was the polynomial fit.
\[
\lim_{x \to 4} [IP_3] = 0.1882(t)^6 + 1.3121(t)^5 + 3.5391(t)^4 + 4.5312(t)^3
\]
(19) \[+ 2.5893(t)^2 + 0.3648(t) + 0.1691 \leq 3,
\]

\[
\lim_{x \to 0} [IP_3] = 3 \mu M; \quad t > 0,
\]
(20)

where, \( t \) denotes time.

The model equations (13)–(20) are solved numerically using Crank Nicholson Method Scheme. This scheme is very useful in those cases where solution needs to be time perfect. This method is implicit and unconditionally stable. Under this scheme the time derivative is approximated using backward difference formula and space derivative is approximated using the average of second order central difference formula evaluated at current and previous time steps [35].

\[
\frac{\phi_i^j - \phi_i^{j-1}}{k} = \frac{1}{2} \left\{ \frac{\phi_i^{j+1} - 2\phi_i^j + \phi_i^{j-1}}{h^2} + \frac{\phi_i^{j+1} - 2\phi_i^{j-1} + \phi_i^{j-1}}{h^2} \right\},
\]
(21)

Since this method is an implicit method it requires solving a system of equations at each time step. Then the resulting system provides simultaneous algebraic equations for unknown nodal concentrations. Gaussian elimination method has been employed to solve the resulting equations for each time step.

3. RESULTS AND DISCUSSION

This section investigates the interdependence of \( Ca^{2+} \) and \( IP_3 \) dynamics inside the cardiac myocyte. Inside the cardiac myocyte, the \( IP_3 \) concentration and \( Ca^{2+} \) concentration are strongly interdependent. Therefore, we have simulated the dependence of \( Ca^{2+} \) and \( IP_3 \) on each other as well as we have tried to understand role of various parameters like source of \( Ca^{2+} \) (\( \sigma \)) and maximum rate of production of \( IP_3 \) (\( V_{Production} \)) on this interdependence of \( Ca^{2+} \) and \( IP_3 \). The parameters used for the computation of numerical results are given in TABLE 1 or in the text (where needed). To facilitate our discussion, all calculations utilize the standard model parameters in TABLE 1, except where noted otherwise.
Table 1. Standard parameters for Ca$^{2+}$ and IP$_3$ signaling.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Values [27]</th>
<th>Parameters</th>
<th>Values [27]</th>
</tr>
</thead>
<tbody>
<tr>
<td>$V_{IPR}$</td>
<td>8.5 $s^{-1}$</td>
<td>$V_{Leak}$</td>
<td>0.01 $s^{-1}$</td>
</tr>
<tr>
<td>$K_{IP3}$</td>
<td>0.15 $\mu M$</td>
<td>$K_A$</td>
<td>0.8 $\mu M$</td>
</tr>
<tr>
<td>$V_{SERCA}$</td>
<td>0.65 $\mu M/s$</td>
<td>$K_{SERCA}$</td>
<td>0.4 $\mu M$</td>
</tr>
<tr>
<td>$K_{Inh}$</td>
<td>1.8 $\mu M$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$V_{Production}$</td>
<td>0.075 $\mu M/s$</td>
<td>$K_{Production}$</td>
<td>0.4 $\mu M$</td>
</tr>
<tr>
<td>$V_1$</td>
<td>0.001 $\mu M/s$</td>
<td>$V_2$</td>
<td>0.005 $\mu M/s$</td>
</tr>
<tr>
<td>$V_3$</td>
<td>0.02 $\mu M/s$</td>
<td>$\lambda$</td>
<td>30</td>
</tr>
<tr>
<td>$D_c$</td>
<td>16 $\mu m^2/s$</td>
<td>$D_e$</td>
<td>16 $\mu m^2/s$</td>
</tr>
<tr>
<td>$D_i$</td>
<td>283 $\mu m^2/s$</td>
<td>$[Ca^{2+}]_T$</td>
<td>1.7 $\mu M$</td>
</tr>
<tr>
<td>$F_c$</td>
<td>0.83</td>
<td>$F_e$</td>
<td>0.17</td>
</tr>
</tbody>
</table>

**Figure 2.** $Ca^{2+}$ and $IP_3$ concentration profile in cardiac myocyte with respect to each other at different positions $x$ varies from $x = 0 \mu m$ to $x = 4 \mu m$. Here, $\sigma = 10 \rho A$ and $V_{Production} = 0.075 \mu M/s$.

The dependence of $Ca^{2+}$ and $IP_3$ concentrations on each other at different positions ($x$) in the cytosol of cardiac myocyte is shown in FIGURE 2. Initially, it satisfied the boundary condition...
at lowest value of $x$. Furthermore, at $x = 1 \mu m$, the $[IP_3]$ is rapidly increases and then at particular value, it becomes steady state after that at the certain value, $[Ca^{2+}]$ becomes fixed and the $IP_3$ concentration again increase suddenly (see in FIGURE 2). Also, we found that, at all value of $x$ except $x = 0 \mu m$ which is source of $Ca^{2+}$ and $x = 4 \mu m$ which is source of $IP_3$, the concentration of $IP_3$ suddenly goes down and it fluctuates and becomes steady state and at the same time $Ca^{2+}$ concentration has been slightly decreases. Same behavior but higher values of $IP_3$ in the variation of $Ca^{2+}$ and $IP_3$ concentration has been found at $x = 2 \mu m$ and $x = 3 \mu m$ but saturation range is longer as compare to lower values. It is observed that $Ca^{2+}$ and $IP_3$ increases proportionally but after some time $IP_3$ concentration becomes steady while $Ca^{2+}$ concentration increases. Thereafter, when $Ca^{2+}$ concentration becomes steady then we can observe a peak in $IP_3$ concentration which rises very quickly and falls. This peak of $IP_3$ concentration is due to the uncaging of $IP_3$ ions in cytosol. These observation clearly represent the nonlinear interdependence of $[Ca^{2+}]$ and $[IP_3]$. Also, it validates the strong dependence of $[Ca^{2+}]$ on $[IP_3]$ and vice versa. These observations in FIGURE 2 indicates that the present mathematical model is more realistic as compared to Pathak et al. [15, 36] as their model lacks the important role of $IP_3$ in the dynamics of $Ca^{2+}$ in cardiac myocyte.

FIGURE 3 shows the dependence of $Ca^{2+}$ and $IP_3$ concentrations on each other at different positions in the cytosol for $\sigma = 6 \rho A$ (solid lines), $12 \rho A$ (dashed lines), $18 \rho A$ (dotted lines) and (a) $V_{Production} = 0.025 \mu M/s$, (b) $V_{Production} = 0.050 \mu M/s$, (c) $V_{Production} = 0.075 \mu M/s$, (d) $V_{Production} = 0.100 \mu M/s$. Here, $\sigma$ represents the source of $Ca^{2+}$ and $V_{Production}$ represent maximum rate of $IP_3$ production. But FIGURE 2, shows the variation of $Ca^{2+}$ and $IP_3$ concentrations at particular source of $Ca^{2+}$ and fixed value of maximum rate of $IP_3$ production. Now, we can see that the effect of different values of source influx ($\sigma$) of $Ca^{2+}$ on interdependent $Ca^{2+}$ and $IP_3$ concentrations in FIGURE 3 at fixed maximum rate of $IP_3$ production ($V_{Production}$). It’s observed that, the same behavior has been found as FIGURE 2 but a quantitative difference can be clearly observed in FIGURE 3. This graphs shows the interdependence of $Ca^{2+}$ and $IP_3$ concentration is slightly affected by the increase in the source influx of $Ca^{2+}$ i.e. $\sigma$ and all the fixed values of $V_{Production}$ (see FIGURE 3(a) to 3(d)). We can observe that all the same colored lines which are parallel to x-axis are slightly away from each other showing
increase in $IP_3$ concentration due to increase in $\sigma$ at different positions ($x$) in the cytosol of cardiac myocyte. And the value of $Ca^{2+}$ concentration at which this interdependence becomes steady is also increases with the increase of value of $\sigma$. But from FIGURE 3(a), 3(b), 3(c) and 3(d), we have observed that at all fixed values of $V_{production}$ the behaviour and values of the interdependent graphs is almost same. This shows that at fixed value of $V_{production}$ if source influx of $Ca^{2+}$ is varied then it will not be able to make any qualitative as well as quantitative difference in the dynamics of interdependent $Ca^{2+}$ and $IP_3$ in cardiac myocyte.
FIGURE 4. $Ca^{2+}$ and $IP_3$ concentration profile in cardiac myocyte with respect to each other at different positions $x$ for $V_{Production} = 0.06 \mu M/s$ (solid lines), $0.12 \mu M/s$ (dashed lines), $0.18 \mu M/s$ (dotted lines) and (a) $\sigma = 5 \rho A$, (b) $\sigma = 10 \rho A$, (c) $\sigma = 15 \rho A$, (d) $\sigma = 20 \rho A$.

Bartlett et al. [37] recently showed how differential regulation of intermediate steps in $IP_3$ creation can have a significant impact on calcium dynamics. Inspired by this we have discussed the effect of maximum rate of $IP_3$ ions production ($V_{Production}$) on $Ca^{2+}$ and $IP_3$ concentrations. FIGURE 4 shows the dependence of $Ca^{2+}$ and $IP_3$ concentrations on each other at different $(x)$ positions in the cytosol for $V_{Production} = 0.06 \mu M/s$ (solid lines), $0.12 \mu M/s$ (dashed lines), $0.18 \mu M/s$ (dotted lines) and (a) $\sigma = 5 \rho A$, (b) $\sigma = 10 \rho A$, (c) $\sigma = 15 \rho A$, (d) $\sigma = 20 \rho A$. Also, this graphs shows the interdependent $Ca^{2+}$ and $IP_3$ concentration is quite affected by the increase in the $V_{Production}$ i.e. maximum rate of production of $IP_3$ ions. We can observe that all the same colored lines which are parallel to y-axis are quite away from each other.
showing increase in $Ca^{2+}$ concentration due to increase in $V_{Production}$ at different positions ($x$) in the cytosol of cardiac myocyte. From FIGURE 4(a), 4(b), 4(c) and 4(d) it is observed that at all the fixed values of $\sigma$, when $V_{Production}$ is varied a quantitative significant change is seen. Also, at higher fixed value of $\sigma$ the point of steady state is also attained at a higher value of $Ca^{2+}$ concentration. As compared to FIGURE 3, it is clearly validated that FIGURE 4 shows much significant quantitative change in the interdependent $Ca^{2+}$ and $IP_3$ concentration. This observation confirms that the impact of maximum rate of $IP_3$ production ($V_{Production}$) is remarkable in the coupled dynamics of $Ca^{2+}$ and $IP_3$ in cardiac myocyte.

From these results, we can say that the $Ca^{2+}$ and $IP_3$ concentrations are strongly dependent on each other as well as it is affected by various parameters like increasing the source of $Ca^{2+}$ and maximum rate of production of $IP_3$ ions. But maximum rate of production of $IP_3$ ($V_{Production}$) is a parameter which can control this dynamics very well. By varying the value of $V_{Production}$ the uneven $Ca^{2+}$ and $IP_3$ concentration due to which diseases like atherosclerosis (hardening of the arteries) happen can be treated. Atherosclerosis is the main cause of heart disease. It occurs because of calcium build-up in the blood vessels resulting in hard and narrow arteries. This then leads to problems such as blood flow obstruction and heart issues [38]. Above results conclude that $IP_3$ plays a vital role in calcium dynamics. As $IP_3$ concentration increases, $Ca^{2+}$ concentration also increases at first then gradually becomes steady. Also, maximum rate of production of $IP_3$ ($V_{Production}$) is able to influence the interdependence more than source of calcium ($\sigma$) because when $Ca^{2+}$ ion are release from the source of calcium then maximum amount of ions get attached with proteins in cytosol which decreases the amount of free $Ca^{2+}$ in the cytosol of the cell. Whereas when maximum rate of production of $IP_3$ ($V_{Production}$) is increased then the releases $IP_3$ not only increase the amount of $IP_3$ in cytosol but it binds with the mouth of $IP_3Rs$ to open them and facilitate the influx of $Ca^{2+}$ ions from ER to cytosol. This results in overall increase in the concentration of the coupled dynamics which can be observed from FIGURE 4. In various models given in literature [15, 36, 39] they have excluded the role of $IP_3$, but many experimental works [23, 40, 41, 42] as well as theoretical works [6, 10, 19, 21] have shown the importance of $IP_3$ dynamics in calcium dynamics of cell. Sneyd et al. [21] have shown that the response to an artificial applied pulse of $IP_3$ in two types of cell. They have found
that long period $Ca^{2+}$ dynamics in pancreatic acinar cells depends on $IP_3$ concentration but in airway smooth muscle, short term $Ca^{2+}$ dynamics do not depend on $IP_3$ concentration. Also, Manhas et al. [10] have recently predicted that calcium-dependent production and degradation of $IP_3$ is a key mechanism for intracellular calcium dynamics in pancreatic acinar cells. So motivated by these works, we have studied a mathematical model to understand effect of $IP_3$ dynamics on intracellular $Ca^{2+}$ dynamics and vice versa in cardiac myocyte, which describes the properties of elemental calcium release events in the presence of $IP_3$.

4. CONCLUSION

In this work, we have studied the interdependence of $Ca^{2+}$ and $IP_3$ dynamics in cardiac myocyte. In which we have obtained the significant influence of source of $Ca^{2+}$ and maximum rate of production of $IP_3$ ions on $Ca^{2+}$ and $IP_3$ concentration dynamics. This model shows that, the variation on $Ca^{2+}$ concentration and $IP_3$ concentration is affected by the source influx of $Ca^{2+}$ ($\sigma$) as well as maximum rate of production of $IP_3$ $V_{Production}$. Also, it is observed that $Ca^{2+}$ source influx has a very minute influence on $IP_3$ dynamics but on the other hand maximum rate of $IP_3$ production ($V_{Production}$) has quit significant impact on coupled $Ca^{2+}$ and $IP_3$ dynamics. That is, both $IP_3$ production and diffusion are significant elements of the calcium dynamics in cardiac myocytes. The physical behaviour shown by the results matches with the behaviour observed in experimental investigations [27, 43]. These findings suggest that, $Ca^{2+}$ and $IP_3$ concentration in cardiac myocyte can be effectively controlled by maximum rate of $IP_3$ production ($V_{Production}$) and it is important parameters during the modeling of treatment for heart diseases like atherosclerosis and heart rhythm problems such as atrial fibrillation.

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Conflict of Interests

The author(s) declare that there is no conflict of interests.
REFERENCES


[6] G. Dupont and A. Goldbeter, One-pool model for Ca$^{2+}$ oscillations involving Ca$^{2+}$ and inositol 1,4,5−trisphosphate as co-agonists for Ca$^{2+}$ release, Cell Calcium, 14 (1993), 311–322.


