Effect of angiotensin II on heart blood flow and hypertension

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Abstract

The primary aim of the research was to predict the effect of the hormone angiotensin II (angII) and a blocking drug Losartan on the heart. It is believed that the hormone is one cause of hypertension. As the hormone will be absorbed by the heart wall during the filling of the heart (diastole), only the blood flow in the left ventricle was simulated during the diastole stage. The simulation assumed that the pulmonary and aortic valves were closed so that the inflow to the atrium is simulated by distributed sources within the atrium. Conservation of mass is maintained by sinks distributed outside the ventricular membrane. The solution of the Navier-Stokes equation used a two step finite difference method. In the usual solution, an initial estimate of wall velocity at each time step is undertaken using the elastic properties of the wall. This procedure yields wall shapes which are dependent on the stress strain properties assumed for the heart wall but may not result in the correct shape of the actual heart. In the present method, the wall velocity and wall shape were derived from a patient cine-angiogram at various times. Thus the correct wall shape was maintained throughout the diastole. The macroscopic flow was calculated including the usual vortices in the left ventricle. For the present purposes the interaction of the blood at the wall surface was of primary interest. The blood components and drug could either diffuse or be convected to the wall. An examination of the interaction at various sites showed that some sites on the wall are more likely to lead to the initiation of hypertension and subsequent hypertrophy of the heart. In addition the effects the Losartan on this process were also calculated.
1 Introduction

The full simulation of biological flows requires multi-scale analysis at several scale levels. The calculations can be performed on a macroscopic scale, a mid or optical microscope scale and an atomic level scale. Such a method has been proposed and applied to the simulation of the interaction of an antihypertensive drug, the calcium channel blocker amlodipine, with a model arteriole, Macpherson and Neti [1]. The method is applied here to the effect of a hypertensive agent and its antagonist which results in cardiovascular disease.

It is known that the effect of the hormone angiotensin II (angII) on the heart and vascular system is to initially cause hypertension, Silverman [2], and subsequently pressure overload Dostal [3]. The angII has the effect of changing the heart shape, size and function (remodeling) Cohn [4]. The changes are due to hemodynamic load and neurohormonal activation. The angII interacts with receptors (known as ATR1) on the ventricle and vascular walls. The interaction occurs at certain docking sites Boucard [5], Noda [6] on the receptor. The effect of the angII is to instigate reprogramming of cardiac gene expressions resulting in molecular, cellular and interstitial changes Paradis [7], Dostal [3]. There are a number of angII antagonists Burnier and Brunner [8] (known as ARBs or ARAs), which act to block the docking sites of the receptors. As well as reducing blood pressure, the ARBs are known to reverse reprogramming of the heart Dostal [3]. The present study simulates the blood flow in the left ventricle during the diastole stage using three scale levels. The first is undertaken at the macroscopic fluid flow as input to the mid scale flow. The second level is a mid scale flow simulating flow at the albumin, platelet or blood cell size. Finally, the third level is at the atomic level and simulates the interaction of the drug and angiotensin II with the ATR1. The latter calculation has properties similar to the calculation of time dependent affinity parameters. The results of the present calculations indicate that for dynamic situations as occur in the heart, short time dependent values of affinity parameters are required.

2 The Simulation

The simulation is undertaken on three scales following Macpherson and Neti [1]. In the present work only the fluid dynamics solutions are described. The microscopic scale solution will be presented elsewhere. The flow in the left ventricle is at a continuum level and is the first level of study. The second level is the interaction at the blood cell size level and is a Monte Carlo process. The third level involving the interactions with the receptors, is undertaken using a direct simulation method known as molecular dynamics.

2.1 Continuum Scale

The state of the ventricle is at the beginning of diastole with the pulmonary and aortic valves closed. The inflow to the atrium is simulated by distributed sources within the atrium. The conservation of mass is maintained by sinks distributed outside the ventricular membrane. The solution generally follows Peskin [9] and
Peskin and Printz [10]. The Navier Stokes equations defined on an x-y Cartesian co-ordinate system are

\[ \rho \left( \frac{\partial \mathbf{u}}{\partial t} + \mathbf{u} \cdot \nabla \mathbf{u} \right) + \nabla p = \mu \nabla^2 \mathbf{u} + \mathbf{F} \]  
\[ \nabla \mathbf{u} = 0 \]  
where \( \mathbf{u} \) is the velocity vector, \( \rho \) is the density, \( t \) is the time, \( p \) is the pressure and the viscosity is \( \mu \).

The boundary force \( \mathbf{F} \) arising from the heart muscles used in Peskin[9] is

\[ \mathbf{F}(\mathbf{s}, t) = \int_0^L \mathbf{f}(s, t) \delta(\mathbf{x} - \mathbf{X}(s, t)) ds \]  
where \( \mathbf{f} \) is the force on the boundary element at the point \( s \) defined on a Lagrangian system where \( \mathbf{X} \) is defined on the Cartesian system and \( \mathbf{X}^n \) is the \( n \)th point on the Lagrangian system. The delta functions are defined in eqn (6)

\[ \delta_h(x) = \frac{1}{4h} \left( 1 + \cos \frac{\pi x}{2h} \right) \left| x \right| \leq 2h \]  
\[ \delta_h(y) = \frac{1}{4h} \left( 1 + \cos \frac{\pi y}{2h} \right) \left| y \right| \leq 2h \]  
\[ \delta_h(x) = \delta_h(x) \delta_h(y) \]  
In the present work the velocity of the ventricular wall is specified from patient cine-angiograms ,Caro et al. [11]. Thus the only change to the usual solution is to replace equation (7) from a data file containing the velocities at each point as a function of time. This ensures that the correct left ventricle variation in shape is obtained with time. The blood flow velocity closest to the membrane was used as the bulk flow input to the blood cell scale calculation.

The finite difference implementation of the above equations uses three correction steps for the time advance of the velocity at the \( n+1 \)th point \( \mathbf{u}^{n+1} \). These steps are

\[ \mathbf{u}^{n+1,0}, \mathbf{u}^{n+1,1}, \mathbf{u}^{n+1,2}, \mathbf{u}^{n+1} = \frac{\mathbf{u}^n - \mathbf{u}^{n+1}}{\Delta t} = \mathbf{F} \]  
\[ \rho \left( \frac{\mathbf{u}^{n+1,1} - \mathbf{u}^{n+1,0}}{\Delta t} + u_x D_x \mathbf{u}^{n+1,1} \right) = \mu D_x^+ D_x^- \mathbf{u}^{n+1,1} \]  
\[ \rho \left( \frac{\mathbf{u}^{n+1,2} - \mathbf{u}^{n+1,1}}{\Delta t} + u_y D_y \mathbf{u}^{n+1,2} \right) = \mu D_y^+ D_y^- \mathbf{u}^{n+1,2} \]  
\[ \mathbf{D} \cdot \mathbf{u}^{n+1} = 0 \]
\[
\rho \left( \frac{u_{n+1} - u_{n+1,2}}{\Delta t} \right) + \hat{D}p_1 = 0
\]

\[p^{n+1} = p_1 - \lambda_p\]

where \(\lambda_p\) is defined in terms of the source \(Q(t)\)

\[\phi_0 Q_s + \hat{D}p_0 = 0\]

the volume flow rate \(Q(t)\) is defined by

\[Q(t) = Q_s - \alpha_s P_{atrium}\]

where \(Q_s\) and \(\alpha_s\) are constants and \(P_{atrium}\) is the pressure in the atrium.

The spatial distribution of sources and sinks \(Q(t)\phi_0(\hat{x})\) utilizes functions two non-negative functions \(w_s\) and \(w_e\) with integral 1 and

\[\phi_0(\hat{x}) = w_a(\hat{x} - \hat{X}_a) - w_e(\hat{x})\]

where \(\hat{X}_a\) is a point in the middle of the atrium, and

\[\lambda = \frac{Q_s - \alpha_s(\phi_0, p_1)h}{Q_s - \alpha_s(\phi_0, p_0)h}\]

The sources were placed in the atrium as a line to simulate the inflow direction. The sinks were placed as a rectangle near the edge of the boundaries. If placed at the boundary, instabilities developed after sometime.

The boundary points \(X\) are moved according to the relation

\[\hat{X}^{n+1}(s) = \hat{X}^n(s) + \Delta t \sum_{\hat{x}} \hat{u}^{n+1}(\hat{x}) \delta_h(\hat{x} - \hat{X}^n(s))h^2\]

The definition of the divergence operator \(\hat{D}\) and the solution of the equations proceeds as in Peskin (1993).

### 2.2 Blood cell scale

The Monte Carlo method has been described previously in Macpherson and Neti [1] so it will only be briefly reviewed here. The blood is considered to be composed of water, erythrocyte, albumin, angiotensin II and ARB losartan. The solution starts with the Landau equation which in the test particle form below has been described as a generalized diffusion equation in velocity space, Chandrasekhar [12]. Expressed in a non-dimensional form it becomes

\[
\partial \phi_t = \partial_{v_r} (-F_r + 0.5 \partial_s T_{rs}) \phi
\]

where \(\phi\) is the velocity distribution, the \(v_r\) differentiation is with respect to non-dimensional velocity \(v/2kT\), subscript \(\tau\) is differentiation with respect to the non-dimensional time defined below. The solution is obtained in terms of the drag force \(F_r\) and a random force \(T_{rs}\).

\[F_r = -8v^{-1}G(v)v_r\]

\[T_{rs} = 2v^{-1}H(v)\delta_{rs} + 2v^{-3}E(v)v_r v_s\]
and H, G and E are tabulated Chandrasekhar [12]. The non-dimensional time is Balescu [13]

$$t = \frac{\beta^{3/2} Bn}{m^{1/2} \tau}$$ \hspace{1cm} (21)

where \( m \) is the mass, \( n \) the number density, \( \beta = 1/kT \) and \( B \) is defined as

$$B = 8\pi^5 \int_{l_m}^{l} l^3 V_{l} dl$$ \hspace{1cm} (22)

The movement of the blood components assumes they are sufficiently far apart so that collisions between the components will be a rare event. This is the usual assumption made for the application of the Landau equation. The time scale is as defined in equation (21).

3 Results

The flow was calculated and an example of the flow is shown in figure 1. The ventricular shape is very important for the interaction with the receptors. Specifically the velocity normal to the membrane is important for the convection of losartan and ang II into Monte Carlo region. Figure 2 shows the velocity normal and relative to the membrane at various times.
The flow is up to 7 cm/sec towards the membrane and up to 3 cm/sec away from the membrane. The flow away from the membrane at position 24 is associated with the mitral valve. The atrium and mitral valve have been assumed fixed in position and hence they cause locally unrealistic disturbances in the flow.

When a drug molecule docks with a receptor then it is removed as shown by the circles figure 3. In figure 3 there are 15 receptors blocked due to losartan and 6 due to angiotensin II at the end of the calculational period. Thus the drug docks more readily than the angiotensin II. Additional drug molecules can enter the Monte Carlo region by diffusion and convection. There are approximately 100 times as many drug and angII molecules as receptors in the left ventricle. Thus if the concentration in the MC region is less than in the main fluid and a molecule docks with the receptor, then that molecule is replaced by a new molecule near the top of the region. These are the delta molecules in figure 3. Now there is convection due to the bulk fluid motion calculated from the continuum calculation and these are the squares. Thus due to convection it is possible for the number of molecules to have a greater concentration in the left ventricle than in the bulk fluid. Under these conditions the molecules are not replaced when they dock with the membrane.

When the normal velocity is 10 cm/sec the convective velocity dominates as shown in figure 4.
The number of receptors are blocked than with 1cm/sec. The number of angiotensin II was only one time that diffusion occurred. In this case more than twice the number of receptors are blocked than with 1cm/sec. The number of angiotensin II is significantly lower with 1cm/sec.

Fig 3 The docking of losartan with convective velocity 1cm/sec

Fig 4 The docking of losartan with convective velocity 10cm/sec
receptor sites that were blocked were 28 at the end of the period. This compared to 38 for losartan and the difference appears to be greater than due to statistical variation. Thus it again appears that with large convective velocities the drug docks more readily than the angiotensin II.

4 Conclusion

Based on the time for the absorption of the drug and angII all receptors in the heart will be blocked during one diastole cycle. This is in agreement with earlier work Schalekamp,2001 where it is suggested that rapid binding of angII to receptors occurs. The rate will depend on the heart shape as the convective velocity is a function of the changing shape. In the same way that the density of receptors are a function of the amount of neurotransmitters present, probably the density of receptors will depend on the amount of angiotensin II present. This would make the changing heart shape very important. As the complete blocking of receptors would indicate instantaneous action of both drugs and angiotensin II then it seems logical that due to the rapid collapse of the ventricle during the systole cycle, that drug and angiotensin II will be released during this period.

5 References