

The variation of dobutamine induced heart stress with heart rate

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Abstract

Dobutamine stress echocardiography is a common test to provoke myocardial ischemia in patients unable to undergo routine exercise stress testing. Heart rate elevation, achieved by staged increases in dobutamine doses, acts as a surrogate for exercise. The physicians monitor the ECG of the patient and echocardiographic images to evaluate for myocardial ischemia. However, the actual mechanical stress on the heart is not readily available to the physician. The motivation for the present preliminary study is to both investigate the feasibility of producing such information for clinicians as well as to investigate the variation between different patients as the heart rate varies. Echocardiograms were obtained from three patients undergoing dobutamine stress tests. Using standard equations of motion, the surface shear stress at the surface of the left ventricle was calculated. The average shear stress around the left ventricle is shown, as well as the peak stresses at selected locations as a function of time. It was found that generally the surface shear stress increased with heart rate around most of the left ventricle. While the time averaged shear stress may be important for diagnosis, the maximum shear stress is probably the limiting factor in terminating testing.

Keywords: heart stress, dobutamine testing, heart rate, heart diagnosis.



1 Introduction

Dobutamine stress echocardiography is a common test to provoke myocardial ischemia in patients unable to undergo routine exercise stress testing. Heart rate elevation, achieved by staged increases in dobutamine doses, acts as a surrogate for exercise. A study is currently underway relating isolated myocardial stress to neurologic activity, without other confounding factors.

The effects of shear stress on the heart are very extensive. Two surveys [1,2] showed that stress can cause changes in the genetic structure of the heart. In patient review it would be useful for a clinician to have details of the stress being applied to the heart. The dobutamine stress test is stopped if a patient develops concerning symptoms or demonstrates evidence of significant myocardial ischemia. In making a decision to terminate a test, information on the level of stress being experienced by the patient would be useful information for the clinician.

As the present preliminary study was both a feasibility study as well as a preliminary investigation for a neural cardiovascular study, available echocardiogram results were used. Three-dimensional MRI results will be used in subsequent studies.

2 Method of calculation

The general method of calculation used here has been described previously [3,4]. In the solution the bloodflow into the left atrium is simulated by a source distributed throughout the atrium. In order to conserve mass sinks are distributed around the periphery of the integration domain. The change in shape is obtained from the echocardiograms and used as boundary conditions for the flow. The source strength has to match the change in volume of the ventricle. The valves have to be modelled as thicker than in reality as Lagrangian integration must go around both sides of the valve. The Navier-Stokes equations are then solved with a predictor corrector scheme [4].

The Navier Stokes equations defined on an x-y Cartesian co-ordinate system for an incompressible fluid are

$$\rho \left(\frac{\partial \hat{u}}{\partial t} + \hat{u} \cdot \nabla \hat{u} \right) + \nabla p = \mu \nabla^2 \hat{u} + \hat{F} \quad (1)$$

$$\nabla \hat{u} = 0 \quad (2)$$

where \hat{u} is the velocity vector, ρ is the density, t is the time, p is the pressure and the viscosity is μ .

The boundary force \hat{F} arising from the heart muscles is

$$\hat{F}(\hat{x}, t) = \int_0^L \hat{f}(s, t) \delta(\hat{x} - \hat{X}(s, t)) ds \quad (3)$$



Here \hat{f} is the force on the boundary element at the point s defined on a Lagrangian system where \hat{x} is defined on the Cartesian system and \hat{X}^n is the n th point on the Lagrangian system

The flow velocities and pressures can be used to calculate the stresses on the surface of the heart walls. These forces can then be used to examine the microscopic interaction with the cells in the heart wall (endocardium).

The first step in the solution involves obtaining the shape of the ventricle at various times. This is often difficult as echocardiogram images are sometimes indistinct. Following a method often used by echocardiographers only five images in a cardiac cycle were selected. One image when the valves were closed, a second image when the valves were fully open, a third just before the atrium starts to contract, one at the end of the ventricle filling (diastole) stage and a final one as the aortic valve opens. A linear variation was assumed between each image, time frame. It was assumed that the motion of the wall would be normal to the surface. As described below the times required for valve opening and atrium contraction can be obtained from Doppler measurements of the velocity through the mitral valve and the shape was obtained from the echocardiogram contained many irregularities. The echocardiogram tracing was obtained as a digital image. If the source were allowed to start while the valves were closed then the program would fail due to excessive pressure. Similarly the wall could not be allowed to start moving until the source started. Thus an initial short period was required without source or wall motion to allow the valves to start opening (these events are independent of fluid motion are dependent on cardiac electrical signals).

The second step required the simulation of the atrium. The atrium changes shape during the diastole stage and thus changes the pressure. However the use of a source in place of the correct inflow pattern to the atrium was an artifice that made the actual atrium shape unimportant. The atrium shape was fixed at near hemispherical shape with valves in the closed and early open positions. After some time the atrium contracts for a period before the mitral valve closed. The shape was expanded and contracted as required for the different sized mitral valves. The source strength was increased slowly as the valves opened in accordance with the increase in volume of the ventricle.

Once the calculation of the flow velocities and pressures were completed the stresses at the walls were calculated. In accordance with the aim of the research, evaluation of wall stresses, the boundary layer had to be modelled properly. Two points were chosen as close to the wall as possible along a line normal to the surface. A finite difference method was used to obtain the derivative of the velocity along this line. Similarly the velocity normal to the wall was calculated along the same line. As only pressure gradients are used in the calculations, an arbitrary constant was added to the pressure to make it relative to atmospheric pressure.

The method of the microscopic calculation of the blood, to obtain details on the affinity involved the effects of dobutamine contained in the blood, on the cells of the myocardium will not be discussed here. It is necessary to have a length scale in between the continuum calculation and the above microscopic



scale. This is undertaken using a Monte Carlo method. These details are presented elsewhere [4]. The basic process of describing the effects of dobutamine starts with the Landau equation which for the test particle takes the form below and has been described as a *generalized diffusion equation in velocity space* by Chandrasekhar [5]. Expressed in a non-dimensional form it becomes [6]

$$\partial \phi_{\tau} = \partial_{v_r} (-F_r + 0.5 \partial_s T_{rs}) \phi \quad (4)$$

where ϕ is the velocity distribution, the v_r differentiation is with respect to non-dimensional velocity $v/2kT$, subscript τ 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} .

$$F_r = -8v^{-1}G(v)v_r \quad (5)$$

$$T_{rs} = 2v^{-1}H(v)\delta_{rs} + 2v^{-3}E(v)v_rv_s \quad (6)$$

The movement of the blood components assumes they are sufficiently far apart so that collisions between the components will not occur. This is the usual assumption made for the application of the Landau equation. Under these circumstances the force on an ion will consist of a drag due to $G(v)$ and a random force due to $H(v)$.

The docking mechanism for dobutamine with the receptor is unknown. It is useful in considering the present results to have an estimate of the fraction of dobutamine, which will dock with the receptor. Both dobutamine and Losartan dock with a G-protein so in order to make an estimate of the fraction of dobutamine absorbed, the docking of Losartan was calculated under the various conditions simulated in the present paper. The density of dobutamine receptors was used to estimate the affinity of the dobutamine to the receptor based on the affinity values calculated for Losartan. This is only presented in order to provide an indication of the possible outcome.

3 Results

The m-mode tracings were not available so that the opening and closing of the valves had to be obtained from the one EKG recording and the heart rate provided. The EKG recording is shown in the bottom left of figure 1. The heart rate is shown as 67 on the bottom right.

The results of the stress calculations are presented for four regions of the ventricle. The regions are the apex (A), the mid endocardium (ME), across the mitral valves (MV) and in the middle of the septum (SE) as shown in figure 2.

Typical variation of maximum and average shear stress over the whole ventricle is shown as a variation of time in figure 3. It can be seen that the peak maximum stress occurs when the aortic valve opens. The average of the shear stress over the whole ventricle is shown as a dashed line.



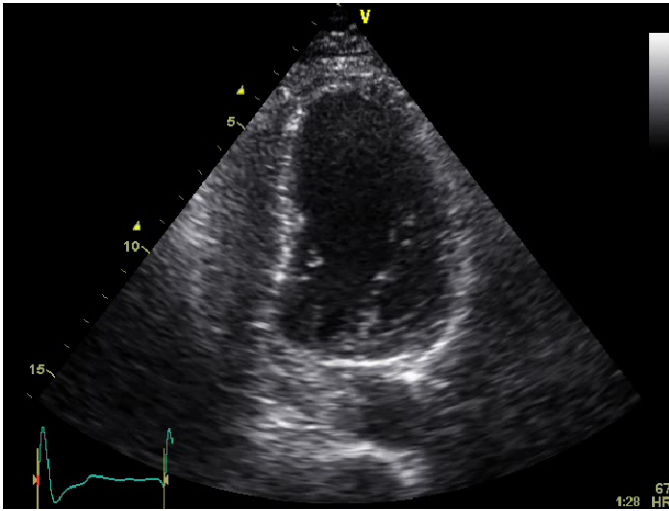


Figure 1: Typical echo recording showing EKG recording and heart rate.

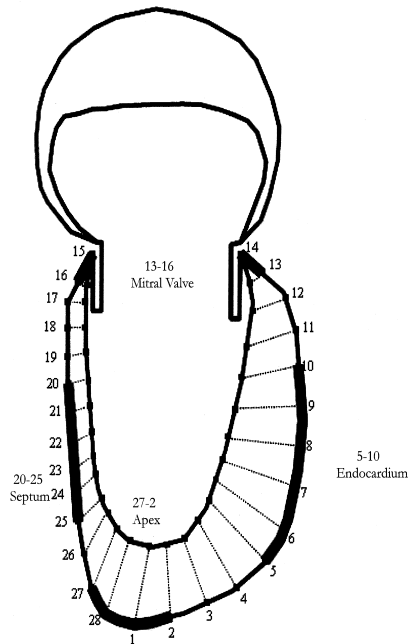


Figure 2: Areas over which the averaged stress was calculated.



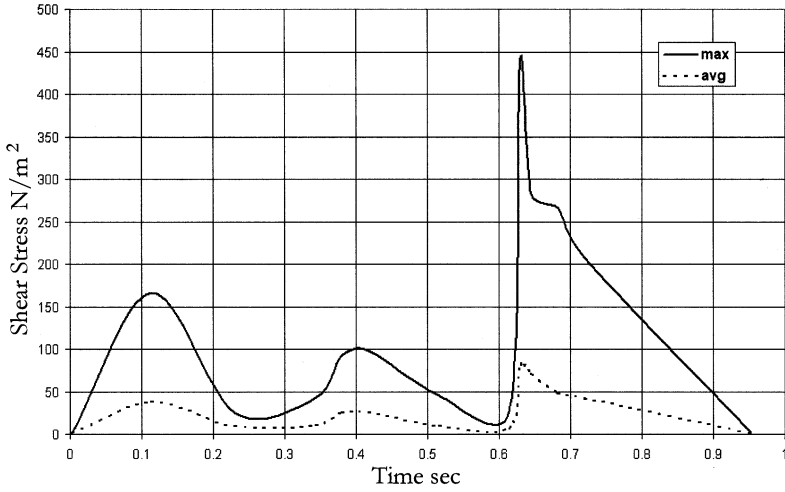


Figure 3: The variation of shear stress over the whole ventricle at a resting heart rate of 63 BPM for patient 1.

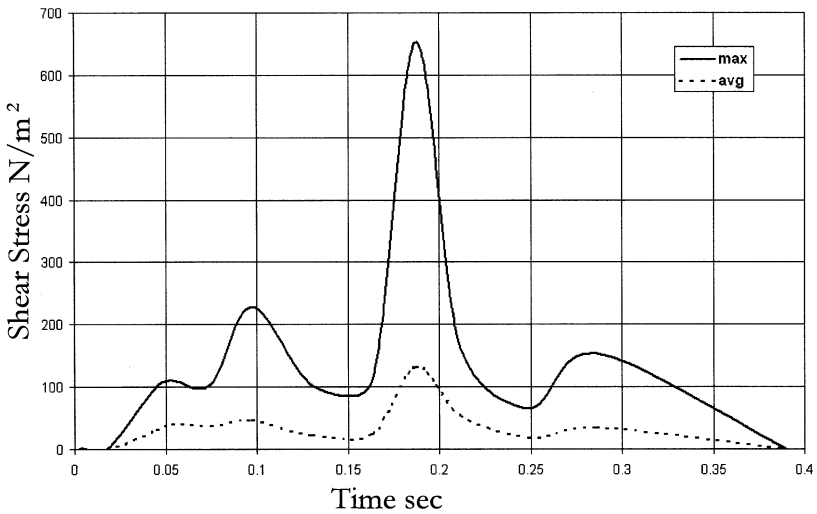


Figure 4: The variation of shear stress over the whole ventricle at the maximum heart rate of 154 BPM for patient 1.

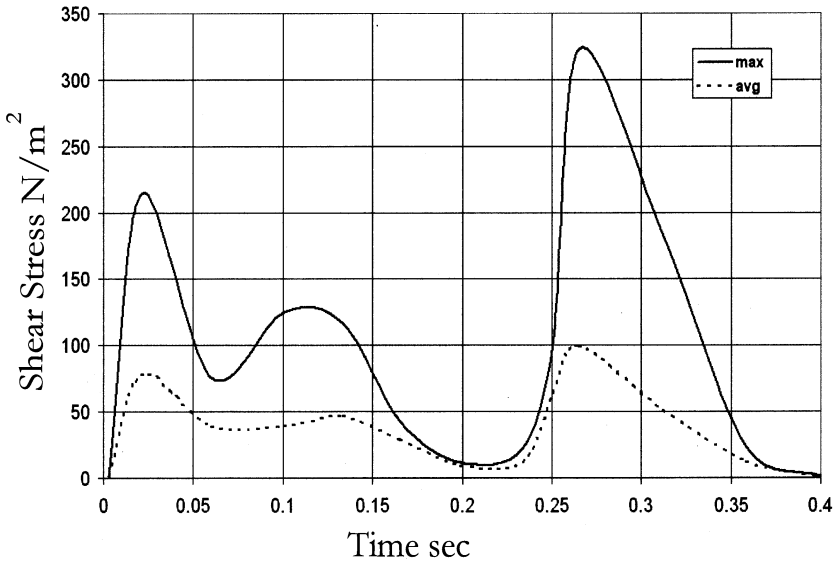


Figure 5: The variation of shear stress over the septum at the heart rate of 150 BPM for patient 1.

It can be seen that the peak stress is more than 50% higher at 154 BP than at 63 BPM over the whole ventricle. Over the septum the peak stress is shifted to the opening of the aortic valve and is less than the peak stress over the endocardium.

The variation of maximum shear stress around the whole ventricle is shown in figure 6 for the three patients. It can be seen that it increases very rapidly with heart rate. Patient 1 was a 55 year old woman, Patient 2 was a 75 year old woman and Patient 3 was a 75 year old woman.

An unresolved problem is whether the maximum stress causes the onset of hypertrophy or the average stress applied over an extended time. In [4] it was shown that there is a finite length of time required for the angiotensin II to dock with the AT receptors on the G-protein. Thus it appears reasonable to assume it is the average sustained shear stress that is the more important stress for the onset of hypertrophy.

The time averaged shear stress over one heart beat in the ME region, as a function of heart rate is shown for the three patients in figures 7.

It can be seen in all patients that the effect of a moderate increased heart rate is to increase the stress very rapidly. However with further increase in heart rate there is comparatively small increase in the time-averaged heart rate. In the case of Patient 3 the time averaged shear stress decreases with high heart rate. This may be a valid result or it could be due to the interpretation of the echocardiogram. Further study using MRI output will resolve this result.

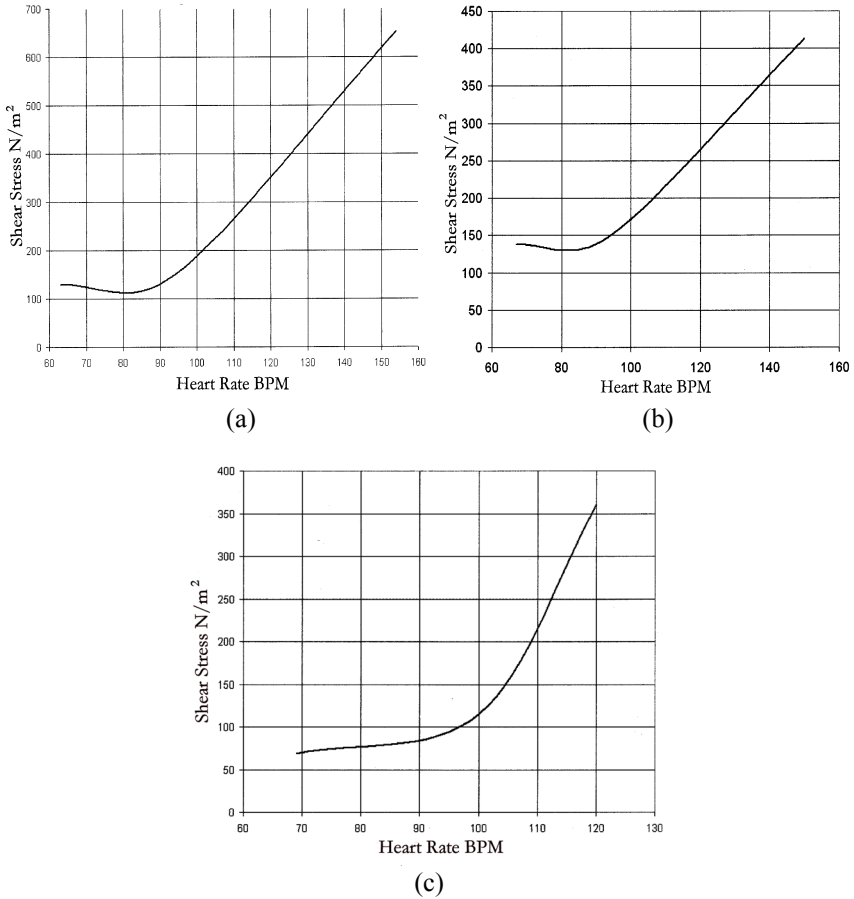


Figure 6: The variation of the maximum shear stress on left ventricle with heart rate. (a) Patient 1, (b) patient 2, (c) patient 3.

4 Conclusions and future work

As the time averaged stress only increases slowly with high heart rate then it appears that the time averaged stress is not the best criteria for terminating the testing. As seen in Figure 6 the maximum shear stress around the ventricle increases very rapidly with the heart rate. Therefore the best termination criterion probably is the maximum stress at any point around the ventricle. Values of the average shear stress would be useful for the physician in determining treatment. Only limited results have been presented for conditions along the septum. However hypertrophy of the septum can occur and will be addressed in future work.



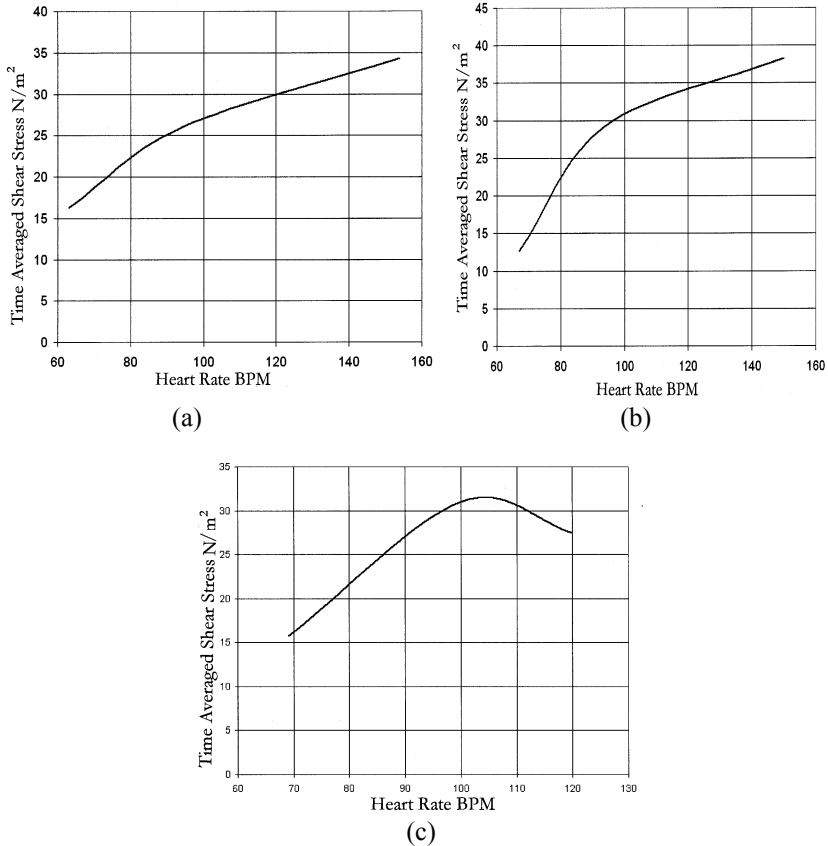


Figure 7: Variation of time averaged shear stress over on heartbeat as a function of heart rate. (a) Patient 1, (b) patient 2, (c) patient 3. The location is in the ME region as in figure 2.

This preliminary study has shown that data useful to a clinician monitoring dobutamine testing can be obtained. In addition diagnostic results can be extracted from the data. Future studies will use MRI data the output of which can be automated. This will be used in a study of a heart-brain study presently underway.

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