

SIMULA

Modeling Muscle flow during exercise

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Modeling Muscle Flow during exercise

Abstract

Objective:

A mathematic model may describe change in bloodflow through arteria femoralis from rest to exercise. To understand the complexity of the hemodynamic change at the onset of exercise this may be helpful and illuminate some of the most important regulating mechanisms. The aim of this study was to test and improve such an existing mathematical model.

Methods:

This mathematic model consist of the baroreflex, a heart, a linear elastic arterial reservoir and two parallel restrictive vascular beds representing exercising and non exercising muscles. Mean arterial pressure, heart rate, stroke volume and bloodflow through the femoral artery on site was measured in ten healthy volunteers. The measured data were compared to the data calculated in the mathematical model using optimizing algorithms minimizing error.

Results and conclusion:

The calculations in our mathematic model fit well with the measured values in healthy volunteers. This indicates that we have isolated and implemented the most important factors in our model for calculation of changes in blood flow during onset of exercise.

Chapter 1 – Exercise physiology

During exercise the circulatory system must adjust to the increased demand of oxygen in the exercising muscle

- An increase in heart rate and stroke volume gives higher cardiac output, transporting more blood and oxygen through the body.
- Blood flow through exercising muscles increases
- Blood pressure is maintained relatively stable by regulating vasoconstriction and vasodilatation in different tissues.

Initiation of circulatory adjustments in exercise

The cardiovascular changes during exercise are caused by altered autonomic nerve activity and local metabolites.

There are two central hypotheses explaining the cardiovascular changes.

1. The **central command hypothesis** supposes that the brain controls the autonomic and respiratory neurons of the brainstem. The fact that the heart rate increase from the first moment of exercise supports this theory. This could be a feed forward mechanism.

During dynamic exercise the heart rate and sympathetic nerve activity increase rapidly. The initial increase is possible mediated by the central command. The set point for arterial pressure is regulated to a higher pressure. The mismatch between the new set point and measured blood pressure is corrected by activating sympathetic nerve activity and inhibiting parasympathetic nerve activity. The result is increased cardiac output and peripheral resistance, which increase blood pressure. (DiCarlo & Bishop, 2001)

2. The **peripheral reflex hypothesis** supposes that metabolic products from exercising muscles like K^+ , O_2 , Adenosine, contributes to the increase in blood pressure and heart rate. The hypothesis can be illustrated with a simple experiment. Before onset of exercise a pneumatic cuff proximal to the exercising muscle is inflated. The cuff keeps metabolites within the exercising muscle. The increased heart rate will last longer than when no inflated cuff is used. This experiment suggests that there is a link between metabolites from exercising muscle and regulation of heart rate and blood pressure. This is a feedback mechanism.

It seems that both of these theories are important in regulating heart rate and blood pressure during exercise.

Directly sympathetic mediated effects acts faster than metabolites on cardiac output and peripheral vasoconstriction.

A third hypothesis is described. The theory here is that properties of the baroreflex are changed.

In our simplified model we use the "central command hypothesis".

Cardiac output and oxygen uptake during exercise

Oxygen uptake

During exercise the cardiac output increase to oblige the increased oxygen consumption. The increase in cardiac output is to a certain point proportionally with the body's total oxygen consumption, and may increase from 5L/min to 20L/min during heavy exercise. Above this point, the metabolism is anaerobic.

The hemoglobin in arterial blood is nearly 100 % saturated with oxygen during rest and exercise and therefore can't be increased. During rest, the hemoglobin in venous blood is about 75% saturated with oxygen. Exercising muscles will extract more oxygen from the hemoglobin than normal. This means that venous blood will have a lower oxygen saturation than 75%, maybe as low as 25%.

Cardiac output

The increased cardiac output is a result of increased heart rate and stroke volume.

$$\text{Cardiac Output} = \text{heart rate} \times \text{stroke volume}$$

The heart rate increase linearly with work load to maximum heart rate of 180-200 beats/min. The max heart rate can be estimated with this formula.

$$\text{Maximum heart rate} \approx 220 - \text{age}$$

The changes in stroke volume is only 10-20% when the pulse frequency is increased during exercise. The highest increment in stroke volume occurs at low heart rates. When the heart rate increase, the diastolic filling time is decreased. During rest the ventricular systole last approximately $\frac{2}{3}$ of the total heart cycle. During exercise, ventricular systole is approximately $\frac{1}{2}$ of the total heart.

The increase in stroke volume is achieved by the Starling mechanism (Starling's law of the heart). Increasing the filling pressure, results in increased end diastolic volume with the same heart muscle compliance.

Changes in blood flow during exercise

During exercise the blood flow to almost every tissue is altered:

Exercising muscles: During heavy exercise, the blood flow to the total muscle mass can increase from 1 L/min to 19 L/min. This increased perfusion is mainly caused by metabolic vasodilatation.

$$\text{Blood flow} = \text{resistance} \times \text{blood pressure}$$

To keep the blood pressure relatively constant with increased perfusion the resistance must be changed. The resistance in non-exercising muscles will increase and divert blood to exercising muscles.

Skin: In skin cutaneous vessels may constrict to support increased perfusion in exercising muscles. Increased core temperature may result in dilation of skin vessels, reducing Total peripheral resistance.

Blood pressure during static and dynamic exercise

In **dynamic exercise** the cardiac output is increased and total peripheral resistance is reduced, and are in balance resulting in small changes in mean arterial pressure (MAP). Systolic pressure increases and diastolic pressure may fall.

In **static exercise** diastolic pressure increases because contracted muscles impair muscle perfusion and activates metabolic receptors within the muscle, leading to increased peripheral resistance. (Alam & Smirk, 1937)

Role of circulating catecholamines

A important contribution to the rise in heart rate and cardiac output is the sympathetic nerves reflexes to the heart (Gullestad *et al.*, 1996). But there are also other pathways, hormonal regulations. In heart transplanted patients practically a denervated heart situation exercise result in increased cardiac output because of neurohumoral responses. This support peripheral reflex hypothesis.

How the tests were carried out is described in (Elstad *et al.*, 2002; Elstad *et al.*, 2008)

Chapter 2 – Overview of the model

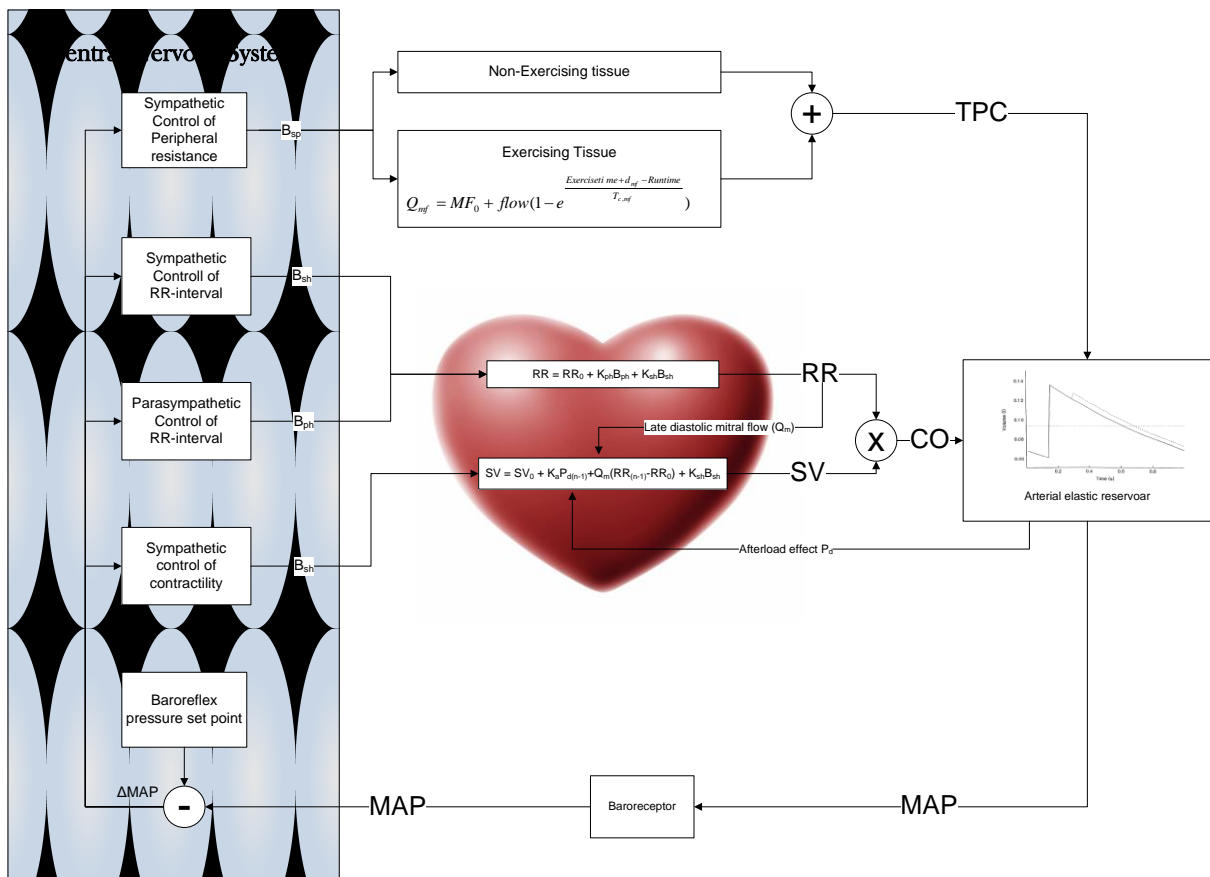


Fig 1: Overview of the model

The model:

The mathematical program consists of a simplified model of the heart, large arteries and peripheral vessels and baroreflex control of arterial pressure. Peripheral vessels are non-distributed and divided into vessels to exercising muscle and vessels to the rest of the body. The venous system is not represented in our model.

The hemodynamic variables are calculated in beat-by-beat sequences whereas the baroreflex (time processing) is modeled in a continuous time scale.

The baroreflex is divided into four parts:

- sympathetic heart contractility control
- sympathetic RR interval control
- parasympathetic RR interval control
- sympathetic control of peripheral arteries

Each of these four baroreflexes have their own gain, time constant and delay, and use variations in MAP from set point (ΔMAP) as input.

To simplify the program we calculate the mean value of the variables before onset of exercise and define this as a baseline and modeling the changes from this. An absolute value is calculated by adding the mean value before onset of exercise with the estimated baseline.

Variables we measured

- RR
- SV
- MAP
- Flow through the femoral artery on one side

The measured variables before onset of exercise (from time = 1 to Counttime) is noted as

- RR_0
- SV_0
- MAP_0
- FF_0
($MF = 2 \times FF$)

```
ModParam(25) = Average(expdata.expmap, 1, COUNTTIME);
```

Chapter 3 – Detailed overview of the physiology of the model

Cardiac function

Preload and afterload are the two most important moments deciding the contraction of the heart.

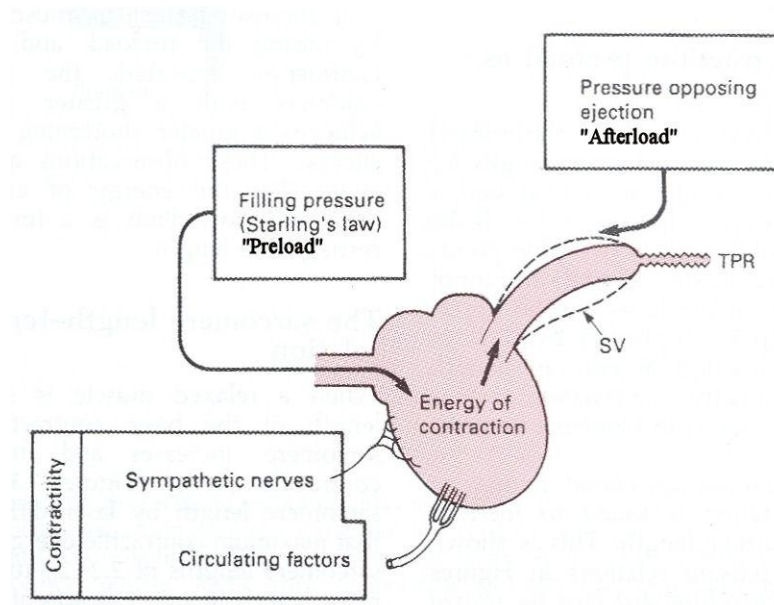


Fig 2: The pumping of the heart is affected by preload, afterload and contractility

Preload

Preload is how much the muscle is stretched before it contracts. End diastolic volume is hence a measure for preload. The larger EDV, the longer the myocytes are stretched, and the larger preload.

A myocyte has an optimal length leading to the most powerful contraction. In a healthy heart under normal circumstances, the preload will not stretch the myocyte to its maximum tension.

By stretching the relaxed myocyte the contractile energy is enhanced. This is the essence of the Starling curve.

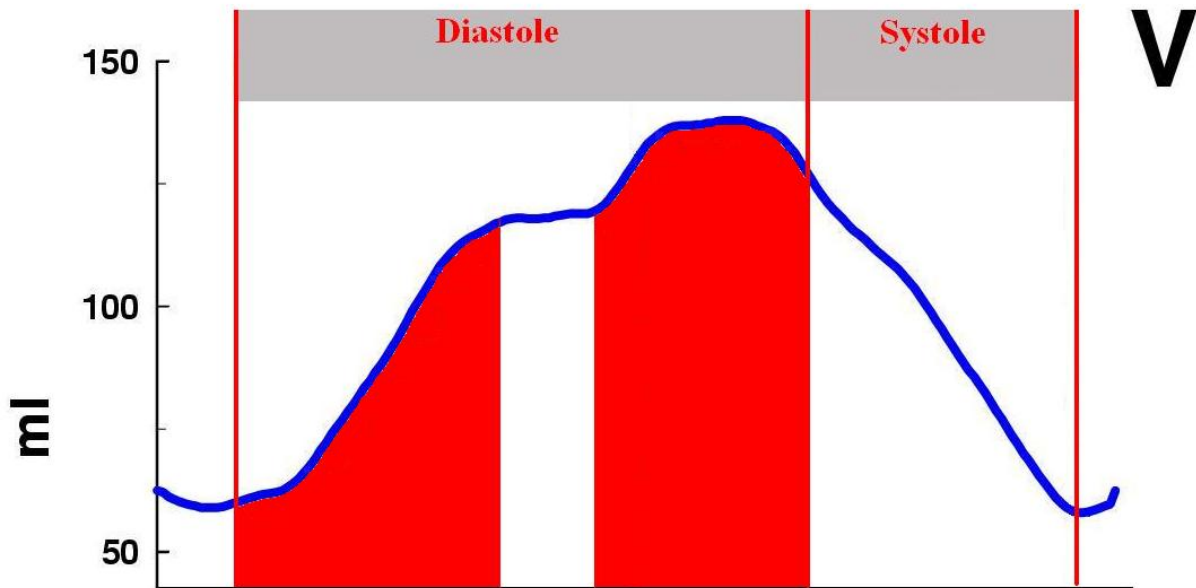


Fig 3: Filling of left ventricle during diastole and systole.

Figure 5 describe the change in blood volume of left ventricle during diastole and systole.

The first red area and the white area represent the passive inflow of blood to the left ventricle. The second red area, represents the contribution of atrial contraction to the end diastolic volume (EDV).

The red areas changes little during changes in RR. These are therefore included in SV_0 . In our model we only look at mitral flow late in diastole which is the white area in diastole. The length of this interval changes with changes in RR.

Preload will decline when heart rate increase because the time to fill the ventricle with blood is shorter than during rest.

In the program we estimate the change in Preload from steady-state to exercise by this formula

$$\dot{Q}_m(RR_{(n-1)} - RR_0)$$

Part of Eqn 1

$Q_m =$ Mitral flow late in diastole ($l s^{-1}$)

$RR_0 =$ RR interval at rest (s)

$RR_{(n-1)} =$ RR interval from previous heart stroke (s)

After-load

Afterload is the force of the contracting heart muscle pumping blood out of the heart during systole. Afterload is hence related to arterial pressure and varies through the whole cardiac cycle.

If afterload is increased, both the velocity of shortening, and the amount of shortening are reduced. By reducing afterload, the contractile shortening which increase the volume of blood ejected per beat is enhanced.

Afterload can be reduced by drugs that lower TPR and hence arterial pressure.

To estimate the change in afterload from steady state to exercise the following formula is applied

$$K_a P_{d(n-1)}$$

Part of Eqn 1

K_a = sensitivity to afterload effect on stroke volume (ml mmHg^{-1})

$P_{d(n-1)}$ = End-diastolic pressure from previous heart stroke (mmHg)

K_a is a property of the heart and it works as a gain. K_a decides the change in mL per change in mmHg.

$P_{d(n-1)}$ is the pressure within the aorta generated by the last heartbeat which the next heartbeat has to overcome.

Contractility

Contractility results in pressure variation, and the maximum rate of rise in pressure dP/dt_{max} can be used as an index of myocardial contractility. The contractile force is affected by the fiber length and hence end-diastolic volume.

Contractility may be affected by chemical influences, resting fiber length, sympathetic nerve activity and parasympathetic nerve activity. Important physiological inotropic stimuli include circulating levels of adrenaline, angiotensin II and extracellular Ca^{2+} -ions.

The increase in contractility increases ejection fraction and hence stroke volume.

The change in contractility from steady-state to exercise, we applied the formula

$$K_{shc} B_{sh}$$

Part of Eqn 1

K_{shc} = sensitivity to sympathetic signal to the heart, contractility (l mmHg^{-1})

B_{sh} = sympathetic signal to the heart (mmHg)

K_{shc} describes a property of the heart, and works as a gain, and decides the change in mL per change in mmHg.

B_{sh} describes the sympathetic signal that the CNS sends to the heart both to regulate the contractility and the RR-interval. This is the only place where CNS can affect stroke volume.

Starling's law of the heart

Ernest Starling experimented with ejection of blood in mammalian hearts. He showed that diastolic stretching of the heart influenced stroke volume.

When central venous pressure is increased, the ventricular end diastolic pressure increases and this increases end diastolic volume. The stretched ventricle develops a greater contractile force. This results in a greater stroke volume.

The left and right ventricles are coupled in series via the lungs. In the heart each ventricle has its own filling and Starling curves. We model only the left side.

Stroke volume (SV)

The change in stroke volume from rest to exercise is estimated by summing up preload, afterload and contractility. The total stroke volume during exercise is estimated by adding the change in stroke volume with the stroke volume in rest.

$$SV = SV_0 + \overbrace{K_a P_{d(n-1)}}^{\text{afterload}} + \overbrace{Q_m (RR_{(n-1)} - RR_0)}^{\text{preload}} + \overbrace{K_{shc} B_{sh}}^{\text{contractility}}$$

Eqn 1

K_a = sensitivity to afterload effect on stroke volume ($ml\ mmHg^{-1}$)

P_d = End-diastolic pressure from previous heart stroke (mmHg)

Q_m = Mitral flow late in diastole ($l\ s^{-1}$)

RR_0 = RR interval at rest (s)

$RR_{(n-1)}$ = RR interval from previous heart stroke (s)

K_{shc} = sensitivity to sympathetic signal to the heart, contractility ($l\ mmHg^{-1}$)

B_{sh} = sympathetic signal to the heart (mmHg)

RR interval

The contraction of the heart is mediated by an electric system within the heart. The electric signal starts in the sino-atrial node in the right atrium and triggers the myocytes in the heart to contract. The sino-atrial node is influenced by sympathetic nerves which speeds the heart up (tachycardia) and parasympathetic nerves which slows it down (bradycardia). The sino-atrial node is also sensitive to temperature, and during fever the heart rate increases approximately by 10beats/min per 10°C.

When the heart rate is over 100beats/min sympathetic stimulus is dominant. In our experiment the heart rate is below 100beats/min, and a parasympathetic stimulus is dominant.

In our model we decided to use RR-interval instead of heart rate. RR-interval is the time between R-waves in an EKG measured in seconds. During the R wave the ventricle contracts.

$$RR (s) = \frac{60}{\text{heart rate}(min)}$$

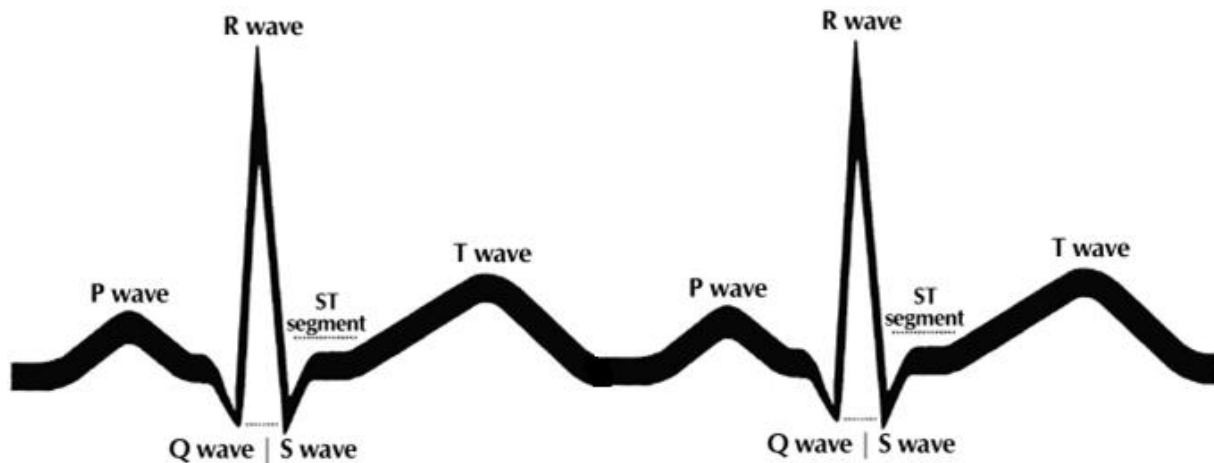


Fig4; EKG signal over two heart cycles

In the program we estimate RR interval by this formula

$$RR = RR_0 + K_{ph_{RR}} B_{ph} + K_{sh_{RR}} B_{sh}$$

Eqn 2

RR_0 = RR interval during rest

$K_{ph_{RR}}$ = Sensitivity to parasympathetic signal to the heart ($s \text{ mmHg}^{-1}$)

B_{ph} = Parasympathetic signal to the heart (mmHg)

$K_{sh_{RR}}$ = Sensitivity to sympathetic signal to the heart ($s \text{ mmHg}^{-1}$)

B_{sh} = Sympathetic signal to the heart (mmHg)

The Cardiac cycle

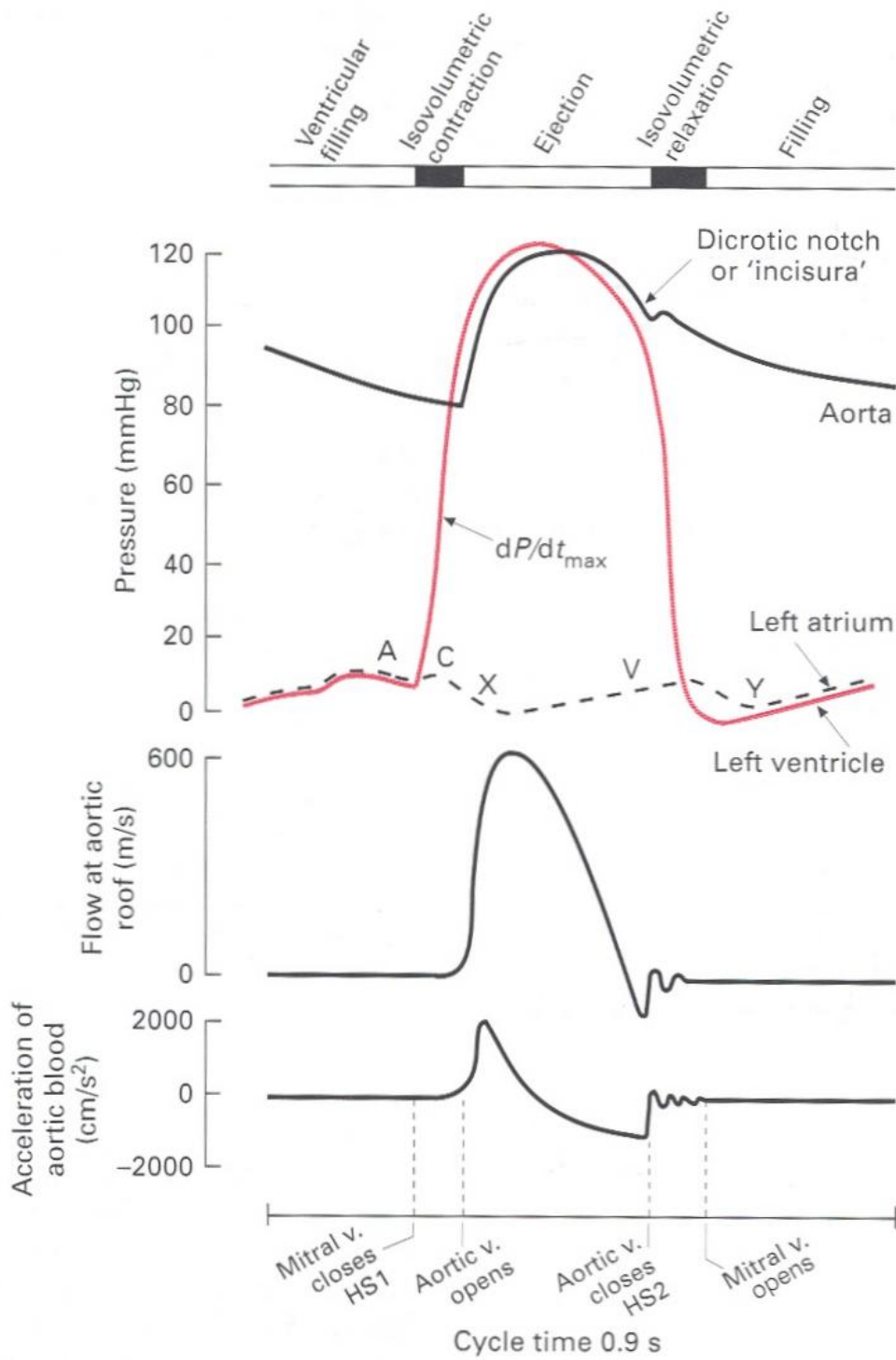


Fig 5: Pressure and flow in right ventricle of the human heart

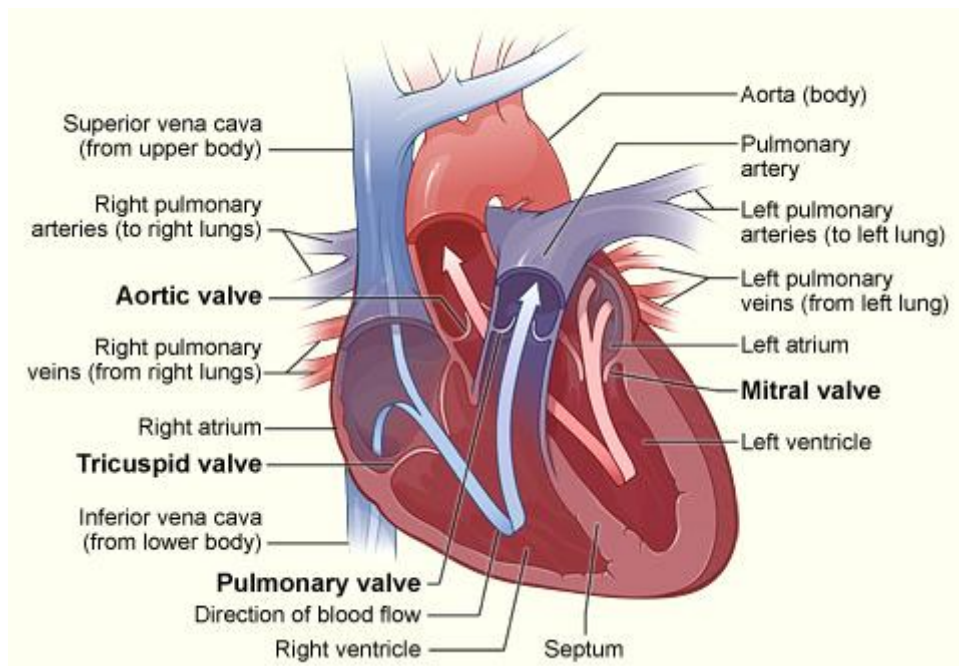


Fig 6: The anatomy of the heart

The cardiac cycle has four phases:

1. **Ventricular filing**
2. **Isovolumetric contraction**
3. **Ejection**
4. **Isovolumetric relaxation**

Phase 4 and Phase 1 is the **diastole**

Phase 2 and Phase 3 is the **systole**

Ventricular filling

Inlet valves (tricus & mitral):	Open
Outlet valves (pulmonary and aortic)	Closed

Ventricular diastole the rest period is the longest phase in the cardiac cycle, lasting nearly $\frac{2}{3}$ of the period. The filling of the ventricle is complicated also influenced by pressure variations within the thorax and the atrial contraction enhancing ventricular filling with 10-20% in younger people and up to 46% in elderly.

The volume of blood in a ventricle at the end of filling phase is called end diastolic volume (EDV) and is about 120mL in an adult human weighing 70 kg. The corresponding pressure is called end diastolic pressure (EDP) and is only a few mmHg. The EDP on the left side is slightly higher than on the right side because of the thickness of the myocard. (The pressure needs to be higher on the left side to be able to pump blood around the whole body than on the right side who only pumps blood through the lungs.)

Isovolumetric contracting

Inlet valves (tricus & mitral):	Closed
Outlet valves (pulmonary and aortic)	Closed

When the pressure in the ventricle rises above the pressure in the atria, the atrioventricular valves closes. The pressure in the ventricle is lower than the pressure in the aorta and in the pulmonary artery, so the pulmonary and aorta valve is also closed.

The muscle contraction will now lead to a steep increasment in pressure.

Ejection

Inlet valves (tricus & mitral):	Closed
Outlet valves (pulmonary and aortic)	Open

When the pressure inside the ventricle exceeds the pressure in the aorta and pulmonary artery, the pulmonary and aortic valves opens, and blood flow out of the heart. Within the first half of the ejection phase, about 75% of the stroke volume is ejected. The blood is ejected faster than it can escape the arterial tree. This lead to temporarily accumulation of blood in the large arteries. This happens because the arteries are elastic. The flow of blood from the arteries to capillaries continues in the diastole.

Average ejection fraction in man is about 0.6-0.7, corresponding to a stroke volume of 70-80mL. The residual end systolic volume of about 50mL acts as a reservoir to increase stroke volume during exercise.

Isovolumetric relaxation

Inlet valves (tricus & mitral):	Closed
Outlet valves (pulmonary and aortic)	Closed

When the pressure in the aorta and pulmonary artery exceeds the pressure in the ventricle the pulmonary and aortic valves close. The pressure drops rapidly because of mechanical recoil because of elastic collagen fibers in the myocard. When ventricular pressure drops below atrial pressure the atrioventricular valves opens and blood flows from the atria to the ventricle.

Peripheral circulation

Large arteries

The walls of the large arteries contain elastic fibers. The arteries works therefore as an elastic reservoir, which expands during systole and decrease during diastole. This pressure wave moves from the heart to peripheral tissues as a palpable pulse.

Because the arteries are elastic they prevent an excessive rise in blood pressure during systole. The resistance in an elastic artery varies with pressure, and the resistance in an elastic artery is less than in a rigid artery. The elastic property of the arteries diminishes with age. This occurs because the walls in arteries become less elastic as a result of atherosclerosis. The elasticity is called compliance.

The pressure pulse from the heart to the brachial artery travels faster than a red blood cell.

The dicrotic notch is a rapid pressure change in blood pressure at the end of systole. It is caused by the aorta valves closing. The valves close because the pressure in aorta is greater than the pressure in left ventricle. Blood in the aorta reverses and closes the aorta valves. This pressure change makes the dicrotic notch.

Large arteries are modeled with these formulas:

$$\dot{p} = \frac{\dot{Q}_h - \dot{Q}_p}{C}$$

Eqn 3

\dot{p} = time- differentiated pressure in aorta (mmHg)

\dot{Q}_h = Flow out of the heart (s^{-1})

\dot{Q}_p = Total flow in the peripheral arteries (s^{-1})

C = Aortic compliance (l mmHg⁻¹; C = 0.00005 l mmHg⁻¹ kg⁻¹)

$$\dot{Q}_p = P_a G_p$$

Eqn 4

\dot{Q}_p = Total flow in the peripheral arteries (s^{-1})

P_a = Instantaneous pressure in the aorta (mmHg)

G_p = TPC (s^{-1} mmHg⁻¹)

The windkessel modell

Windkessel is a German word for air chamber. When water is pumped into the chamber the air are going to be compressed. This reduce the pressure amplitude. The condition for water being pumped out in a cycle with no active pumping is that the air pressure in the camber is higher than the outside air pressure. The compressible air in the chamber can be compared to the elasticity in the major arteries.

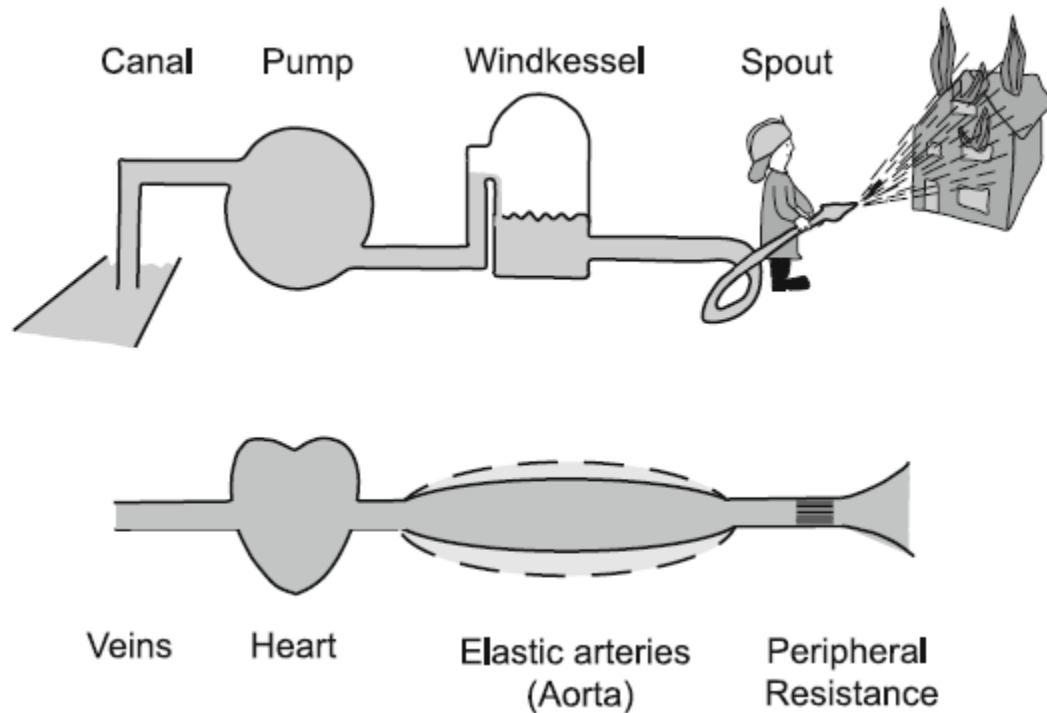


Fig 71: The windkessel model compared to the human body

Peripheral resistance

Turbulent blood flow occurs when r is high (aorta) or when \bar{v} is high (high cardiac output).

Laminar blood flow through a vessel, the velocity of blood flowing nearest to the vessel wall is close to zero, and the blood flowing in the centre of the vessel has the greatest velocity.

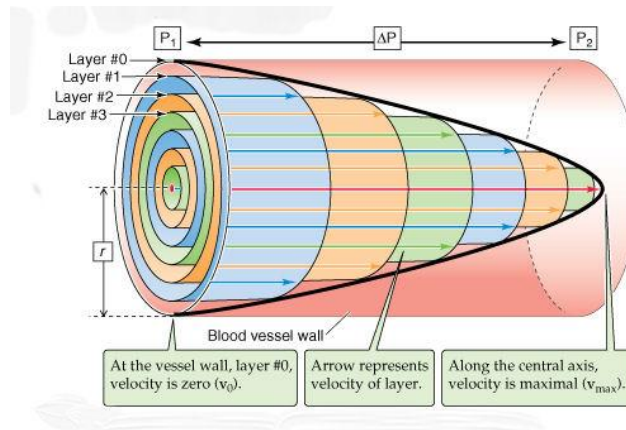


Fig 8: Laminar blood flow

The friction arises from internal friction between adjacent lamina of fluid. This friction is called viscosity. In our model we assume a laminar flow.

The most important factor is the radius of the tube. A reduced radius will increase the friction between two adjacent lamina.

Poiseuille formulated a formula for resistance in a steady laminar flow of a Newtonian fluid such as water and plasma along a strait tube.

$$R = \frac{8\eta \times L}{\pi r^4}$$

R = resistance
 η = Fluid viscosity
 L = length of the tube
 r = radius of the tube

A non-Newtonian fluid is a fluid where viscosity changes with applied shear stress. Blood is a non-Newtonian fluid but plasma is a Newtonian fluid.

Many blood vessels are able to change luminal size by contraction and relaxation (Vasoconstriction and vasodilatation). Vessels contract when they are exposed to catecholamines or some local hormones.

$$G = G_0(1 + K_{sp}B_{sp})$$

Eqn 5

G = Conductance in peripheral vascular bed ($s^{-1} \text{ mmHg}^{-1}$)
 G_0 = Total peripheral conductance TPC before exercise ($s^{-1} \text{ mmHg}^{-1}$)
 K_{sp} = Sensitivity to sympathetic signal to the heart (mmHg^{-1})
 B_{sp} = Sympathetic signal to the peripheral vessels (mmHg)

$$G_p = G_r + G_e$$

Eqn 6

G_p = TPC ($s^{-1} \text{ mmHg}^{-1}$)
 G_r = Conductance in the non-exercising parts of the body ($s^{-1} \text{ mmHg}^{-1}$)
 G_e = Conductance in the exercising part of the body ($s^{-1} \text{ mmHg}^{-1}$)

$$G_e = Ex_{cond}G_p \quad \text{Before and}$$

Eqn 7

$$G_e = \frac{\dot{Q}_{mf}}{MAP} \quad \text{after onset of exercise}$$

Eqn 8

G_e = Conductance in the exercising part of the body ($s^{-1} \text{ mmHg}^{-1}$)

Ex_{cond} = Fraction of TPC in the exercising parts of the body (fraction; $Ex_{cond} = SV_0/MF_0$)

G_p = TPC ($s^{-1} \text{ mmHg}^{-1}$)

\dot{Q}_{mf} = Muscle flow ($l \text{ s}^{-1}$)

In our experiment, the person is laying down, so the potential energy equals zero. The kinetic energy is also low because of the velocity of blood flow is low in our experiment. The hydrostatic pressure is the most important factor in our model.

Baroreflexes

Baroreflexes are regulated by the brain which receives information about cardiac filling and arterial pressure. The two most important sensors are pressure receptor around the wall of systemic arteries and pressure sensors within the wall of the heart

Baroreceptors are stretch sensitive nerve endings in the adventitia layer in the vessel wall. They are localized in the carotid sinus in the internal carotid and the aortic arch

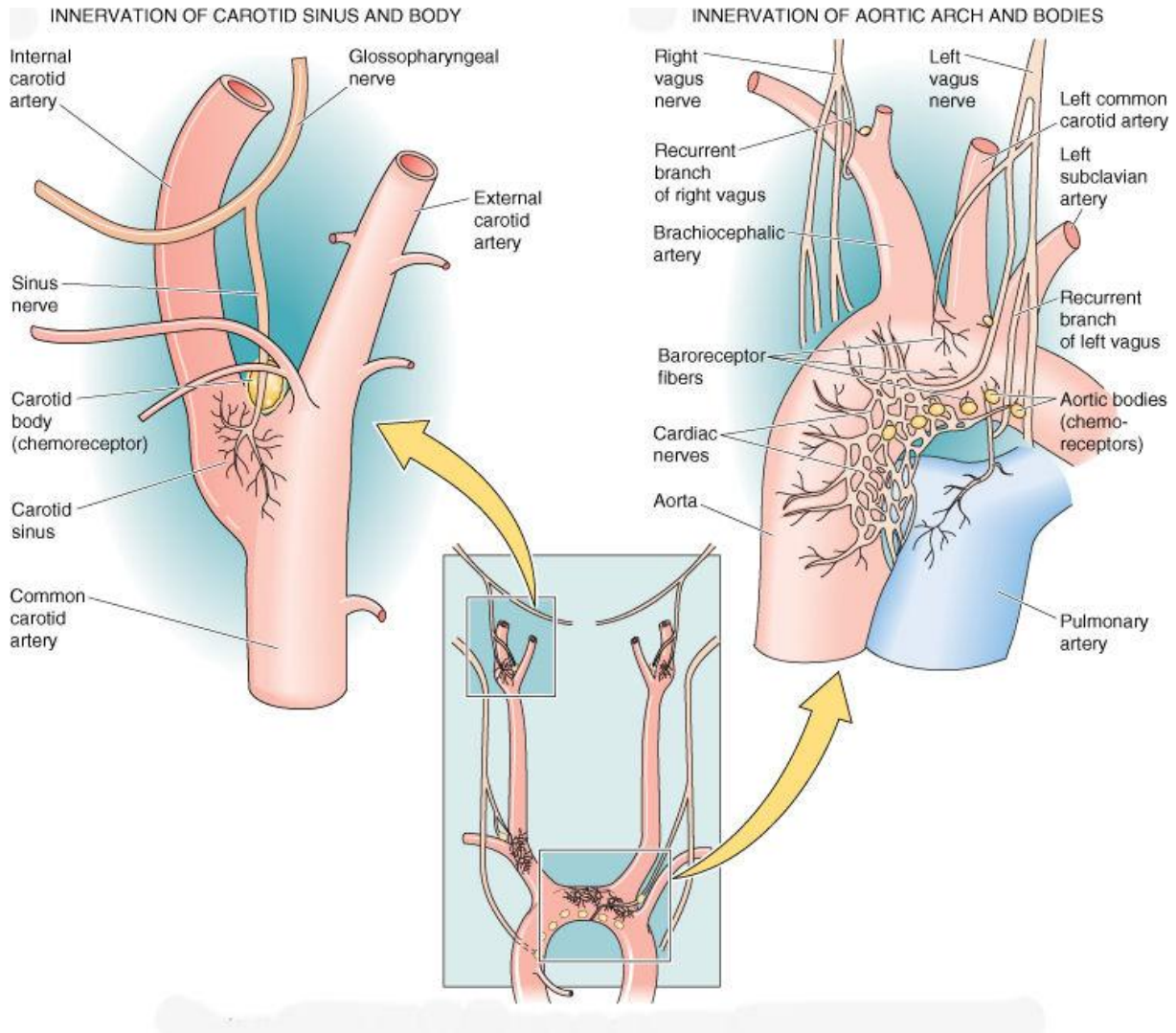


Fig9: Anatomy of the baroreceptors

The Carotid baroreceptors are sensitive to pulse pressure and MAP. Stimulation the aortic nerve causes a reflex depression of the heart rate via increased vagal and decreased sympathetic nerve activity and blood pressure via inhibiting sympathetic peripheral activity. The reduced sympathetic stimuli of peripheral vessels lead to reduced vasoconstriction and hence reduction in total peripheral resistance. The increased vagal stimuli and reduced sympathetic stimuli to the heart leads to bradycardia and reduced contractility.

Bradycardia from vagus mediated activity is faster than changes in vascular resistance

In our model we use MAP minus set point for arterial pressure as input, and output are sympathetic signal to peripheral vascular bed, and sympathetic and parasympathetic signals to the heart.

$$B(t) \equiv \frac{1}{T_c} \int_{-\infty}^{t-d} [P(t') - P_s(t')] e^{-(t'+d)/T_c} dt$$

Eqn 9

$B(t)$ = Baroreflex signal (mmHg)
 $T_{c,ph}$ = Baroreflex time constant, parasympathetic to the heart (s; $T_{c,ph} = 0.25s$)

$T_{c, sh}$	= Baroreflex time constant, sympathetic to the heart (s; $T_{c, sh} = 10s$)
$T_{c, sp}$	= Baroreflex time constant, sympathetic to the peripheral vessels (s; $T_{c, sp} = 10s$)
d_{ph}	= Baroreflex delay, parasympathetic to the heart (s; $d_{ph} = 0.25s$)
d_{sh}	= Baroreflex delay, sympathetic to the heart (s; $d_{sh} = 1.00s$)
d_{sp}	= Baroreflex delay, parasympathetic to the peripheral vessels (s; $d_{sp} = 6.00s$)
$P(t)$	= Time-dependent mean artery pressure (mmHg)
$P_s(t)$	= set point for arterial pressure control (mmHg)

t' is an integration variable

As elicited in this presentation many variables influence hemodynamic in the initial period of exercise. Modeling circulation is therefore a complicated procedure. Despite this we have tried to make a model of the hemodynamic and comparing it with measured data in healthy volunteers.

Chapter 4 – Detailed overview of the Model

The Program

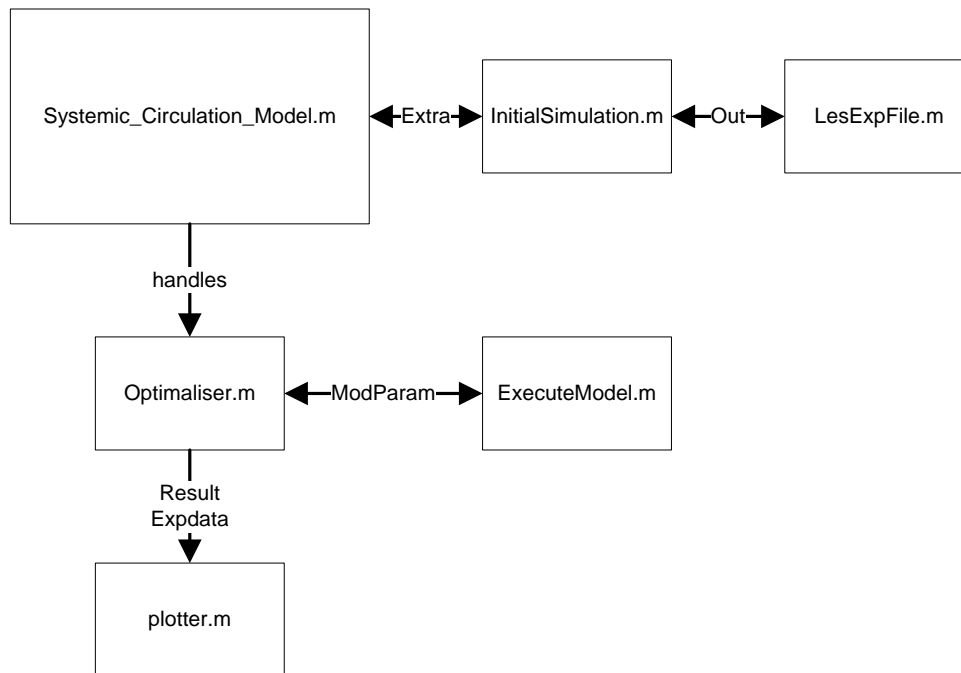


Fig 10: Simplified overview of the program

Systemic_Circulation_Model.m

This program controls the Graphical user interface where the user can change the parameters (ModParam) and checks ModParam for limits.

InitialSimulation.m

This program sets ModParam to an initial value set in the program, and then sends it to ExecuteModel.m which returns the new value for MAP, RR, SV, MF and stores it in the struct extra.

The average value for MAP, RR, SV, MF before onset of exercise and is also calculated.

LesExpFile.m

This program reads the experiment data from file and calculates variance in RR, SV, MAP and MF. Ex_{cond} is also calculated here.

In our input file the data is arranged like this:

1. Time (s)
2. RR (s)
3. SV (mL/beat)
4. MAP (mmHg)
5. FV (mL/beat) in the right femoral artery
6. FV (mL/beat) in the right femoral artery
7. FV + FV with 2s delay (mL/beat)
8. FV + FV with 2s delay (L/beat)
9. Change in "FV + FV with 2s delay" (L/beat)

All measurements of flow in the femoral artery is only done on one side.

Optimaliser.m

This program uses the `fminsearch()` to find a minimum of a scalar function of several variables, starting at an estimate (unconstrained nonlinear optimization).

The variables are updated with `ExecuteModel.m` and plotted with `Plotter.m` when optimization is finished.

ExecuteModel.m

This program takes the inputs from `ModParam`, and estimates the next value of

- RR-interval
- Stroke volume
- Mean arterial pressure
- Muscle flow through femoral artery

Plotter.m

This program plots four graphs;

- RR-interval
- Stroke volume
- Mean arterial pressure
- Muscle flow through femoral artery

Each graph has a green plot which is the measured data, and a red line which is the result from our estimation.

Detailed overview of ExecuteModel.m

```
WindKessel=T_WindKessel(windcompl,map0,sv0,rr0);
```

This method uses an analytical solution of a differential equation for the windkessel model. It calculates end diastolic pressure and volume ejected/remaining in the arterial tree before onset of exercise, based on the compliance, mean arterial pressure, stroke volume and RR interval.

```
Cond = sv0 / (rr0 * map0);
```

Calculates total peripheral conductance.

```
while (RunTime < SIMTIME)
```

While the time the experiment has left is less than the time we look at (up to 110 seconds)

```
MapError = LastMap - SetPoint(RunTime, EXERCISETIME,
```

```
ExerciseState == exerc, ExerciseState == downcnt, BaroSetpoint);
```

Calculates the deviation in mean arterial pressure from `SetPoint`. `SetPoint` is calculated based on runtime, exercisetime and whether the test person is exercising or not. If the person is at rest, Eqn 7 is used, and if the person is exercising, Eqn 8 is used to calculate conductance.

```
[MapError,BaroAdapt] = NewVal(MapError,BaroAdapt);
```

```
[Heart,NewSv,NewRR]=NewBeat(LastEdp, mem, mem2, Heart);
```

Calculates a new stroke volume and a new RR-interval according to Eqn and

```

if (RunTime >= COUNTTIME) {
TotCond = Condone(PerSympSig, nonexbody)+Condtwo(PerSympSig,
MuscFlow(RunTime, EXERCISETIME, MuscFlowFunc,MF0), map0, restex);
    Calculates the sum of conductance in the two parallel non-distributed circuits. Condone uses
    Eqn and Condtwo uses a modification of Eqn 8 ( $G = G_0 + Q_{mf} / MAP$ ) during exercise and
    Eqn 7 during rest.

NewMf = MuscFlow(RunTime, EXERCISETIME, MuscFlowFunc,MF0);
    The flow through the femoral artery is calculated with Eqn 10.

WindKessel=Cycle(SYSTDUR, TotCond, WindKessel);
    Calculates time constant of the volume decay in artery, mean arterial pressure and the
    volume left in the artery.

WindKessel=Cycle(NewRR - SYSTDUR, TotCond, WindKessel);

}

```

Modeling the heart

When we are modeling the heart, we assume a perfect starling mechanism. This means that the end-systolic ventricular volume is constant. In other words, all the volume that flows into the heart is pumped out during the next systole. We also assume a linear relationship between increased afterload and reduction of stroke volume. Changes in RR-interval on preload are approximated by late diastolic filling of the left ventricle.

For each heart stroke a new value for RR interval and SV are calculated

$$RR = RR_0 + K_{ph}B_{ph} + K_{sh}B_{sh}$$

Eqn 2

NewBeat.m

```
newrr = o.rr0 + parasymp * o.parasens0 + symp * o.sympsens0;
```

K_{ph} = Sensitivity to parasympathetic signal to the heart ($s \text{ mmHg}^{-1}$)

B_{ph} = Parasympathetic signal to the heart (mmHg)

K_{sh} = Sensitivity to parasympathetic signal to the heart ($s \text{ mmHg}^{-1}$)

B_{sh} = Parasympathetic signal to the heart (mmHg)

Strokevolume is estimated by adding strokevolume during rest, afterload, preload and contractility.

$$SV = SV_0 + \overbrace{K_a P_{d(n-1)}}^{\text{afterload}} + \overbrace{Q_m (RR_{(n-1)} - RR_0)}^{\text{preload}} + \overbrace{K_{shc} B_{sh}}^{\text{contractility}}$$

Eqn 1

NewBeat.m

```
newsv = o.sv0 + (o.lastrr - o.rr0) * o.mitf0 + (map - o.edp0) * o.af10 -
symp * o.sympcontsens0;
```

K_a = sensitivity to afterload effect on stroke volume (ml mmHg^{-1})
 P_d = End-diastolic pressure (mmHg)
 Q_m = mitral flow late in diastole (s^{-1})
 K_{sh} = sensitivity to sympathetic signal to the heart (l mmHg^{-1})
 B_{sh} = sympathetic signal to the heart (mmHg)

K is a property of the heart and it works as a gain.

- K_a decides the change in mL per change in mmHg
- K_{sh} decides the change in mL per change in mmHg
- K_{ph} decides the change in RR interval (s) per change in mmHg

$P_{d(n-1)}$ is the pressure within the aorta which the last heartbeat generated, and the next heartbeat has to overcome.

B_{sh} is the signals that the CNS sends to the heart and regulates the contractility and RR.

In this model chemical influences to the myocyte is disregarded, and the only stimuli is sympathetic and parasympathetic control from CNS.

Modeling the large arteries

The large arteries are modeled as a linear elastic reservoir with certain compliance, which receives blood from the heart in each systole. The flow out of the large arteries is modeled as an exponential pressure dependent volume reduction with a time constant depending on TPC (G_p) and windkessel compliance (C). The outflow to peripheral vascular bed is continuously through the whole cardiac cycle.

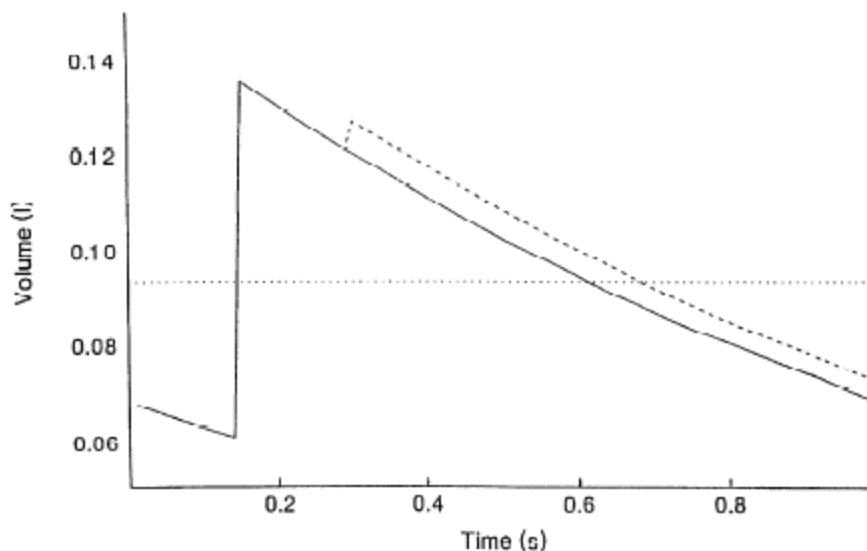


Fig 11: Exponential pressure dependent volume reduction in vessel

After onset of exercise the extra blood to exercising muscle (Q_{mf}) is withdrawn from the reservoir during the whole cycle.

For each windkessel cycle, MAP is calculated by integration, and EDP is read just before the next systole.

The total arterial compliance is the change in volume per change in pressure.

$$C = \frac{\Delta V}{\Delta P}$$

(Westerhof *et al.*, 2008)

We modeled the large arteries in our body with a two-element windkessel model.

$$\dot{p} = \frac{\dot{Q}_h - \dot{Q}_p}{C}$$

Eqn 3

p = time- differentiated pressure in aorta (mmHg)

\dot{Q}_h = Flow out of the heart (s^{-1})

\dot{Q}_p = Total flow in the peripheral arteries (s^{-1})

C = Aortic compliance ($mmHg^{-1}$; $C = 0.00005 \text{ l } mmHg^{-1} \text{ kg}^{-1}$)

Ohm's law gives us this relationship between pressure, resistance and flow

$$Pressure = Resistance \times Flow$$

$$Flow = Pressure \times \frac{1}{Resistance} = Pressure \times TPC$$

$$\dot{Q}_p = P_a G_p$$

Eqn 4

\dot{Q}_p = Total flow in the peripheral arteries (s^{-1})

P_a = Instantaneous pressure in the aorta (mmHg)

G_p = TPC ($s^{-1} mmHg^{-1}$)

The volume and pressure in the windkessel are calculated in two steps. During the first 0.15s of a new cycle – there is a pure exponential volume reduction. At the end of this interval the end diastolic pressure P_d is read, and is used to calculate the next stroke volume. The stroke volume is added to the reservoir in one step and the exponential volume decay during the rest of the cycle is calculated.

Cycle.m

```
o.tc = o.compl0 / pc;    %Calculate time constant of volume decay*/
exf = exp(-(rr / o.tc));    %Compute exponential function
coefficient*/
newmap = o.volume * o.tc * (1 - exf) / (rr * o.compl0);
%Compute mean arterial pressure by integration*/
o.volume = o.volume*exf;    %Compute volume at end of cycle*/
o.pint = o.pint+ newmap * rr;
o.tsum = o.tsum+ rr;
```

T_WindKessel.m

```
SYSTDUR = 0.15;
```

```
o.tc = compliance * map * rr0 / sv0;
```

```
o.compl0 = compliance;    %Set compliance value*/
```

```

o.f = exp(-(rr0 / o.tc));
o.f2 = exp(SYSTDUR / o.tc);

o.volume = sv0 * o.f2 * o.f / (1 - o.f);

%Calculate exact initial end-diastolic volume*/
o.Edp = o.volume / compliance;
o.pint = 0.0;
o.tsum = 0.0;

o=class(o, 'T_WindKessel');

```

Modeling the peripheral resistance vessels

The peripheral circulation is represented by two parallel resistances, representing the legs, and the rest of the body. This division was chosen to permit the exercising muscles to be excluded from the baroreflex control of peripheral resistance. The conductance in both of the parallel circuit is calculated beat-by-beat.

$$G_p = G_r + G_e$$

Eqn 6

$G_p = \text{TPC} (s^{-1} \text{ mmHg}^{-1})$
 $G_r = \text{Conductance in the non-exercising parts of the body} (s^{-1} \text{ mmHg}^{-1})$
 $G_e = \text{Conductance in the exercising part of the body} (s^{-1} \text{ mmHg}^{-1})$

$$G = G_0(1 + K_{sp}B_{sp})$$

Eqn 5

Condone.m

```

function out=Condone(innerv,o)

    out=o.g0 * (innerv * o.sens0 + 1.0);

```

$G = \text{Conductance in peripheral vascular bed} (s^{-1} \text{ mmHg}^{-1})$
 $G_0 = \text{Total peripheral conductance TPC before exercise} (s^{-1} \text{ mmHg}^{-1})$
 $K_{sp} = \text{Sensitivity to symphathetic signal to the heart} (mmHg^{-1})$
 $B_{sp} = \text{Symphathetic signal to the peripheral vessels} (mmHg)$

Before onset of exercise the conductance in the exercising part of the boy is a given fraction of TPC.

ExecuteModel.m

```

Cond = sv0 / (rr0 * map0);
nonexbody=ResistVessel(Cond * (1.0 - restexfrac),symppergain);
restex=ResistVessel(Cond * restexfrac,symppergain);

```

The fraction of TPC representing the exercising muscle during rest Ex_{cond} is calculated by dividing the flow through the muscle by the strokevolume and RR-interval.

InitialSimulation.m

```

ModParam(13) = ModParam(28) / (ModParam(27) * ModParam(26));

```

After onset of exercise the conductance is estimated by Ohm's law.

$$G_e = Ex_{Cond}G_p \quad \text{Before and}$$

Eqn 7

$$G_e = \frac{\dot{Q}_{mf}}{MAP} \quad \text{after onset of exercise}$$

Eqn 8

G_e = Conductance in the exercising part of the body ($s^{-1} \text{ mmHg}^{-1}$)

Q_{mf} = Muscle flow (s^{-1})

Ex_{Cond} = Fraction of TPC in the exercising parts of the body

G_p = TPC ($s^{-1} \text{ mmHg}^{-1}$)

Condtwo.m

```
function out=Condtwo(innerv,muscflow,mapsetp,o)

    if (o.exercise)
        out=o.g0 + (muscflow / mapsetp);
    else
        out=o.g0 * (innerv * o.sens0 + 1.0);
    end
```

Modelling femoral flow

In this model we use an analytical solution of a differential equation to model blood flow through both legs:

MuscFlow.m

```
out = MF0 + o.flow0 * (1.0 - exp((ExerciseTime + o.dly0 - Runtime) /
o.tc0));
```

$$Q_{mf} = MF_0 + flow \left(1 - e^{-\frac{\text{Exercisetime} + d_{mf} - \text{Runtime}}{T_{c,mf}}} \right)$$

Eqn 10

d_{mf}	MuscFlDly	Muscle flow delay (s; $d_{mf} = 1.8s$)
Q_{mf}	MuscFlow	Muscle flow ($l \text{ s}^{-1}$; adjusted)
$T_{c,mf}$	MuscFlTc	Muscle flow time constant (s; adjusted (constrained to less than 13,2 s))
MF_0	MF0	Muscle flow at rest ($l \text{ s}^{-1}$)
Flow	flow0	Maxflow through the femoral artery
Exercisetime		Total exercising time (seconds 110s)
Runtime		how long the exercise has lasted.

Modeling the baroreflexes

The time processing of the input from peripheral baroreflexes is modeled by three separate time domain processing objects, each with its own preset time constant and delay. The input is MAP minus the set point for arterial pressure and the output are a sympathetic signal to the heart (B_{sh}), parasympathetic signal to the heart (B_{ph}) and sympathetic signal to peripheral vascular bed (B_{sp}).

$$B(t) \equiv \frac{1}{T_c} \int_{-\infty}^{t-d} [P(t') - P_s(t')] e^{-(t'+d)/T_c} dt$$

Eqn 9

$B(t)$	= Baroreflex signal (mmHg)
$T_{c, ph}$	= Baroreflex time constant, parasympathetic to the heart (s; $T_{c, ph} = 0.25s$)
$T_{c, sh}$	= Baroreflex time constant, sympathetic to the heart (s; $T_{c, sh} = 10s$)
$T_{c, sp}$	= Baroreflex time constant, sympathetic to the peripheral vessels (s; $T_{c, sp} = 10s$)
d_{ph}	= Baroreflex delay, parasympathetic to the heart (s; $d_{ph} = 0.25s$)
d_{sh}	= Baroreflex delay, sympathetic to the heart (s; $d_{sh} = 1.00s$)
d_{sp}	= Baroreflex delay, sympathetic to the peripheral vessels (s; $d_{sp} = 6.00s$)
$P(t)$	= Time-dependent mean arterial pressure (mmHg)
$P_s(t)$	= set point for arterial pressure control (mmHg)

t' is an integration variable.

Intervall_Sjekk.m

Controls that variables returned from `Optimaliser.m` is between the minimum and maximum value, defined in `Systemic_Circulation_Model.m`. If a variable is lower than the minimum, the value of the variable is set to the minimum. If a variable is above the maximum, the value of the variable is set to maximum.

Estimating error

`AnyErr.m` estimates the error for MAP, SV, RR and MF, and weights it by dividing the error with the variance in measured data before onset of exercise.

LesExpFile.m

```
out.rrwh = 1 / Variance(file(:,rr), 1, SIMTIME);
out.svwh = 1 / Variance(file(:,sv), 1, SIMTIME);
out.mapwh = 1 / Variance(file(:,map), 1, SIMTIME);
out.mfwh = 1 / Variance(file(:,mf), 1, SIMTIME);
```

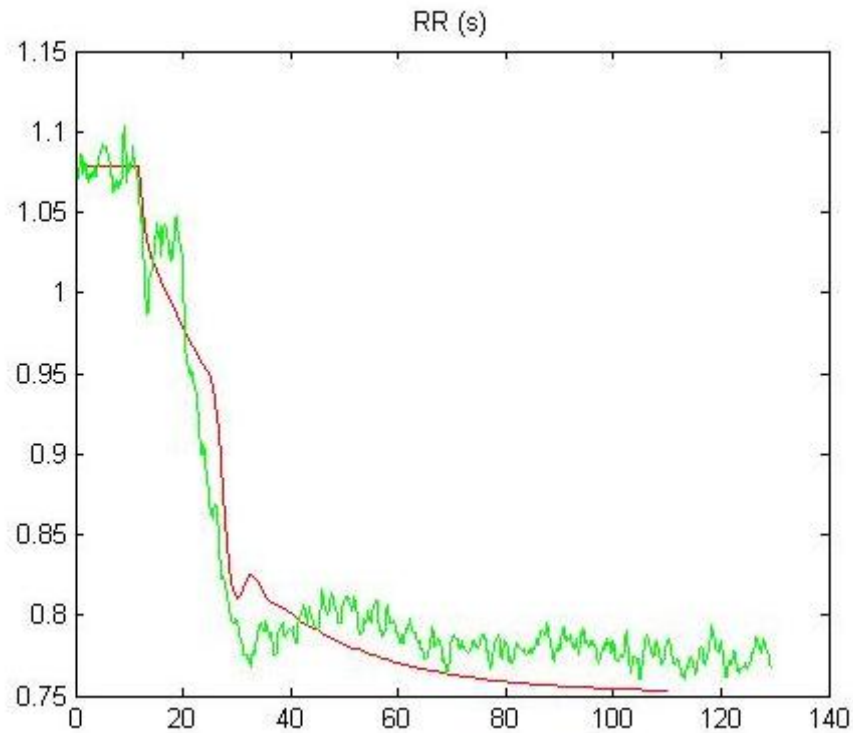
AnyErr.m

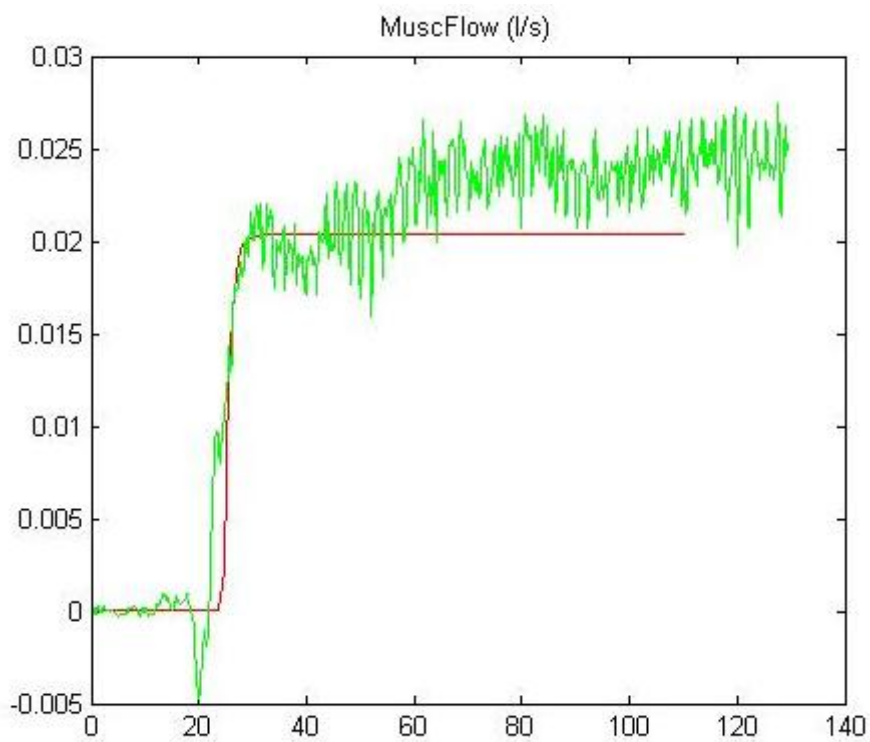
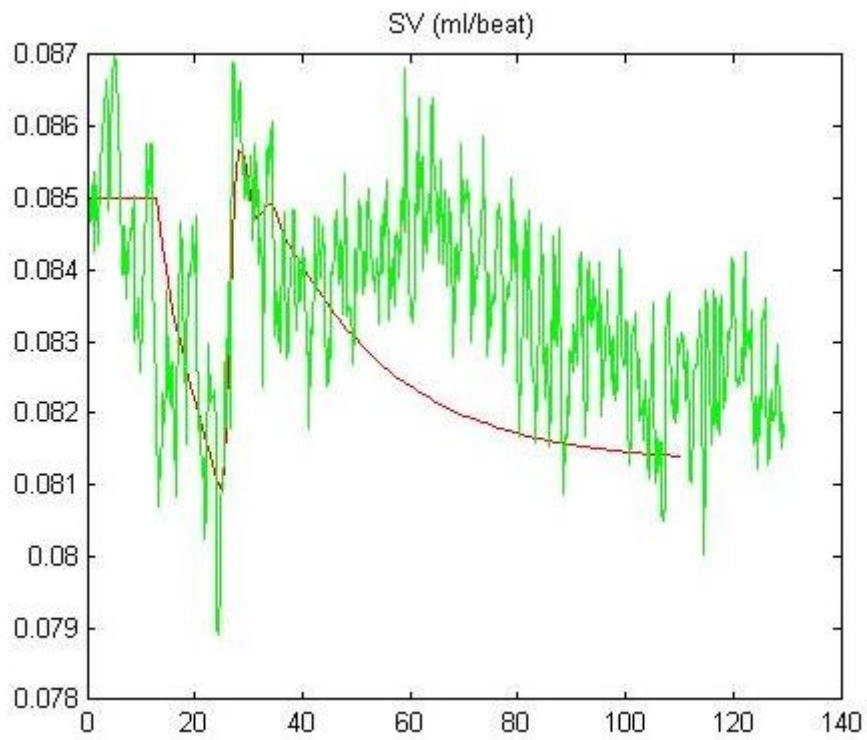
```
out=expdata.mapwh * Err_map + expdata.svwh*Err_sv + expdata.rrwh * Err_rr +
expdata.mfwh * Err_mf;
```

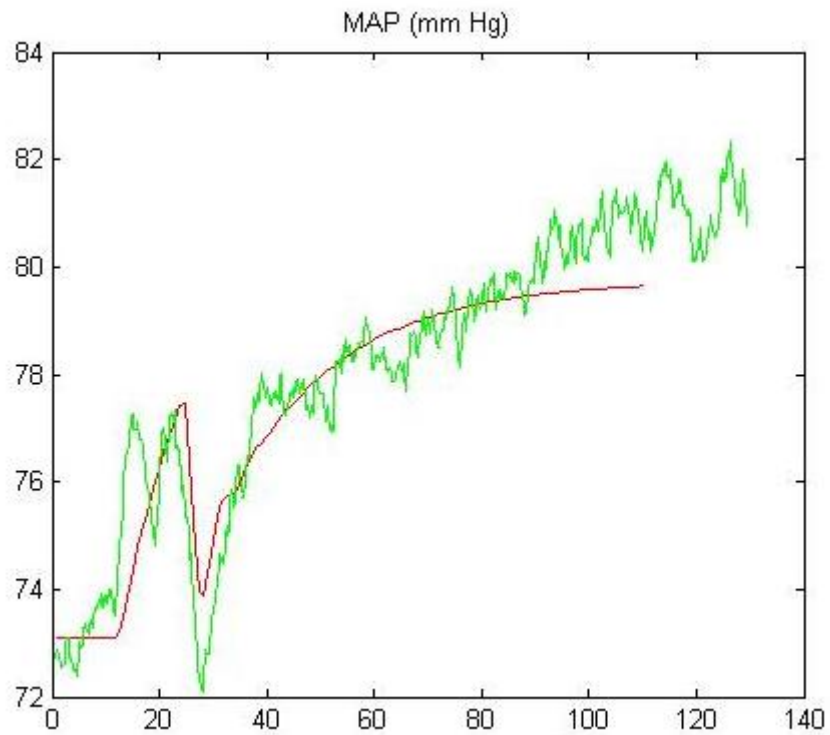
Chapter 5 Results

The data was collected from 50 healthy volunteers. During the experiment the volunteers were laying down with extended legs and the right ankle placed against weights. The RR-interval, cardiac strokevolume (SV), MAP and the flow through the femoral artery was measured at rest and followed after onset of exercise.

The results, RR-interval, SV, muscle flow, and MAP are presented and the green graph represents the mean value of the measured data, and the red graph represents the results from our model.







Chapter 6 Conclusion

As the graphs shows, the calculations in our mathematic model fit well the values measured in healthy volunteers and embrace some of the complexity of hemodynamics.

Glossary

B(t)		Baroreflex signal (mmHg)
B _{ph}		Parasympathetic signal to heart, RR (mmHg)
B _{sh}		Sympathetic signal to the heart, Contractility (mmHg)
B _{sp}		Sympathetic signal to peripheral vessels (mmHg)
C	WkComp	Aortic compliance (l mmHg ⁻¹ ; C=0.00005 l mmHg ⁻¹ kg ⁻¹)
d _{ph}	ParaRrDel	Baroreflex delay, parasympathetic to the heart, RR (s; d _{ph} = 0.25s)
d _{sh}	SyRrDel	Baroreflex delay, sympathetic to the heart (s; d _{sh} = 1.00s)
d _{sp}	SyPerDel	Baroreflex delay, sympathetic to peripheral vessels (s; d _{sp} = 6.00s)
d _{mf}	MuscFlDly	Muscle flow delay (s; d _{mf} = 1.8s)
G		Conductance in peripheral vascular bed (l s ⁻¹ mmHg ⁻¹)
G _e		Conductance in the exercising parts of the body (l s ⁻¹ mmHg ⁻¹)
G ₀		Total peripheral conductance (TPC) before exercise (l s ⁻¹ mmHg ⁻¹)
G _r		Conductance in the non-exercising part of the body (l s ⁻¹ mmHg ⁻¹)
G _p		TPC (l s ⁻¹ mmHg ⁻¹)
K _a	AfterLoadSens	Sensitivity to afterload effect on strokevolume (mL mmHg ⁻¹ ; adjusted)
K _{ph}	ParaRrGain	Sensitivity to parasympathetic signal to the heart, RR (s mmHg ⁻¹ ; adjusted)
K _{sh_{RR}}	SyRrGain	Sensitivity to sympathetic signal to the heart, RR (s mmHg ⁻¹ ; adjusted)
K _{sh_c}	SyCoGain	Sensitivity to sympathetic signal to the heart, contractility (l mmHg ⁻¹ ; adjusted)
K _{sp}	SyPerGain	Sensitivity to sympathetic signal to peripheral vessels (l mmHg ⁻¹ ; adjusted)
Ex _{cond}	RestExFrac	Fraction of TPC in the exercising part of the body ($= \frac{MF}{SV \times RR}$)
\dot{p}		Time-differentiated pressure in the aorta (mmHg s ⁻¹)
P(t)		Time-dependend mean arterial pressure (mmHg)
P ₀	MAP0	Mean arterial pressure before exercise (mmHg)
P _a		Instantaneous pressure in the aorta (mmHg)
P _d		End-diastolic pressure (mmHg)
P _s (t)		set point for arterial pressure control (mmHg)
\dot{Q}_h		Flow out of the heart (l s ⁻¹)
Q _m	MitrFl	Mitral flow late in diastole (l s ⁻¹ ; adjusted)
Q _{mf}	MuscFlow	Muscle flow (l s ⁻¹ ; adjusted)
\dot{Q}_p		Total flow in peripheral arteries (l s ⁻¹)
RR		RR interval (s)
RR ₀	RR0	RR interval before exercise (s)
SV		Strokevolume (l)
SV ₀	SV0	Strokevolume before exercise (l)
T _{c,ph}	ParaRrTc	Baroreflex time constant, parasympathetic to the heart, RR (s; = 0.25s)
T _{c,sh}	SyRrTc	Baroreflex time constant, Sympathetic to the heart (s; =10s)
T _{c,sp}	SyPerTc	Baroreflex time constant, Sympathetic to peripheral vessels (s; = 10 s)
T _{c,set}	BaroTc	Setpoint time constant (s; adjusted)
T _{c,mf}	MuscFlTc	Muscle flow time constant (s; adjusted)(constrained to less than 13,2 s)
t _{count}	BaroTcCount	Time when countdown is started (s)
t _{ex}		Time when exercise is started (s)

Ditionary

Cardiac Output (CO) - The volume blood the heart pumps within 60 seconds

$$CO = \text{Heart rate} \times \text{strokevolume}$$

Central venous pressure (CVP) - The pressure in the great veins where they enter the right atrium

Chronotope - A stimuli that alter the frequency of contraction of the myocytes

Diastole - The period when the heart muscle is relaxed and blood from the veins can fill the heart

End diastolic volume (EDV) - The volume of blood in the heart after diastole

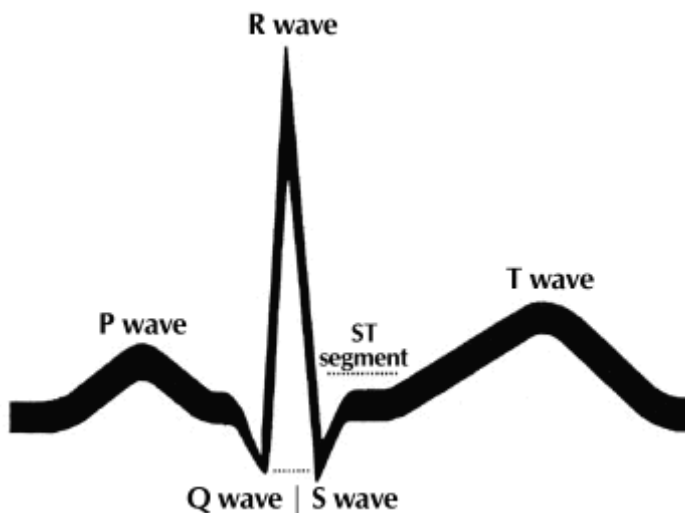
Inotrope - A stimuli that alter the force of contraction of the myocytes

Mean Arterial Pressure (MAP) - $MAP = \frac{P_{systole} + 2P_{diastole}}{3}$ during rest and $MAP = \frac{P_{systole} + P_{diastole}}{2}$ during exercise

$$MAP = CO \times TPR$$

The true value can be calculated by dividing the area under the pressure wave with by time

RR-interval - The time between R-waves in an EKG. $1/HR = RR$



Figur 1

Strokevolume - The volume the heart pumps out during systole

Systole - The period when the heart muscle is contracting and pumps blood into the arteries

Total peripheral conductance (TPC) - $TPC = \frac{1}{TPR}$

Total peripheral resistance (TPR) - The sum of resistance that the blood has to work against when it flows from the left ventricle to the right atrium

Figure List

Fig 2 – “An introduction to Cardiovascular Physiology, 3rd edition”

Fig 3 – <http://www.biomedical-engineering-online.com/content/figures/1475-925X-3-6-1.gif> accessed 13 dec 08

Fig 5 – “An introduction to Cardiovascular Physiology 3rd edition”

Fig 6 - http://www.nhlbi.nih.gov/health/dci/images/heart_valves.jpg accessed 13 dec 08

Fig 7 – (Westerhof *et al.*, 2008)

Fig 8 – “Medical Physiology, updated edition”

Fig 9 – “Medical Physiology, updated edition”

Fig 11 – (Toska *et al.*, 1996)

ModParam List

symppergain = ModParam(1);
symppertc = ModParam(2);
sympperdel = ModParam(3);
symprrgain = ModParam(4);
sympcontgain = ModParam(5);
symprrtc = ModParam(6);
symprrdel = ModParam(7);
parasympgain = ModParam(8);
parasymprtc = ModParam(9);
parasymprdel = ModParam(10);
afterloadsens = ModParam(11);
mitrflow = ModParam(12);
restexfrac = ModParam(13);
windcompl = ModParam(14);
adaptfac = ModParam(15);
muscfw = ModParam(16);
musctc = ModParam(17);
muscdly = ModParam(18);
venousfrac = ModParam(19);
venousdly = ModParam(20);
setpstep = ModParam(21);
beforefrac = ModParam(22);
barotc = ModParam(23);
barotcc = ModParam(24);
map0 = ModParam(25);
rr0 = ModParam(26);
sv0 = ModParam(27);
MF0 = ModParam(28);

File List

Main

- AnyErr.m
- Average.m
- ErrFvalVec.m
- ExecuteModel.m
- InitialSimulation.m
- Intervall_Sjekk.m
- LesExpFile.m
- Optimaliser.m
- plotter.m
- Systemic_Circulation_Model.m

@DelayFifo

- DelayFifo.m
- GetVal.m
- SetVal.m
- GetTime.m
- IncReadPtr.m

@ResistVessel

- Condone.m
- Condtwo.m
- ExerciseOn.m
- ResistVessel.m
- SetVal.m

@T_BaroAdapt

- NewVal.m
- SetVal.m
- T_BaroAdapt.m

@T_BaroSetpoint

- SetPoint.m
- SetVal.m
- T_BaroSetpoint.m

@T_Heart

- NewBeat.m
- SetVal.m
- T_Heart.m

@T_MuscFlowFunc

- MuscFlow.m
- SetVal.m
- sv.m
- T_MuscFlowFunc.m

@T_Windkessel

- AddVolume.m
- Cycle.m
- GetEdp.m
- GetMap.m
- GetVal.m

@TimeConstDly

- CalcNewExp.m
- GetVal.m
- OLD_GetFifo.m
- SetVal.m
- TimeConstDly.m

Data

Reference List

Alam M & Smirk FH (1937). Observations in man upon a blood pressure raising reflex arising from the voluntary muscles. *J Physiol* 89, 372-383.

DiCarlo SE & Bishop VS (2001). Central baroreflex resetting as a means of increasing and decreasing sympathetic outflow and arterial pressure. *Ann N Y Acad Sci* 940, 324-337.

Elstad M, Nadland IH, Toska K, & Walloe L (2008). Stroke volume decreases during mild dynamic and static exercise in supine humans. *Acta Physiol (Oxf)*.

Elstad M, Toska K, & Walloe L (2002). Model simulations of cardiovascular changes at the onset of moderate exercise in humans. *J Physiol* 543, 719-728.

Gullestad L, Myers J, Noddeland H, Bjornerheim R, Djoseland O, Hall C, Gieran O, Kjekshus J, & Simonsen S (1996). Influence of the exercise protocol on hemodynamic, gas exchange, and neurohumoral responses to exercise in heart transplant recipients. *J Heart Lung Transplant* 15, 304-313.

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Westerhof N, Lankhaar JW, & Westerhof BE (2008). The arterial Windkessel. *Med Biol Eng Comput*.