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Neuronal and Hormonal Cardiac Control Processes in a Model of the Human Circulatory System

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Abstract. Cardiac control is mainly effectuated by the autonomic nervous system, by the sympathetic and parasympathetic nerves as well as by the hormonal transmitter substances of the sympathetic system, the catecholamines adrenaline and noradrenaline. A computer model of the human circulatory system is presented including neuronal and hormonal cardiac control processes which are mainly effective in short-term circulatory regulation. The performance of this model is demonstrated by means of two examples: The simulation of an exercise situation and the simulation of the baroreceptor reflex in a hypertensive person compared to a normotensive person. The results are consistent with physiologic data.

Keywords: *Computer model, human circulatory system, cardiac control, autonomic nervous system, simulation*

Introduction

The validation of new, innovative concepts for medical devices is particularly difficult, as experiments on humans are in principle not feasible in the majority of cases. In general, animal experiments serve this purpose but the transferability of these 'simulations in vivo' on humans is often limited and, besides, they are ethically questionable. Computer simulations offer a resort out of this difficulty. In other fields of science and engineering the methods of simulation have been applied for a long time and with considerable success. These methods should also be made available to medical applications in order to become independent from the limitations of clinical trials and animal experiments.

The advantages of the computer simulation are reproducibility and comparability of results. Extensive statistical methods that have to be used in clinical trials and animal experiments in order to ensure comparability can be omitted when using a standardised computer model. Moreover, the simulated experiments can be more far-reaching, e.g. for testing innovative strategies bearing incalculable risks without lethal consequences in case of a failure.

In this paper, a computer model of the human circulatory system is presented. It has been designed in order to develop advanced control strategies for circulatory assist devices such as

cardiac pacemakers or artificial hearts. In order to produce significant and meaningful results, the model incorporates the main hormonal, neuronal and metabolic control mechanisms of the human circulatory system.

Methods

Model Description

The model which has been realised using the MATLAB toolbox Simulink can be divided into three main parts (see Figure 1):

- circulatory dynamics,
- control mechanisms of the circulatory system which are necessary to maintain homeostasis:
  - the autonomic nervous system,
  - the renin-angiotensin system,
  - local metabolic control,
  - vascular stress relaxation, and
- physiologic subsystems influencing circulation dynamics (such as the respiratory system, the kidneys, electrolyte and water balances etc.).

Furthermore, individual patient disease states such as hypertension or renal insufficiency can be taken into consideration during a simulation. More detailed information about the model can be found in [1], [2], [3], and [4].

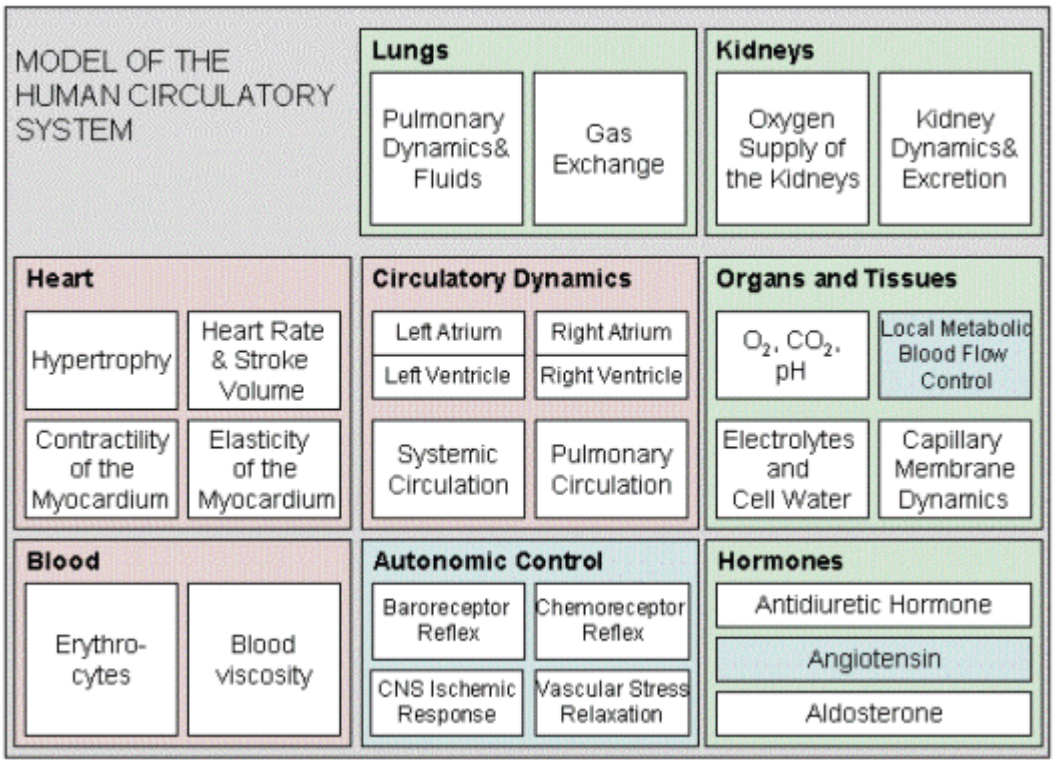

Figure 1. The model of the human circulatory system (circulatory dynamics: red, control mechanisms: blue, other physiologic subsystems: green)

Circulatory Dynamics

The block *Circulatory Dynamics* (see Figure 2) is the core of the model. This section calculates the flow of blood around the circuit from arteries, to veins, to heart, to lungs, and back to heart again. It also calculates the flow resistances of the vessels and the effect of various factors on these flow resistances. In other words, this section represents the basic hemodynamics of the circulatory system. The subsystem *Systemic Arteries* contains a very detailed and anatomically correct representation of the systemic arterial tree consisting of 130 segments, thin-walled cylindrical tubes, to each of which s pecific mechanical properties (length, diameter, wall thickness, Young's modulus) are assigned. Peripheral branches are terminated by a resistance term representing smaller vessels like arterioles and capillaries. Blood flow and pressure are expressed by the intensity of current and voltage in an electrical analogue based on the Navier-Stokes equations for fluid flow in elastic tubes; resistance, inductivity, and capacitance are implemented according to the physical properties of the arterial tree and the rheology of the blood [5]. Thus, by means of the following equations blood pressure and flow can be calculated for each segment:

$$p_{i-1} - p_i = \frac{9\rho l}{4\pi^2}\frac{dq_i}{dt} + \frac{81\mu l}{8\pi r^4}q_i = L\frac{dq_i}{dt} + Rq_i \qquad (1)$$

$$q_i - q_{i+1} = \frac{3\pi r^3 l}{2Ed}\frac{dp_i}{dt} = C\frac{dp_i}{dt} \qquad (2)$$

Equations (1) and (2) are difference-differential equations linking flow and pressure with terms of resistance (R), inductance (L), and capacitance (C); k is the segment number, l is the vessel length, E is Young's modulus, r is blood density, μ is blood viscosity, r is the vessel radius, d is the thickness of the vessel wall, p is blood pressure, q is blood flow and t is time.

During a simulation the resistance of each segment can be influenced by various factors:
- hormonal control by the renin-angiotensin system,
- local metabolic control, and
- sympathetic stimulation.

The representation of the systemic veins and the pulmonary vessels is analogous, even though less detailed.

This model structure has two major advantages. It enables simulating pulsatility from the side of the vessels, and it provides a high resolution for blood pressure and flow in time and position (especially within the systemic arterial tree).

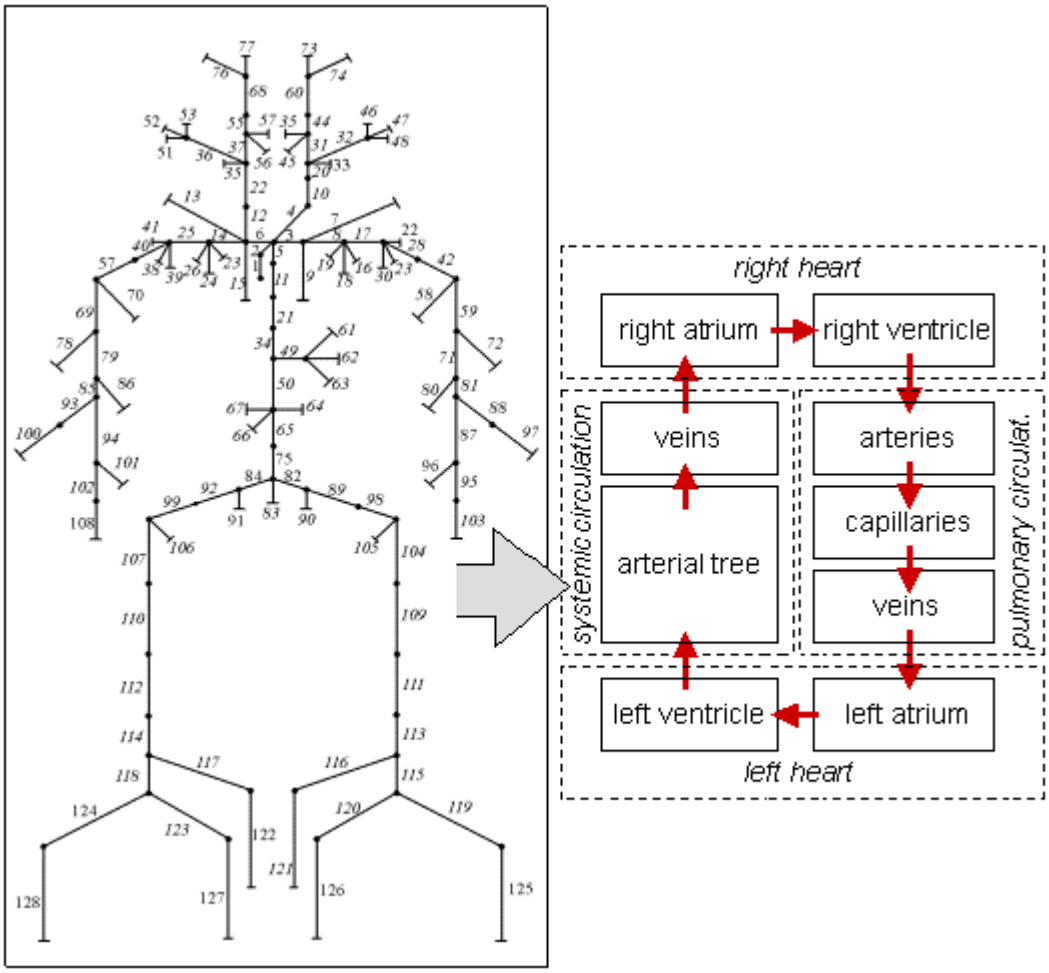

Figure 2. Structure of the subsystem Circulatory Dynamics

The Heart

The model of the heart (see Figure 3) is distributed between two subsystems: The block *Circulatory Dynamics* contains the valve mechanisms and the computational routines for blood pressure and flow in the different chambers of the heart, whereas the block *Heart* comprises the calculation of heart rate and stroke volume, contractility and (time-variable) elasticity of the myocardium as well as the effects of hypertrophy or deterioration.

The heart rate is calculated as a function of right atrial pressure *PRA*, reduction of cardiac performance by hypoxia *HMD* and autonomic stimulation *AU* (chronotropic effect). Via the right atrial pressure both the direct effect of this parameter on the sinus rhythm of the heart as well as the Bainbridge reflex are taken into account. The contractility of the left and the right heart are computed separately (see Figure 3). The contractility of the left heart depends on autonomic stimulation *AUH* (inotropic effect), reduction of cardiac performance by hypoxia *HMD*, the degree of deterioration of the left ventricle *HSL* and the degree of hypertrophy *HPL*. The parameter *HSL* enables the effects of a myocardial infarction or myocarditis to be considered during the simulation. The contractility of the right heart is calculated by analogy. The contractilities of the left and the right heart and the heart rate serve to calculate the elasticities of the ventricles and the atria. These parameters are variable in time, which makes it possible to simulate the several phases of the heart cycle and which is furthermore one prerequisite for a pulsatile model of the human circulatory system.

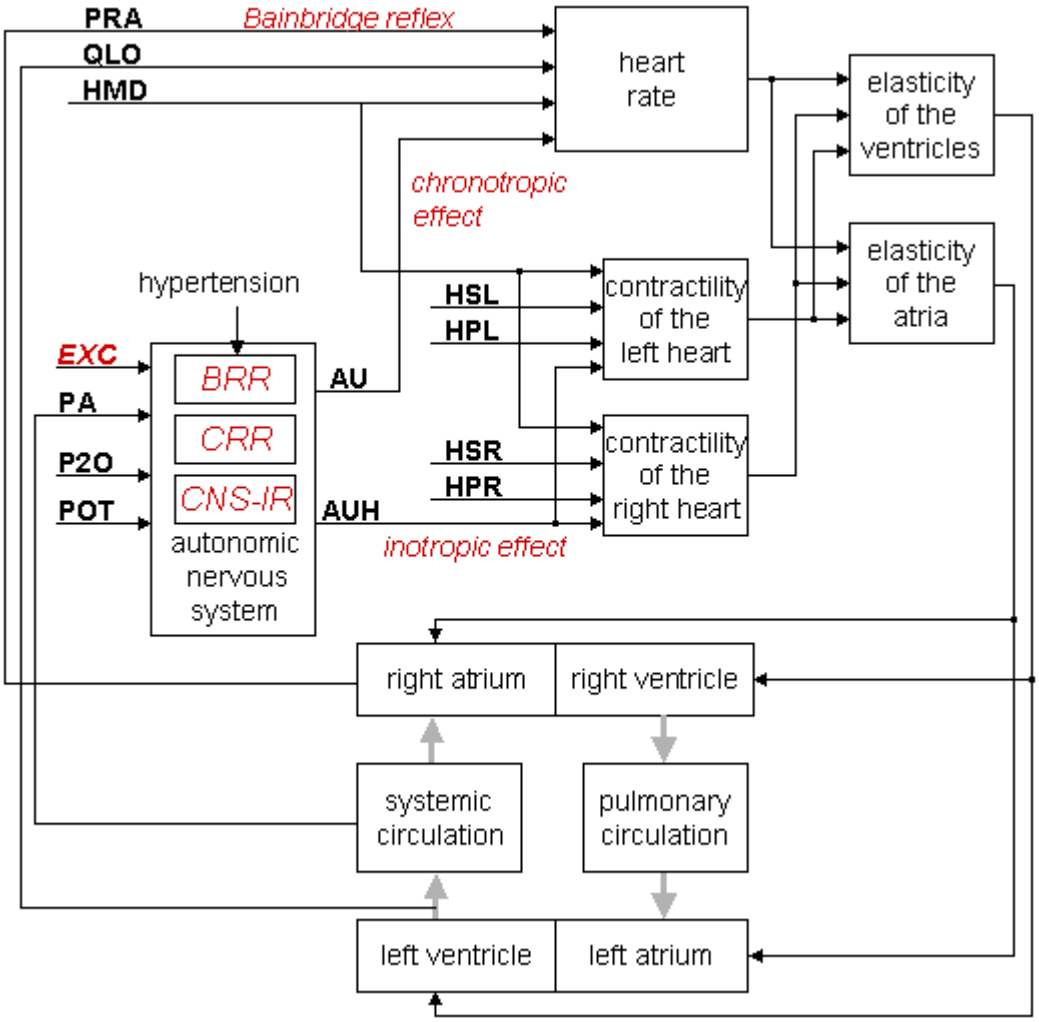

Figure 3. The model of cardiac control

Autonomic Control

The neuronal and hormonal control of the circulation, including the control of the heart is mainly effectuated by the autonomic nervous system and its hormonal transmitters, the catecholamines ([6], [7]; see also section Physiological Background: Cardiac Control).

Autonomic control of the circulation primarily operates through the sympathetic system, though to a slight extent through parasympathetic signals to the heart. These have been lumped together, and there are basically three separate feedback mechanisms in this computational block. These are: (1) feedback from the baroreceptor control system; (2) feedback from the peripheral chemoreceptors in the carotid and aortic bodies, and (3) feedback control of the circulatory system caused by central nervous system ischemia, that is, ischemia of the vasomotor centre in the brainstem. Another input that affects the autonomic nervous system is also included: The activation of the autonomic nervous system during exercise.

The basic structure of the three reflex mechanisms implemented in the subsystem *Autonomic Control* is depicted in figure 4. The input variables are the arterial pressure, the partial oxygen pressure in different types of tissue (muscle and non-muscle tissue) and the intensity of exercise. The output variables have effects on the heart - on the heart rate as well as on the contractile force of the heart - and on the total peripheral resistance of the vascular system. Each reflex mechanism is implemented by a characteristic curve which is defined in sections in order to take the specific operating ranges of the different reflexes into account.

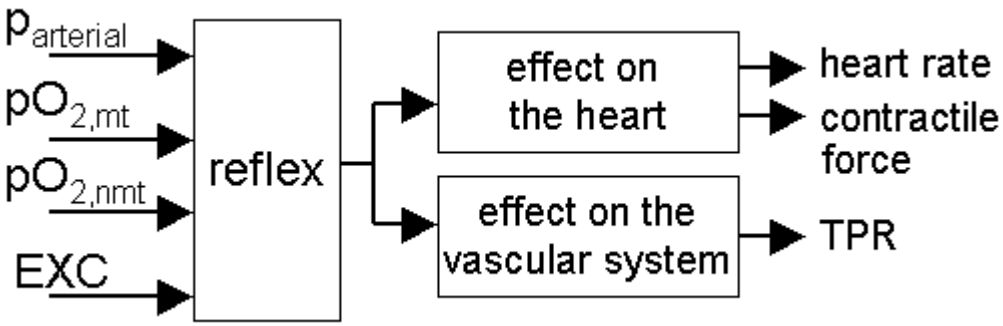

Figure 4. Basic structure of the vegetative reflexes implemented in the subsystem Autonomic Control

Resetting of the Baroreceptor Reflex

In order to be able to adapt this model of the human circulatory system to hypertension, a disease which is frequently found in western, industrialised countries, the subsystem also comprises the resetting of the baroreceptor reflex. This mechanism shifts the operating range of the baroreceptor reflex to higher values of mean arterial pressure. The baroreceptor reflex adapts to the permanently elevated mean arterial pressure without changing its fundamental behaviour. In the baroreceptor reflex model, for simulating the hemodynamics of a hypertensive subject, the limits of the operating ranges in the characteristic curve are shifted to the right to a higher mean arterial pressure.

For a normotensive subject the time constant for the resetting of the baroreceptor reflex is T_{reset} = 33 h in order to be able to simulate the slow adaptation of the baroreceptor reflex to a permanently elevated mean arterial pressure in long-term simulations.

For a hypertensive subject T_{reset} equals 0 at the "normal" elevated mean arterial pressure. The resetting mechanism is nevertheless active; in case of a deviation from the "normal" elevated pressure T_{reset} still is 33 h, i. e. the functionality of the reflex is preserved.

Simulations

In order to show the performance of the model regarding to short-term circulatory regulation with special respect to cardiac control, two situations are simulated:
(1) an exercise situation (strain = 150 W) and
(2) the behaviour of the baroreceptor reflex in hypertensive subjects compared to normotensive subjects.

Results

Exercise situation

Figure 5 shows the effects of a strain of 150 W, caused for instance by speedy swimming, on various haemodynamic parameters. These are:
- mean blood flow in the kidneys, in muscle and non-muscle tissue,
- mean arterial pressure,
- heart rate and
- stroke volume.

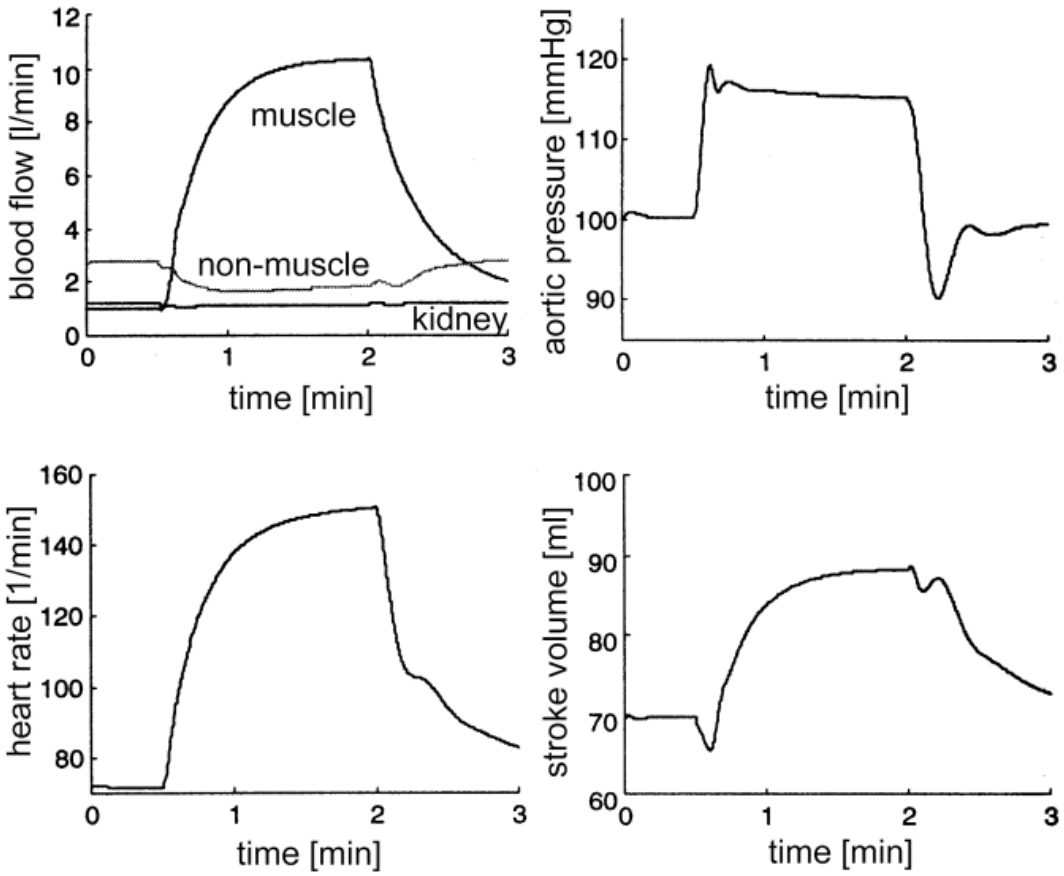

Figure 5. Haemodynamic response to muscle exercise (strain = 150 W)

The exercise starts at t = 30 s and lasts until t = 120 s. The reaction of the model describes the effects of the short-term circulatory control mechanisms. Mean arterial pressure, heart rate and stroke volume are increased during the exercise phase. Furthermore, a shift in blood flow can be perceived. The increased requirements of the muscles are partly satisfied at the expense of the blood flow through the non-muscle tissue. The blood flow through the kidneys remains constant due to the autoregulation mechanism of this organ.

The changes in the simulated circulatory situation described above correspond to the physiologic changes in a real exercise situation [6][7].

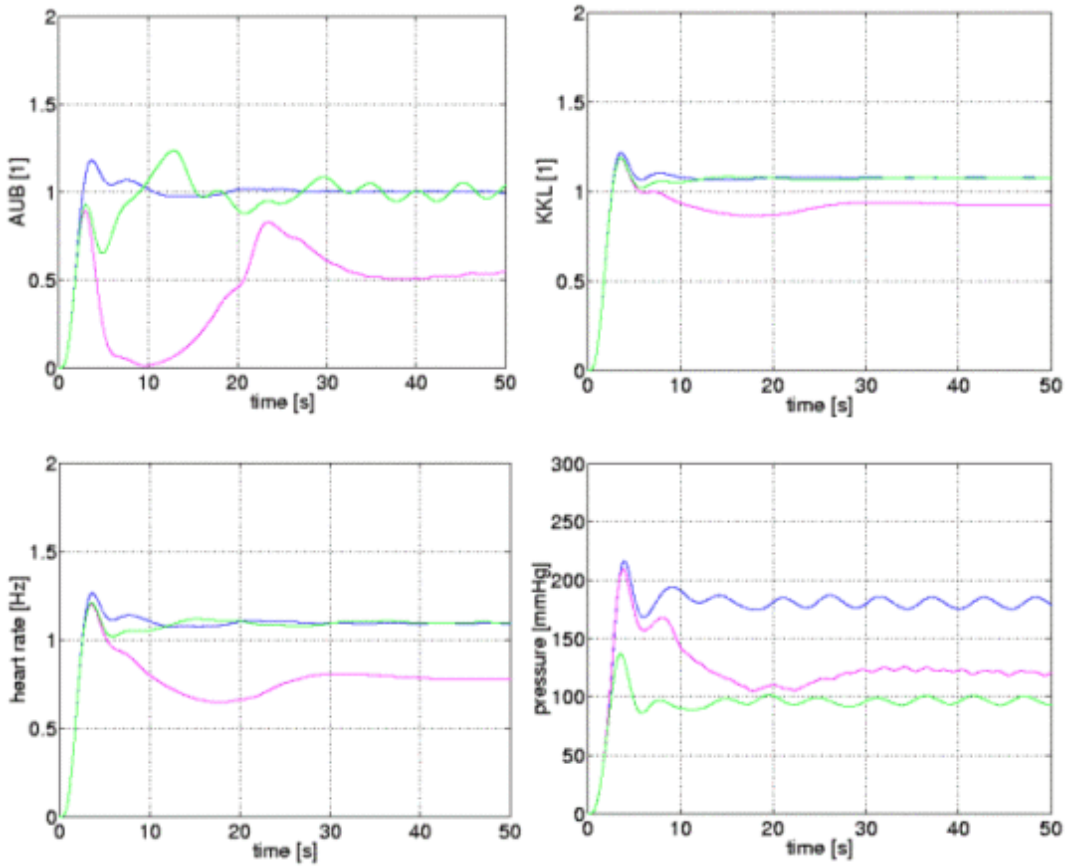

Figure 6. Activity of the baroreceptor reflex AUB, heart rate, contractility of the left ventricle KKL, and mean arterial pressure in hypertensive subjects with resetting (blue lines) and without resetting (red lines) compared to normotensive subjects (green lines).

Baroreceptor reflex

In Figure 6 three scenarios are compared: The behaviour of parameters related to the baroreceptor reflex in
- hypertensive subjects (MAP = 180 mmHg) with resetting
- hypertensive subjects (MAP = 180 mmHg) without resetting, and
- normotensive subjects (MAP = 100 mmHg).

The parameters inspected are the following:
- activity of the baroreceptor reflex *AUB* (normal basic activity = 1),
- heart rate *HR*,
- contractility of the left ventricle *KKL*, and
- mean arterial pressure.

In the hypertensive subject the elevated mean arterial pressure is maintained stable because of the resetting mechanism (blue curves). In case of a failure of the resetting mechanism in the hypertensive subject the baroreceptor reflex would be activated and the mean arterial pressure would be reduced. The red curves in the plots show the effects in detail: A reduction in baroreceptor reflex activity due to the elevated pressure leads to reductions in heart rate and contractility that in their turn make the mean arterial pressure decrease. In the simulation the resulting mean arterial pressure is approximately 130 mmHg compared to a mean arterial pressure of 100 mmHg in normotensive subjects. This deviation is consistent with the data provided by [8]. The complete reduction to a normotensive mean arterial pressure can only be achieved by the long-term control mechanisms (regulation of water balances by the kidneys and hormonal regulation). The green curves show the parameters discussed above for the normotensive subject. The oscillations up to t = 25 s are due to the settling process of the system.

Conclusions

The pulsatile model of the human circulatory system described in this paper contains the main mechanisms for overall circulatory regulation (autonomic control, local metabolic control, hormonal control by the renin-angiotensin system, vascular stress relaxation). Neuronal and hormonal cardiac control processes which are mainly effective in short-term circulatory regulation, are also implemented. These are:
- the exercise response of the autonomic nervous system,
- the vegetative reflexes (baroreceptor reflex, chemoreceptor reflex, ischemic response of the CNS),
- the chronotropic effect of the sympathetic and parasympathetic system,
- the inotropic effect of the sympathetic and parasympathetic system,
- the Bainbridge reflex, and
- direct stimulation of the sinus node by an elevated pressure in the right atrium.

Thus, all the relevant cardiac control processes with the exception of the dromotropic effect of the sympathetic and parasympathetic system are implemented.

The simulation results presented for an exercise situation and for hypertensive subjects are in accordance with the physiologically expected behaviour. Thus, the model can be used to investigate the results of experiments that are impossible or too dangerous to be undertaken in the laboratory. It also can be used to simulate a test stand for advanced control strategies in cardiac assist devices.

In order to further improve the simulations, current investigations concentrate on implementing higher selective input parameters for the different vegetative reflexes, the pulsatile characteristics of the baroreceptor reflex [9] and the dromotropic effect of the sympathetic and parasympathetic system.

Acknowledgements

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