

ANALOG SIMULATION OF CARDIOVASCULAR PHYSIOLOGY: EXERCISE IN MAN

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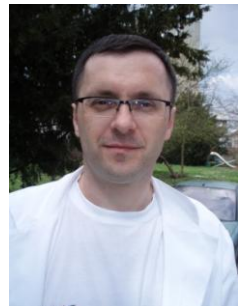
Abstract

A computer analysis of an equivalent electronic circuit is developed. Thus it is possible to simulate the human cardiovascular system (including the negative intrathoracic pressure), and the negative feedback loops (control of venous tone, of myocardial contractility, and of heart rate). In this investigation exercise is simulated by decreasing the peripheral resistance. If negative feedback loops are operative, sympathetic tone is increased simultaneously. Sympathetic tone and negative feedback then stabilise the system, the final outcome is an increased blood flow. The extent of negative feedback action can be assessed only if a simulation is repeated in conditions, when negative feedback is not operative. Despite pronounced venoconstriction left atrial pressure is slightly decreased. There is little change in diastolic arterial pressure. Despite peripheral resistance is decreased mean arterial pressure is slightly increased and cardiac output almost doubled. In second condition if feedback mechanisms in exercise are not operative, heart rate is constant, 60/min. A profound decrease in arterial and mean arterial pressure occurs. Transiently cardiac output is markedly increased but in steady state condition the increase is almost negligible. Venous volume is slightly increased and there is almost no change in left atrial pressure. It is clear that in exercise feedback mechanisms are essential in increasing and maintaining arterial pressure and cardiac output. In experiments in which single loops are set out of action not simultaneously, but one after the another, it can be observed that the most effective homeostatic mechanism is venoconstriction. It is venoconstriction, by increasing the filling of both ventricles, *the mechanism* which allows the increased ventricular contractility and increased heart rate to display full action and increase the blood flow.

Keywords: Computer simulation, Cardiovascular physiology, Homeostasis in exercise.

Presenting Author's biography

Tomaž Podnar received the M.D and Ph.D. degrees in 1989 and 2001, respectively, from the Faculty of Medicine in Ljubljana, Slovenia. He is currently paediatric cardiologist at the Cardiology Unit, University Children's Hospital Ljubljana, Slovenia. His research interests includes transcatheter treatment of congenital heart defects, cardiovascular physiology and pathophysiology of congenital heart defects.



1. Introduction

The modelling methodology was extensively used in physiology as well in medicine - both for teaching purposes and research (reviewed in [2], cf. also [5, 6]). However, recently it was reported that various physiological processes can also be simulated by designing - using suitable computer software - equivalent electronic circuits [1, 4, 7, 9, 10].

Essentially, the early physical electronic model [6] in which variables were measured by oscillographic recording was replaced by computer software. The circuit was drawn on the computer screen, analysed and results shown by a suitable graphs.

This means that in recent investigations it was possible many circuits to upgrade by attaching negative feedback loops. The simulations of this type included relatively complicated systems e. g. cerebrospinal pressure disturbances; pulmonary ventilation and control of breathing; various phenomena in cardiovascular (patho)physiology [1, 3, 4].

In cardiovascular simulation circuits this meant that mean aortic pressure actually controlled various target mechanisms e. g. the venous tone, the heart rate, the contractility of the right and of the left ventricle. If e. g. peripheral resistance was decreased, as an immediate consequence aortic pressure was decreased. However, through negative feedback mechanisms the veins contracted, the heart rate and the contractility of both ventricles was increased. Thus, after a brief transient phenomenon was over, as a final consequence cardiac output was increased, thus "compensating" the initially decreased aortic pressure.

It is clear that by using equivalent circuits complex phenomena of homeostasis of the cardiovascular system could be studied [8].

Recently it has been shown that, by using a highly upgraded electronic analog circuit, complex clinical conditions could be simulated satisfactorily [12]. These investigations included also the study of changes induced by exercise, a 50 % decrease in peripheral resistance, if homeostasis was active and if the latter was reset to a higher level, simulating an increased sympathetic tone.

The aim of this paper is to present a similar simulation of exercise, in a more extreme resistance decrease, but in two conditions:

- homeostasis (including the sympathetic tone) fully active (i. e. feedback loops closed) or
- homeostasis inactive (i. e. feedback loops open).

2. Methods

Circuit is drawn and analysed by using Electronics Workbench Personal version 5.12 software. For details refer to [4, 7, 8, 12].

The principle of analog simulation is straightforward. It is based on the assumption that electrical variables can be equivalent (i. e. correspond) to physiological variables as shown in Table .

Table 1: Equivalent quantities and units in simulation of cardiovascular system

Electrical variables	Physiological variables
voltage, 1 V	pressure, 10 mm Hg
ground potential, 0 V	atmospheric pressure, 0 mm Hg
current, 1 $\mu\text{A} = 60 \mu\text{As}/\text{min}$	blood flow, 100 ml/s = 6000 ml/min
resistance, 10 V/1 $\mu\text{A} = 10 \text{M}\Omega$	resistance, 100 mm Hg/100 ml/s = 1 U
capacitance, 1 $\mu\text{F} = 1 \mu\text{As}/1\text{V}$	capacitance, 100 ml/10 mm Hg
charge, 1 μAs	volume, 100 ml

To allow analog simulations in cardiovascular physiology the electronic circuit should be made up of a circular chain of resistor/capacitor segments.

Resistors are connected in series.

Capacitors are connected in parallel.

In the systemic circuit one capacitor terminal is connected to ground and the other terminal to the chain of systemic resistors.

In the pulmonary circuit (which includes also both ventricle capacitors) one capacitor terminal is connected to an oscillating (at breathing frequency) negative voltage while the other terminal is connected to the chain of pulmonary resistors.

The circular series of resistor/capacitor segments thus simulates two sections of the cardiovascular system:

- the high-resistance systemic circuit, subdivided into a low-capacitance arterial and a high-capacitance venous system and
- the low-resistance and high-capacitance pulmonary circuit.

The right and left ventricle are simulated by capacitors which rhythmically change their

capacitance. This is achieved by use of a relatively complex subcircuit. In this way the contraction and relaxation of the right and of the left ventricle is simulated.

The duration of systole is constant, 0.2 s. Therefore, if heart rate is increased, the duration of systole is shortened correspondingly.

The time constant of contraction and of relaxation is 100 ms and 25 ms, respectively.

During contraction and relaxation of the left ventricle the time course of ventricular volume can be recorded. As expected, two interesting phenomena can be observed:

- At the start of systole the ventricular volume begins to decrease only after the isometric contraction time is over. In this time period ventricular pressure becomes equal to the aortic pressure. Thus, left ventricular systolic ejection is started.

- At the start of diastole the ventricular volume begins to increase only after the isometric relaxation time is over. In this time period ventricular pressure becomes equal to the left atrial pressure. Thus, left ventricular diastolic filling is started.

The pulmonary and aortic valve are simulated by diodes featuring a relatively low saturation current. The tricuspid and mitral valve are simulated by diodes featuring a relatively large saturation current. The back-leakage of blood through heart valves is about 1 - 2 % of stroke volume. Therefore blood flow calculated from stroke volume and heart rate is slightly larger than that measured at the capillary level.

After the "cardiovascular" circuit is charged (filled with blood) and the contraction/relaxation process of both ventricles started, current (flow of blood) appears and arterio-venous gradient is built up (for details refer to [9, 10]). This means that while arterial pressure is increased, venous pressure is decreased. If the ventricular pumping action is decreased (ventricular failure), a reverse process can be observed. The most striking observation in a failing ventricle is an increase in atrial pressure [9, 10, 12].

Some basic parameters defining normal conditions (cf. [12]):

Mean circulatory pressure	6.25 mm Hg
blood volume	4525 ml
systemic arterial capacitance	14 ml/mm Hg
systemic venous capacitance	560 ml/mm Hg
pulmonary capacitance	83 ml/mm Hg
right ventricle capacitance	30 ml/mm Hg
left ventricle capacitance	30 ml/mm Hg
systemic resistance	about 1.1 U
pulmonary resistance	about 0.15 U

intrathoracic pressure -4/-2 mm Hg

Thus the ratio between systemic arterial and systemic venous capacities is about 1: 40. The ratio between pulmonary and total systemic capacities is about 1: 7.

Some basic variables in normal conditions (cf. [12]):

arterial pressure	122/88 mm Hg
mean arterial pressure	about 98 mm Hg
left atrial pressure	about 4/2 mm Hg
cardiac output (blood flow)	about 5100 ml/min
left ventricle variables	
- maximal rate of contraction	2119 mm Hg/s
- isometric contraction time	46 ms
- isometric relaxation time	67 ms
- end-diastolic volume	about 200 ml
- end-systolic volume	about 110 ml
- stroke volume	about 90 ml
- ejection fraction	about 55 %

If feedback loops are open and if heart rate is increased, maximum blood flow can be observed at heart rate 120/min. This is exactly the same characteristic as observed *in vivo* (for details refer to [7]).

The circuit used in present simulations is, in principle, the same as described, featuring a negative intrathoracic pressure, oscillating at 12/min, the frequency of breathing. Negative feedback controls four target organs as described in [12]. Present minor modifications involve only a more pronounced peripheral resistance decrease (down to about 40 % of normal) and a stronger, but slower (time constant about 5 s) increase in sympathetic tone.

Results are expressed graphically as described [4, 7, 8, 10, 12]).

In this paper in graphs the same acronyms are used as reported earlier [7, 10, 12]:

AoP	aortic pressure
MAoP	mean aortic pressure
CO	cardiac output
CVV	"contractible" volume of veins
ITP	intrathoracic pressure
LAtP	left atrial pressure

Note that heart rate control is exerted discontinuously, in discrete steps, 60/min, 75/min, 90/min. More steps could be added to approach the continuous heart rate control. However, this would make the circuit very complex without significantly contributing to the understanding of cardiovascular physiology.

The sympathetic tone increase (MAoP resetting mechanism) includes procedures whereby the resting value of MAoP, “clamped” at about 98 mm Hg (normal level) is shifted and then “clamped” again at a higher level (as described for clamping the membrane potential at various levels. For details refer to [12]).

To abolish the action of negative feedback in all feedback loops there are manually controlled switches.

When in this study simulation is started various initial transient phenomena show up as reported [7, 10]. But in about 40 s a steady state level of all variables (AoP, MAoP, CO, etc.) is established. Therefore the simulation graph is started not at 0 s, but at 50 s of simulation time and, until various parameters are changed, the initial part of the record shows normal conditions in the cardiovascular system. They are very close or identical to those observed in man.

3. Results

Results are shown in

- Fig. 1 (homeostasis active) and
- Fig. 2 (homeostasis inactive).

Both illustrations show the time course of AoP, MAoP, CO, CVV, LATP and ITP. Records are started and stopped at 50 s and 200 s, respectively.

Parameter change, decreased arteriolar and capillary resistance (about 40 % of control level) is introduced at 100.5 s.

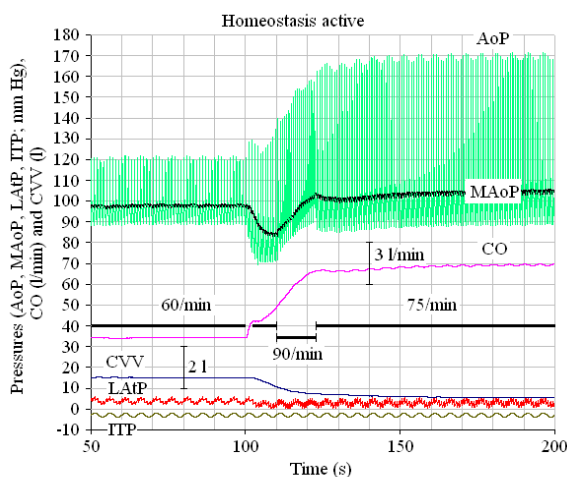


Fig. 1: The effect of decreasing the peripheral

resistance (by about 40 % of normal level, at 100.5 s of simulation time) in closed feedback loop conditions (including increased sympathetic tone). Effect shown as the time course of AoP, MAoP, heart rate, CO, CVV, LATP and ITP. Transiently the heart rate is increased from 60/min to 90/min, until in steady state conditions it stabilises at 75/min. Note that despite venoconstriction (decreased CVV) LATP is slightly decreased. Little change in diastolic AoP. Note that despite peripheral resistance is decreased MAoP is slightly increased, about 105 mm Hg and CO almost doubled.

If homeostasis is active (Fig. 1; feedback loops closed and sympathetic tone increased, cf. [12]) a transient phenomenon shows up when systolic AoP is slightly increased and MAoP decreased for about 10 s. Then, these variables are increased above resting level and pulse pressure doubled. CO is gradually and strongly increased. Heart rate transiently increased to 90/min, but finally maintained at 75/min. Steady state in all variables established at about 150 s of simulation time.

If, however, homeostasis is inactive (Fig. 2, feedback loops open) the sequence of events is quite different. While the heart rate is constant throughout simulation time, AoP and MAoP are strongly decreased. CO and CVV slightly increased, and almost no change in LATP.

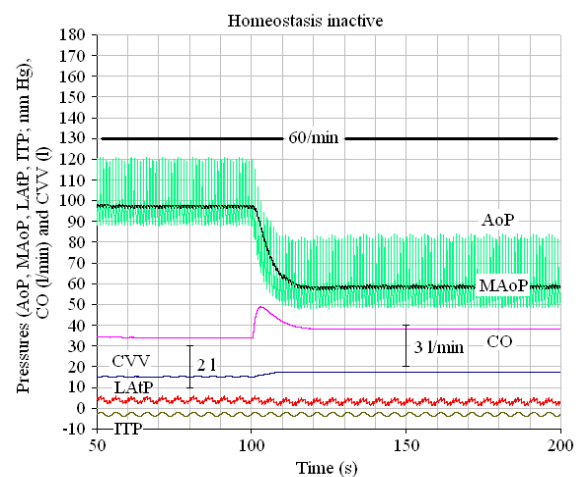


Fig. 2: The effect of decreasing the peripheral resistance (by about 40 % of normal level, at 100.5 s of simulation time) in open feedback loop conditions. Effect is shown as the time course of AoP, MAoP, heart rate, CO, CVV, LATP and ITP. Heart rate is constant, 60/min. Note the profound AoP and MAoP decrease. Transiently CO is markedly increased but in steady state condition the increase is almost negligible. CVV slightly increased, almost no change in LATP.

4. Discussion

General comments:

The student version EWB 5.1 does not allow analysis of the present circuit because the number of components is too large. EWB 5.0c can be used provided the voltage-sensitive switches are defined according to the instructions. It seems that in the latter software the pulse generators are slightly different compared to EWB 5.12. Therefore in graphs obtained by EWB 5.0c there is a time shift of about 0.2 s.

Parameters should be altered preferably during diastole. Therefore resistance is decreased not at 100 s (beginning of systole) but at 100.5 s (approximately in mid-diastole). The same rules should be observed if it is desired to return to the initial setting of parameters. Sometimes, in the analysis the time step of analysis should be adjusted.

It should be pointed out that in present circuit

- a flow-dependent control of pulmonary vascular resistance is not simulated and
- the control of peripheral (arteriolar) resistance is not included into the negative feedback.

In principle it would be possible to include both features. However, this would considerably contribute to the complexity of the circuitry, without contributing very much to the understanding of underlying physiological mechanisms.

Specific comments:

Present data support and extend those published earlier [4, 7, 8, 10, 12].

If homeostasis is active (Fig. 1), a large decrease in peripheral resistance is compensated not only by increased sympathetic tone (the 'resetting of MAoP, cf. [12]), but also by an increased heart rate, by increased contractility of the right and left ventricle, and by venoconstriction. LA_tP is slightly decreased - despite venoconstriction - because contractility of left ventricle is increased. Transient phenomena appear because of the delay in the feedback loops and because of redistribution of blood within the cardiovascular system. This can be clearly seen in the delay of pulse pressure increase. Only after enough blood is shifted from veins to arteries, the pulse amplitude can achieve its maximum amplitude and steady state level. As shown in Fig 1, this is achieved in about 30 s.

It is clear that data, obtained by present simulation, agree very well qualitatively, and to some extent even quantitatively with those changes observed *in vivo* [11].

It seems that the increase of the sympathetic tone (the resetting of MAoP) is the main factor which maintains or even increases the arterio-venous pressure gradient, thus profoundly increasing CO.

In active homeostasis MAoP is the *controlled variable* which, by resetting and by negative feedback, defines the action of *controlled parameters*, i. e. of the tone of the venous system, of the contractility of both ventricles and heart rate. In this condition the cardiovascular system behaves exactly as expected. It is also clear that the efficiency of homeostasis is critically dependent on the gain and time constant in negative feedback. Both latter factors are, as shown earlier [3, 4, 10, 12], critical determinants of the stability of the homeostatically controlled system.

If, however, homeostasis is inactive (Fig. 2), the sequence of events is quite different. Decreased peripheral resistance results in a profound AoP and MAoP decrease. A translocation of blood volume follows from arteries to veins. Therefore CVV is slightly increased. These results clearly show that a decrease in peripheral resistance results in an only marginal CO increase, because the arterio-venous pressure is decreased.

To obtain Fig. 2 all four feedback loops should be open (their action abolished). However, if single loops are set out of action not simultaneously, but one after the another, it can be observed that the most effective homeostatic mechanism is venoconstriction. It is venoconstriction, by increasing the filling of both ventricles, *the mechanism* which allows the increased ventricular contractility and increased heart rate to display full action and increase the blood flow.

5. References

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