

Integrated approach for modeling physiological, biomechanical, and molecular-genetic aspects of human cardiovascular system in health and essential hypertension

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High blood pressure (hypertension) is a state that affects hundreds of millions of people worldwide and is a leading cause of morbidity and mortality in developed countries. Primary or essential hypertension (EH) accounts for 90-95% of patients with diagnosed hypertension, besides secondary and renal. EH is an important risk factor for development of various pathologies of cardiovascular system (CVS). To date a set of different physiological, biochemical and genetic factors underlying EH development is known. This fact indicates that different approaches for treatment and prophylaxis should be used. However, until the moment there is no consensus of opinion, general approach or catalogue, which would describe this formally.

To date, a set of models simulating CVS, its distinct parts (organs and vessels) and haemodynamics was created. But those models are too limited to give a comprehensive view of CVS as an integral part. We assume that integration of physico-mathematical and biological approaches would allow to create such comprehensive model. In such a way, for improvement of understanding the problem and optimization of EH treatment we have to do following tasks: to design a formalized catalogue of causes and mechanisms of EH development and mathematical models of human CVS. For solution of the first task, we applied BioUML workbench (<http://www.biouml.org>). 47 diagrams and models describing biological processes of CVS were created by manual annotation and deposited in the BMOND database (<http://bmond.biouml.org>) (Table 1).

For solution of the second task we created an integrated model of CVS on the basis of models published earlier:

- one dimensional model of blood flow circulation (Lamponi, 2004): it takes into account large arteries of human body and blood circulation [1];
- long-term mathematical model involving renal sympathetic nerve activity, arterial pressure, and sodium excretion (Karaaslan et al., 2005): it takes into account the kidney and renal sympathetic nerve activity [2];

- mathematical model of blood circulation system (Proshin and Solodyannikov, 2006): heart and blood circulation [3].

Development of comprehensive model of CVS will contribute to investigations of mechanisms of arterial hypertension development and design of a medical computer program for early diagnostics, treatment and prognosis of possible complications.

1. Daniele N. Lamponi. One dimensional and multiscale models for blood flow circulation. Pour l'obtention du grade de docteur es sciences. Ecole Polytechnique Federale De Lausanne, 2004.

2. Karaaslan F, *et al.* (2005) Long-term mathematical model involving renal sympathetic nerve activity, arterial pressure, and sodium excretion. *Ann Biomed Eng.* V.33. P.1607-30.

3. Proshin A.P., Solodyannikov Y.V. (2006) Mathematical Modeling of Blood Circulation System and Its Practical Application. *Automation and Remote Control.* V.67, №2, P.329–341.

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Table 1. The list of diagrams representing description of CVS and related processes.

Diagram ID	Diagram name
<i>Renin-angiotensin-aldosterone system</i>	
DGR0252	A scheme of classical renin-angiotensin system (RAS)
DGR0253	The scheme of tissue renin-angiotensin system (RAS)
DGR0254	Human angiotensin receptors
DGR0255	Angiotensin II effects on human vascular system
DGR0256	Angiotensin II-induced signaling in human vascular smooth muscle cells
DGR0257	Immediate signaling effects of angiotensin II on human vascular smooth muscle cells
DGR0258	Effects of angiotensin II on renal hemodynamics
DGR0259	Aldosterone-induced regulation of Na ⁺ and water reabsorption in distal part of nephron
DGR0264	Regulation of renin synthesis and secretion in rat juxtaglomerular cells
DGR0265	Kidney-protective effects of transgenic AT2 receptor in mouse model of ischemic renal injury
DGR0262	Vasopressin effects on the normal regulation of urine concentration by the kidney
<i>The kidney</i>	
DGR0266	Epidermal growth factor signaling in renal tubule epithelial cell in rats
DGR0319	Regulation of sodium and water reabsorption by central nervous system
DGR0263	COX-1 and COX-2 of human kidney.
<i>The heart</i>	
DGR0281	Regulation of the heart action by centers located in medulla oblongata
DGR0318	Factors defining cardiac output
<i>Cardiovascular system in general</i>	

DGR0268	A scheme of regulation of blood pressure in human
DGR0269	Human thyroid disorders and cardiovascular system
DGR0275	Regulation of arterial blood pressure
DGR0282	Noradrenaline and adrenaline effects on smooth muscle contraction
DGR0283	Factors inducing vascular smooth muscle relaxation
DGR0284	Metabolic control of microcirculation
DGR0285	Regulation of blood pressure
DGR0322	Human cardiovascular system
DGR0260	Metabolites of arachidonic acid in regulation of blood pressure
DGR0261	Kallikrein-kinin system and vasodilation
<i>Models of cardiovascular system and related processes</i>	
DGR0267	The kidney model
DGR0272	Scheme of model of cardiovascular system of Karaaslan et al., 2005
DGR0316	Model of human cardiovascular system (Karaaslan et al., 2005)
<i>Hypertension</i>	
DGR0273	Risk factors modulating arterial hypertension development
DGR0274	Physiological abnormalities associated with arterial hypertension in ISIAH rats
DGR0317	Relationships between arterial hypertension, vascular remodeling and atherosclerosis development
DGR0320	Classification of hypertension
<i>Tyrosine hydroxylase – important regulator of cardiovascular processes</i>	
DGR_TH1	Signal transduction pathways involved in activation of GRE and AP-1 sites in rat adrenomedullary tyrosine hydroxylase promoter
DGR_TH2	Induction of CRE-site in Tyrosine Hydroxylase promoter region is responsible for maintaining both basal and inducible level of transcription
DGR_TH3	The AP-1 and CRE pathway cross-talk
DGR_TH4	Regulation of transcription rate of rat adrenomedullary tyrosine hydroxylase by angiotensin II
DGR_TH5	Activation of transcription factor binding sites pattern in tyrosine hydroxylase gene
DGR_TH6	Activation of tyrosine hydroxylase gene in rat pheochromocytoma cell lines
DGR_TH7	HIF-1 and AP-1 crosstalk
DGR_TH8	Regulation of Tyrosine Hydroxylase by protein phosphorylation
DGR_TH9	Induction of Tyrosine Hydroxylase gene expression by immobilization stress
DGR_TH10	The biosynthesis of catecholamines
DGR_TH11	Protein and non-protein factors - inductors of TH gene
DGR_TH12	Close interactions of tyrosine hydroxylase in cell
DGR_TH13	AP-1 – activator of tyrosine hydroxylase gene
DGR_TH14	Tyrosine hydroxylase in regulation of tonus of blood vessels