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A FORMAL ANALYSIS OF MECHANISMS INCREASING ARTERIAL PRESSURE

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Предложено расширенное представление о механизмах регуляции среднего артериального давления в норме и при артериальной гипертонии. У позвоночных (в частности, у человека) есть многомасштабная энергетическая мегасистема, ведущая борьбу против продолжительной нехватки АТФ в клетках. Механизмы, балансирующие скорости производства и расхода АТФ в каждой клетке, находятся во взаимосвязи с механизмами и вегетативными системами организменного масштаба. Развитие артериальной гипертонии скорее является компенсаторной реакцией на нехватку энергии, чем болезнью.

Ключевые слова: артериальная гипертония, энергетика, физиология кровообращения, модели.

Запропоновано розширене уявлення про механізми регуляції середнього артеріального тиску в нормі та при артеріальній гіпертонії. У хребетних (зокрема, у людини) є багатомасштабна енергетична мегасистема, яка веде боротьбу проти тривалої нестачі АТФ в клітинах. Механізми, які балансують швидкості продукування та використання АТФ в кожній клітині, находяться у зв'язку з механізмами та вегетативними системами організму. Розвиток артеріальної гіпертонії скоріше є компенсаторною реакцією на нестачу енергії, ніж хворобою.

Ключові слова: артеріальна гіпертонія, енергетика, фізіологія кровообігу, моделі.

INTRODUCTION

Arterial hypertension (AH) is a multi-factor disease mostly developing gradually [1, 2]. About 30% of adults are affected by AH. However, its etiology is clear only for 5% of diseased people [3]. AH eventually leads to associated serious pathologies (heart failure, brain hemorrhagic stroke, renal diseases) [2–5]. In fact, therapies of AH are often aimed rather to mitigate its symptoms than really eliminate the disease [3]. Despite advanced drugs and cure, the number of diseased people is not reducing [3]. Experts recognize that there are still some cases of essential AH uncovered by its theories [2, 5, 6]. This disappointment gives a reason to suspect that our knowledge of physiological mechanisms responsible for a homeostasis of arterial pressure (AP) contains serious gaps. Naturally, mathematical models of AP's physiological control could not be free of these gaps. To come to most comprehensive models, we need to extend our understanding of a role playing by cardiovascular system (CVS) in human organism. The extended view of CVS must include both CVS's autonomous control mechanisms and

conditions in which functions of these mechanisms become modulated via factors born out of CVS.

This article has two **goals**. The fist one — theoretical goal is to provide special formalized analysis determining both mechanisms of normal AP and causes of its changes. The second one — medical goal is to facilitate a search for cardinal curing of AH.

BASIC INFORMATION

Most theories of AP's homeostasis silently assume that a stabilization of mean arterial pressure (MAP) is the goal of control mechanisms [4–6]. In frame of this concept, alterations of MAP are interpreted as undesirable aberrations of CVS. In particular, AH is considered as a disease that should be cured in ways leading to normalization of MAP (or its end-systolic and end-diastolic peaks).

A cardinally new view of AP's role in organism is proposed in recent general theory of reversible adaptation [7–9]. In fact, the conceptual leap concerns both AP's role and fundamentals of organs integration for providing of vegetative functions. To mostly relief represent the new concept, it is useful to compare it with a traditional concept.

In traditional physiology, every organ is considered to be an upper-scale structure that has its specialized function(s) and autonomous control systems. Under environmental violations, these organs and systems generally provide organism's homeostasis. In contrast, the energy concept showed that a group of upper-scale organs, direct or indirectly involved in modulation of cell's mean rate of ATP-production, form an exclusive functional system aimed to provide of long-term energy balance (EB) in every specialized cell of the organism. This functional system was called an energy megasystem (EMS) because of its enormously large size and complexity. It is important to remember that the CVS is one of constituent systems of EMS thus a functional activity of CVS is reciprocally associated with the activity of remained structures of EMS.

In human cells, ATP is produced both via anaerobe glycolisis in cytoplasm and via oxygenation of pyruvic acid in mitochondria. The pyruvate is a common chemical output of intracellular transformations of carbohydrates, fatty acids, fats, and proteins. Normally, mitochondria are main producers of ATP. As the aerobic cell does not store a large amount of ATP-molecules, their mean mitochondrial synthesis rate (v_s) is tightly associated with a mean rate (v_d) of dissociation of ATP. Although intracellular mechanisms balancing v_s with v_d are known, because of limited efficiency, under chronic increase of v_d, these mechanisms do not provide long-term EB.

The energy view on human physiology revealed several hidden internal relationships of organs and systems. Most of these relationships was evolutionary saved because they accelerate cells' fight against chronic energy deficit [7]. Indeed, the long-term lack of ATP suppresses most cellular activities including cell's and entire organism's reactivity to dangerous environmental challenges. So, in conditions of unstable environment, those multicellular organisms that accelerated mitochondrial enlargement in inhibited cells, had more chances to survive. It is

reasonable to state that such a type of organism is the energetically most advanced.

In human cells, molecules of ATP are main consumables. Both the metabolism and the reactivity of every cell are vulnerable to deficit of ATP. A lack of energy suppresses or interrupts several biochemical transformations and affects cellular reactivity to extracellular signals. So, even under rest conditions, a functional integrity of entire organism or its physiological systems critically depends upon compensatory incomes of consumables necessary for a synthesis of ATP.

Mitochondrial total surface is main long-term determiner of v_s [7]. Under continuous situation of $v_s < v1_d$, eventually an energy deficit will appear. So, cytoplasm concentrations of various interim chemicals eventually elevate. Some of these chemicals (e.g., hypoxia inducible factors [2]) increase v_s and activate mechanisms of proliferation/hypertrophy of mitochondrion. Theoretically, this negative feedback should work until a new rate of ATP production ($v1_s \geq v1_d$) eliminates the deficit of energy. In real conditions, the mitochondrial up-build requires appropriate material incomes.

The aerobic cell cannot store a large numbers of ATP molecules, thus the increased v_s automatically decreases the number of consumables (carbohydrates and oxygen). There are multiple mechanisms compensating this lack of consumables. Under local (regional) deficit of either oxygen or glucose, local vasodilatation (provided by chemicals leaved suffering cells) does increase blood flow and compensate the moderate lack of incomes. However, in case of a large affected region, the regional vasodilatation drops MAP and decreases blood flows. There are several ways to overcome such energy problems. An increase of MAP is a way leading to elimination of a severe deficit of ATP only in case of sufficient blood concentrations of glucose and oxygen. In case of low glucose, special low molecular chemicals produced by energy suffered cells activate mechanisms of glucose neogenesis from liver glycogen.

There are three subways for compensating of low blood oxygen. A mobilization of blood from its depots is the first and most rapid way but this way has very limited resource. An increase of lung ventilation is the second rapid way supporting blood erythrocytes' oxygenation. At last, an increase of a rate of erythropoiesis is the main but inertial way capable to provide additional erythrocytes for transporting of oxygen toward cells. These mechanisms all together prompt every cell to overcome its energy problems if only the organism possesses sufficient internal material resources. In versus case, these materials have to be taken from outside therefore, those behaviors that are integrated in food search and assimilation are also involved in EMS.

This general view of organism's mechanisms, evolutionary saved for optimal fighting of energy deficit in cells, is the basis for comprehending of causes and mechanisms for both fluctuations and long-term shifts of MAP. To facilitate this comprehension and to create a basis for advanced mathematical models, let us formalize current physiological knowledge concerning neural-hormonal control of MAP.

A FORMAL DESCRIPTION OF MECHANISMS REGULATING MAP

Assume $P_A(t)$ and $P_V(t)$ denote momentum values of AP and central venous pressure appropriately. In practice, physicians use AP's two characteristics: end-systolic and end-diastolic peaks. But these extreme values of $P_A(t)$ depend on measurement site on arterial tree. Besides, for a given time τ, a mean blood flow between every two vascular segments is determined by their mean pressure gradients. Usually, τ represents the duration of a cardiac cycle. To calculate cardiac output $Q(\tau)$, one needs mean value of total peripheral resistance $R_T(\tau)$, as well as mean values $\overline{P}_A(t)$, $\overline{P}_V(t)$ of $P_A(t)$, and $P_V(t)$ respectively.

$$\overline{P}_A(t)=\frac{1}{\tau}\int_0^{\tau}P_A(t)dt\ ;\ \overline{P}_V(t)=\frac{1}{\tau}\int_0^{\tau}P_V(t)dt\ ;\ Q(\tau)=(\overline{P}_A(t)-\overline{P}_V(t))/R_T(\tau).$$

To clarify common and specific mechanisms fluctuating human hemodynamic characteristics, as well as to determine distinguish signs of these mechanisms in comparison with mechanisms shifting both $\overline{P}_A(t)$ and $P_A(t)$, we must remember that the CVS is an open non-stationary system. Fluctuations of $P_A(t)$ and $\overline{P}_A(t)$ in physiological conditions suggest that characteristics of CVS are time-variables. Energy-based modulators of $\overline{P}_A(t)$ are not the exclusive external influences on CVS. Hemodynamic effects of modulators can be realized via changes of limited number of CVS's characteristics: $Q(t)$, vascular tone $T_v(t)$, blood volume $V_S(t)$. So, every controller of human hemodynamics should have an access at least to one of parameters that determine $Q(t)$, $T_v(t)$, and $V_S(t)$.

As $\overline{P}_A(t)$ is in the focus of our analysis, it is worth to stress that $\overline{P}_A(t)$ is most sensitive to variations of $V_S(t)$. Traditionally, kidneys are assumed to be main regulator of $V_S(t)$. Indeed, under dropping of $\overline{P}_A(t)$, cells of juxtaglomerular complex release renin that go to circulate. In liver cells, renin causes a release of *angiotensin I* (non-active protein). After a lung circulation, the *angiotensin I* is transforming into an *angiotensin II* which is a vasoconstrictor increasing $\overline{P}_A(t)$. Besides, *angiotensin II* compels special cells to produce a hormone *aldosterone*. In renal tubules, *aldosterone* increases a fluid reabsorption rate. Totally, these endogenous chemical agents increase $\overline{P}_A(t)$ via increasing of both $V_S(t)$ and $Q(t)$ [5, 7].

In frame of this concept, there is assumed to be none interim alteration between the decrease of $\overline{P}_A(t)$ and decrease of filtration rate in juxtaglomerular cells thus, the rennin-angiotensin system is considered to be a regulator of $V_S(t)$. This concept could be true in case of absolutely passive filtration in renal capsules. In case the filtration is at least a partially active process provided by ATP, there will be a time delay between a drop of pressure in renal arterioles and release of renin. Indirectly, this supposes that a dependence of renin from $\overline{P}_A(t)$ is rather

associative than causal. This qualification, seeming to be secondary, is crucial in frame of energy concept of arterial pressure. The fact that currently nine versions of angiotensines (with unclear contributions in hemodynamic shifts) are discovered gives additional reason for revising of traditional view on renal control of $V_S(t)$ and $\overline{P}_A(t)$ [5, 6]. It was supposed that renin or its functional analogues are universal indicators of energy lack in cells of different specialization [8].

So, practically all our specialized cells take part in determining of CVS's state and a value of $\overline{P}_A(t)$. This is the essence of novel energy concept of AH's etiology [7, 8]. A brief description of this concept given below is to facilitate understanding of main intracellular and upper-scales mechanisms responsible for both fluctuations and long-term shifts of $\overline{P}_A(t)$.

Under given central venous pressure, $Q(t)$ depends on heart rate $F(t)$ an ejection fraction (EF). Under constant total peripheral resistance, EF can be characterized by a coefficient $k(t)$ calculated as a quotient of stroke volume of ventricle to its end-diastolic volume [7].

The integral vascular tone $T_v(t)$ reflects values of arterial and venous unstressed volumes $U_A(t)$, $U_V(t)$ and volumetric rigidities $D_A(t)$, $D_V(t)$ respectively. In every vascular compartment, its vascular resistance $R_v(t)$ depends on $V(t)$, $U(t)$, and $D(t)$ [8]. An exact formula connecting these characteristics of CVS with $P_a(t)$ hardly can be identified but a large amount of successive mathematical models are based on approximations like

$$P_A(t) \approx \Psi(V_S(t), U_S(t), T_v(t), R_v(t), F(t), k(t)) . \quad (1)$$

For convenience, CVS's characteristics included in Ψ – function in (1), further are denoted x_i.

$$P_A(t) \approx \Psi(x_i(t)) . \quad (2)$$

Assume $x_i(0)$ is a value of every variable x_i under unstressed regulators. In every other physiological state, and for every t, variables $x_i(t)$ represent regulator alterations of the $x_i(0)$ on $\Delta x_i(t)$. Every $\Delta x_i(t)$ has its extreme values, so $|\Delta x_i(t)| \le x_i^{Ext}$. Within this interval, the value of $\Delta x_i(t)$ can be calculated as an algebraic sum of effects, caused by $j = \overline{1,m}$ physiochemical influences. For a part of such influences, their sources are known (baroreflector, chemoreflector influences, descending nervous influences of brain upper structures, and a variety of humoral agents). Another group of influences (e.g., temperature, metabolic, exogenous activators or inhibitors) can have mainly local effects (e.g., modulating only the basic rate of heart pacemakers). A formal description of these opportunities looks as:

$$x_i(t) = \begin{cases} x_i(0) \pm \Delta x_i(t), & |x_i(t)| \le x_i^{Ext}, \quad \text{where} \quad \Delta x_i(t) = \sum_{r=1}^{m} \Delta x_{ir}(t), \\ x_i^{Ext}, & |x_i(t)| > x_i^{Ext} \end{cases} \tag{3}$$

where

$$\Delta x_{ir}(t) = \begin{cases} 0, & Y_{ir}(t) \le y_{ir} \\ a_{ir}(Y_{ir}(t) - y_{ir}) + b_{ie}, & y_{ir} < Y_{ir}(t) < Y_{ir}{}^{s} \\ \Delta x_{ir}{}^{s}, & Y_{ir}(t) \ge Y_{ir}{}^{s} \end{cases}. \tag{4}$$

A piecewise linear relations (4) commonly represent characteristics of specialized receptors. The formula (4) tooks into account that every such receptor is not active until its activity threshold y_{ir} had been overcome. The formula (4) also supposed that every receptor has its saturation level $Y_{ir}{}^{s}$. Within these extreme values $y_{ir} < Y_{ir}(t) < Y_{ir}{}^{s}$, the receptor activity $Y_{ir}(t)$ is proportional to an over-threshold value of real biological variable (e.g., blood transmural pressure or chemical parameters). Certainly, this linear approximation does not cover the entire diapason of receptors' activity. Nevertheless, the reduced formulas (3) and (4) are capable to model main cardiovascular reflector responses Δx_{ir} to internal/external challenges of moderate values characteristic for physiological conditions. For every receptor, the sensitivity coefficient a_{ir} is considered to be constant for the entire diapason of receptor function. It is assumed that the summands b_{ie} are not zero only for those x_i that surely are under additional influences.

Formalizations (3) and (4) cover every variable of CVS. However, the multiple control of the hemodynamics has several nuances that should be special commented. To accentuate some of these nuances, it is useful to compare the control of the heart pump function with the control of regional vascular tones. Let us look inside the control of $F(t)$.

It is known that under normal physiological conditions, the rate of right atrium's pacemakers is the main determiner of $F(t)$. From the other hand, the pacemakers are sensitive to changes of both blood temperature (T^o) and blood chemical state (z). So, the basic rate (f_a) of right atrium's pacemakers is a function of at least two independent variables: $f_a(T^o, z)$. Under $z = const$, the function $f_a(T^o, z)$ is practically linear within $33\,^{\circ}\text{C} \le T^o \le 41\,^{\circ}\text{C}$. Under $T^o = const$, variations of z could either increase f_a or decrease it.

Descending nervous modulations of $F(t)$ can reach the right atrium's pacemakers via appropriate nervous fibers of cardiac sympathetic or parasympathetic nerves. The sympathetic fibers cause positive chronotropic effect while the parasympathetic pathways have negative chronotropic effect. Denote these effects ΔF_S and ΔF_V respectively. Then, descending modulator effects

caused both by brain supra-bulbar structures and by main hormonal modulators (adrenalin, noradrenalin, and acetylcholine) can be formalized as

$$F(t) = f_a(T^o, z) + \Delta F_s - \Delta F_v . \quad (5)$$

Note that the formula (5) is indifferent to nature of modulators. In practice, a differential diagnosis of AH and its cure require information about investment of every modulator in a measured alterations of $F(t)$. This last sentence is explained below.

Assume, an elevation of $P_A(t)$ is caused by an increase of $Q(t)$. The gain of $Q(t)$ is possible due to three independent alterations: 1) via increase of $\overline{P}_V(t)$; 2) via increase of $F(t)$; 3) via increase of heart contractility. Suppose $\overline{P}_V(t) = const$. Then nervous alterations either increase the frequency of sympathetic impulses or decrease the frequency of parasympathetic impulses in the respective descending heart nervous branches. So, the total effect is in a gain of $Q(t)$. In addition, several hormonal agents are also capable to gain of $Q(t)$. Indisputable, the therapy of AH should be based on differentiation of these mechanisms. But even possessing of reliable methods for such differentiation, there is still one more important problem: it is necessary to clarify the primary cause of alterations in every regulator mechanism.

The main effect of reflexes activated because of ascending impulses born in cardiac or arterial mechanoreceptors is to damp cyclic violations of $P_A(t)$ [2, 5, 7]. Chemoreceptor reflexes normally are aimed to increase MAP, as well as to intensify lung ventilation. Two these alterations commonly provide the due composition of the arterial blood [5]. As to relative roles of CVS's nervous and humoral control mechanisms, researchers agreed only if the discussion concerns the speed of these mechanisms [2]. Analogically, there is no consensus concerning roles of a variety of chemicals modulating heart pump function and /or vascular tone [5]. The last sentence also concerns local effects of low molecular metabolites (e.g., $H^+, OH^-, CO, CO_2, NO, SO_2$) [2, 3, 12]. So, this ambiguity of thoughts formed the conceptual relief on which the energy concept of arterial pressure (ECAP) explained main mechanisms of cardiovascular variability had appeared [8].

Suppose in (2) some state of arterial pressure $P_A(t) = P_A^*(t)$ is already chosen to be the basic state. In accordance with common concept of homeostasis, the value of $P_A^*(t)$ is often close to a special but virtual value $P_{AN}^*(t)$ also called as the normal value of $P_A(t)$ under rest. However $P_{AN}^*(t)$ is not argued physiologically. $P_{AN}^*(t)$ is statistically calculated as the mean value of $P_A(t)$ in a population of practically healthy people under rest. Thus, $P_{AN}^*(t)$ does not mandatorily represent the normal arterial pressure for an individual. To overcome this conceptual disparity, recently a concept of individual physiological norm is proposed [9]. According to the new interpretation, the individual physiological

norm is a synonymous to organism-scale energy balance. But the energy production/consumption rates can be balanced on different levels of ATP-production. This means that instead of an exclusive state of virtual homeostasis, every organism can have a lot of normal states. Therefore, multiple combinations of $x_i(t)$ are capable to provide the values of $P_A^*(t)$.

In the dimension of state parameters $x_i(t)$ of CVS, two states of CVS could be determined of different $x_i(t)$. Although the inequality $x_i(t) \neq x_i(0)$ appears in both states, mechanisms responsible for these inequalities are not the same. Indeed, in one case, the situation of $x_{1i}(t) \neq x_i(0)$ appears because of stressed regulators while in opposite case of $x_{2i}(t) \neq x_i(0)$ none regulator of CVS is stressed.

Normally, regulator shifts of Δx_i are reversible and do not continue for a long-time. Besides, such shifts do not cause ultrastructural re-build. However, there is another type of alterations covering both effectors (myocardium, vascular smooth muscles) and of regulator mechanisms' characteristics (activation thresholds, parameters of the sensitivity and saturation of receptors). Mechanisms responsible for transitory alterations $x_{1i}(t) \neq x_i(0)$ are known. Moreover, physiologists and physicians are sure that the alterations have compensatory character. Nevertheless, both initiator and realizing mechanisms of this goal are still unknown yet. In frame of the problem of AH, this physiological uncertainty does origin medical problems.

As a rule, most patients addressing for a cure already have signs of a developed pathology. The multiple regulators of hemodynamics, possible individual ontogenetic variations of every regulator are factors complicating both a correct diagnosis of AH and its due cure [3, 13]. Despite these initial problems, under AH's extreme cases, the doctor must provide an appropriate cure of AH.

Currently, the cure is aimed to return important characteristics of CVS to their so-called normal values thus the cure is mostly targeted to elimination of symptoms [3]. Is such a cure correct? The question is not rhetorical because the so-called normalization of AH does not take into account the real complexity of EMS and the multiplicity of individual adaptations [7]. The current medical technologies are not capable to effectively fight AH via drugs inactivating initial shifts. Thus AH's cure displays only transitory effects that are mainly disappearing soon after the intake of drugs is stopped [3, 5]. From the platform of EMS, such transitory results evidently show that the cure do not act against new stabile values of $x_{2i}(t)$. In other words, the palliative effect acts only at level of regulators forming $\Delta x_i(t)$, but there is no structural returning to $x_i(0)$.

So, all we know about physiology of CVS concerns its own reflexes aimed to control AP. The traditional hemodynamic approximation does not point out determinants of MAP. A search for deep mechanisms indirectly modulating AP, and likely being associated with functions of other physiological sub-units, could bring us to an extended concept of AP. During this search, the initial quest is: why the organism needs AP in general?

According to [6, 7], normally, current level of AP should not be less than a pressure providing blood flows sufficient for production of due amount of ATP in

cells. In statics, every cell tries to control its mitochondria for reaching an optimal summary surface sufficient to balance v_s with v_d. This balance does not depend on physiochemical fluctuations in local intercellular environment. In fact, such a multi-parametric optimization suggests that MAP does properly vary depending on blood chemical composition. As this composition is resulted of efforts developed in different physiological sub-systems of EMS, the level of MAP has to be inversely proportional to activities of mechanisms that regulate blood glucose, number of erythrocytes, lung ventilation, as well as a concerted function of the digestive system. This branched system supposes a huge number of situations satisfying energy needs of cells.

There is one more aspect that should have been analyzed. This aspect concerns correct understanding of causes transforming the physiological control of AP to its pathological shifts. Last several years, local rennin-angiotensin systems [6, 10] and AMP-activated protein kinase [11–16] are in the focus of investigations. At the moment, experts proposed a lot of hypotheses concerning roles of tissue factors in control of cardiovascular activity, but practically every hypothesis silently assumes that there should be some general control of AP. In this paper, another idea based on casual mutations is provided.

The concept of EMS [7] assumed that the upper-scales sub-units of EMS had been evolutionary saved because they accelerate the fight of cells against energy imbalance. An indirect effect of this system is that alterations (geometric sizes, functional) of sub-units of EMS will be synchronized. Although clinicians had accumulated a lot of evidences that under certain diseases, a hypertrophy of some organs (liver, kidneys, heart, and glandules) happened, only the energy concept explains why and how these alterations correlate.

The evolutionary view of complex regulator ensembles suggests that our organs and systems are not mandatorily optimal as one could suppose. Although the anatomy, genetics, and biochemistry provided of many arguments for this assertion, until recently, analogical physiological arguments were absent. Namely, the parallelism of efforts developed by a huge number of cells (fighting for common and scarce resources) is the best argumentation of a thought that the long-term optimum and the acute-optimum cannot be provided simultaneously [7]. The upper-scales regulators become activated to create a due productiveness of cell-scale energy producers – mitochondria. So, the upper-scales regulators are under chemicals produced by every cell. Perhaps, intravascular endothelial cells, representing organism's biggest producer of hormones, play the main role in modulation of MAP-level. However, the energy concept of AP ensures that the long-term level of MAP reflects total contribution (including opposite efforts) of practically all cells. Therefore, an advanced cure of pathological shifts of AP requires a creation of medical technologies based on the concept of individual physiological norm [9].

CONCLUSIONS

The CVS is only a part of EMS that counteracts against lack of ATP in cells. EMS also includes regulators of lung ventilation, of erythropoiesis, of blood glucose, and mechanisms regulating the biogenesis of mitochondria. The AP's

responsibility concerns only transporting of chemical ingredients to and from cells. The level of AP is reciprocally associated with the activity of remained functional blocks of EMS thus their low activity can be compensated via increasing of AP.

A transitory increase of AP supposes one of following scenarios: a) EMS's non-hemodynamic reactions are delayed; b) the lack of ATP disappeared due to spontaneously decreased rate of ATP-consumption. A steady growth of AP indicates that assistant blocks of EMS cannot provide the adequate power.

A hypotensive cure of AH is advisable only under real risk of a haemorrhage. In versus cases, the organism is searching for providing of cell energy balance using non-cardiovascular mechanisms.

A healthy person can have AP essentially different of so-called normal AP. Under blocking of mechanisms that increase AP, the counteracting mechanisms use alternative ways for fighting the energy lack. In particular, persons having more erythrocytes and/or more effective mitochondria do have lower values of AP.

It is necessary to develop medical technologies capable to provide both a differential diagnostics of main forms of AH and their elimination on initial stages of development.

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