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Human Circulatory Response Physical Modeling in Anesthesiology and Critical Care (Review)

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The narrative review discusses the problem of modeling patient's circulatory responses to various challenges during anesthesia, surgery and intensive care. The authors justify the point of view that in order to avoid perioperative critical incidents such a forecast should be based on a goal-targeted clinical tests – physical modeling of the system response using safe test stimuli, physically similar to disturbing challenges by their biomechanical nature. As an examples, authors analyze the prediction of circulatory response to neuraxial block using a test dose of nitroglycerin, to induction of general anesthesia using esmolol test, to volume load infusion using preload maneuver tests, a hemodynamic test for the surgical hemostasis consistency, optimal PEEP titration balancing the contradictory requirements of alveolar recruitment and pulmonary capillaries blood flow support.

Keywords: systemic hemodynamic response, general anesthesia induction, neuraxial block, nitroglycerine, esmolol, phenylephrine, surgical hemostasis, positive end-expiratory pressure.

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Introduction

Tests of physical analog models and physical modeling of processes have long been used when a reliable forecast of the behavior of objects is needed, the failure or abnormal operation of which is associated with unacceptable damage, and accurate measurement of quantitative characteristics and/or correct mathematical description are difficult [1]: in shipbuilding and aircraft industry, unique buildings and structures — bridges, dams, TV towers. Leonardo da Vinci (1452–1519) also built large-scale physical models of his inventions, checking their performance; mechanic I.I. Polzunov (1728–1766), the shipbuilder S.O. Makarov (1849–1904), aerodynamicist N.E. Zhukovsky (1847–1921) can be named among the Russian pioneers of physical modeling.

With respect to medicine high-risk situations where a chain of unexpected events can quickly lead to disaster abound in the so-called critical condition medicine (A.P. Silber, 1977 [2]), combining anesthesiology and intensive care in Russian- and French-speaking countries, and emergency care and pain management in German-speaking countries [3]. Head of the Department of Physical Methods of Treatment of the Imperial Clinical Institute of Grand Duchess Elena Pavlovna in St. Petersburg (now I.I. Mechnikov NWSMU) Professor V.A. Stange (1856–1918) proposed a „test for tolerance to chloroform anesthesia" [4] which constitutes the measurement of the time of arbitrary breath retention on inspiration back on December 18, 1913, at the XIIIth Congress of Russian Surgeons which is used to this day [5]. The functional diagnostics have improved over the years, and more complex and sophisticated tests have been used to assess the risk of increasingly aggressive operations and life support methods for the patient in advance [6]. There remained, however, a problem that had been ignored for some time.

The fact is that both the Stange test and the numerous tests proposed later solved (with varying success!) the problem of assessing the body's resistance to oxygen deficiency — hypoxia, since it was considered both the

most typical problem of anesthesia and surgery, and the central plot of intensive care [7]. On the other hand, greater opportunities for increasing oxygen delivery and consumption were associated with higher resistance to any damaging effects since the acute adaptation of the body to changed conditions is always energy-dependent [8]. By default, it was assumed that if the oxygen transport systems of the body have sufficient functional reserve, then the patient will cope with all stress factors in the operating room and intensive care unit. But if in sports and extreme medicine, where „the critical moment" usually coincides with the peak growth of aerobic metabolism, such an approach has generally justified itself [9,10], then during surgery and anesthesia the challenges presented to the body are of a qualitatively different nature.

In fact, what does a widespread bicycle ergometric breakdown have in common with operating conditions [11]? The central hypometabolic effect of most drugs — hypnotics and analgesics, turning off muscle tone with neuromuscular blockers, blood loss, nociceptive (pain) stimuli mechanically induced by the surgeon and parasympathetic reflexes against the background of suppressed sympathetic activity [12] — all these components of operational stress and protection from it have very little resemblance to functional tests designed to assess the maximum aerobic metabolism, and they cause a qualitatively different response from the body.

Physical activity tests, tests for tolerance to hypoxemia and hypercapnia, characterizing the overall endurance of the body" (no one knows the exact definition of this ancient concept!) do not answer specific and extremely important questions for the doctor — how the blood circulation of this particular patient will react to the suppression of myocardial contractility by induction of general anesthesia or to a drop in vascular tone as a result of a neuroaxial block, to blood loss and its replenishment, to what extent these shifts can be countered by an increase in preload of the heart, etc. It is necessary to model the behavior of blood circulation for such a substantive forecast observing the similarity condition, i.e. based on the biomechanical similarity of disturbing influences and the nature of the response [1,13]. The creation of physical models of human hemodynamic reactions to various influences, primarily minimally invasive ones, seems very promising, and we found it useful to provide an analytical overview of the search in this direction available to biophysicists and medical engineers.

1. Conditions for the consistency of hemodynamics: assessment and priorities

The assessment of any physiological function presupposes an accurate understanding of its purpose and the importance of this function in the life support of the whole organism. Supposedly, almost everything in the behavior of hemodynamics is explained by the priority of oxygen delivery to tissues formulated at the end of the 19th century by the German physiologist Eduard F.W. Pfluger and logically completed in the papers of Arthur Guyton in the 1960s. Today, however, physiology and pathology provide more and more facts of blood circulation regulation according to other target criteria: for example, in case of fever or high ambient temperature, the blood flow in the integumentary tissues repeatedly exceeds their oxygen demand, demonstrating the work on cooling the core of the body by heat transfer through the shell [14,15]. In case of a septic shock, high oxygen flow by itself does not ensure uniformity and adequacy of its delivery to tissues, which for the first time caused the current definition of shock (2014) to shift the focus from insufficient delivery of O_2 to a interruption of its consumption [16]. Thus, the goal of blood circulation in the most generalized form is to maintain the optimal amount of blood flow (perfusion) for each tissue, dictated by various current tasks of systemic and local metabolism and energy.

And here is the main paradox of hemodynamic management: even the best equipped clinics in the world do not have a method for measuring tissue blood flow today while they have a variety of methods for measuring numerous parameters of blood circulation (including their real-time monitoring), often successfully overcoming its severe disorders! This indicator with a dimension of ml/100 g of tissue per minute can be measured in a physiological experiment (for example, by the method of hydrogen clearance), but is completely unavailable in clinical conditions. This forces the use of a surrogate parameter — minute circulatory volume (MCV), or cardiac output (CO), representing the sum of all tissue blood flows in either of the two circulatory circles, equal to the minute capacity of each of the ventricles of the heart. With the exception of the mentioned septic shock situation, sufficient output (in relation to the body surface area, the normal values of the cardiac index (CI) are $2.7-3.6\,l \cdot \mathrm{m}^{-2} \cdot \mathrm{min}^{-1}$) — one of the main criteria for the consistency of blood circulation.

The forced substitution of inaccessible tissue blood flow by a „gross"-output, the distribution of which may contradict the priority of adequate perfusion of each tissue and organ, sometimes leads to funny paradoxes. So, when clamping the aorta for its prosthetics, the authors of [17] prefer one drug to another, because the first one increases cardiac output — leaving open the question where this increased flow is directed when mechanically shutting off half of the body from circulation. In other paper the preference in the cardiac surgery is given to a drug increasing the initially normal heart performance for reducing the blood pressure (BP) [18]. The problem is not at all in individual ignorance: one of the Soviet pioneers of mathematical modeling of blood circulation V.A. Lischuk rightly believed [19] that the main scientific and practical challenge here is the question „What is good and what is bad"?

However, even the output measurement methods appeared in practice much later than a much simpler measure-

ment of blood pressure: the Roman pediatrician Szipione Riva-Rocci proposed palpating the pulse distal to the cuff of a mercury pressure gauge already in 1896, the American neurosurgeon Harvey Cushing introduced the recording of the dynamics of blood pressure in the operating room in 1903, a doctoral student Nikolai Sergeyevich Korotkov described the noise of a turbulent flow over an artery at the Military Medical Academy in St. Petersburg in 1905. German physiologist Hans von Recklinghausen invented cuff pressure oscillometry in 1931, which is the basis for automatic noninvasive measurement, and in the first postwar years polymer vascular catheters allowed L.H.Peterson et al. implementing direct (invasive) blood pressure measurement. German internist Adolf Jarisch Jr. wrote already in 1928: „It is a pity that measuring the blood flow is much more difficult than measuring the pressure. This led to an excessive interest in measuring blood pressure. Most organs, however, need more blood flow than pressure“ (quoted by [20]).

And, although the idea of the first method of calculating the MCV was expressed by the discoverer of the law of diffusion, Adolf Fick, back in 1870, the measurement of the output became possible on a daily basis exactly a century later with the invention of a balloon catheter provided with the thermistor for the pulmonary artery by H.J.Swan and W.Ganz (1970). The mass application of the method of prepulmonary (i.e. in the right chambers of the heart and pulmonary artery) thermodilution began, which is still considered a reference for verification of the accuracy of other methods, including newly proposed ones. (It should be noted that this method was never verified *in vivo* based on a defined flow! — since such an opportunity is created so far only by artificial blood circulation, which in English is rightly called cardiopulmonary bypass — Cardiopulmonary bypass.)

At the same time, a normal cardiac output is only a necessary, but not a sufficient condition for adequate hemodynamics. There are areas in the vascular bed whose hydraulic resistance remains high even with maximum vasodilation. So, a second network of capillaries is connected in series through the outflow arteriole in the kidneys, following the glomerular filter of high resistance, feeding the epithelium of the tubules, which requires a lot of energy to operate ion pumps and molecular transporters. Venous blood from the unpaired organs of the abdominal cavity is collected into the portal vein, and then in the liver it is distributed again through the second network of capillaries. The same portal circuit with two consecutive capillary networks supplies blood to the hypothalamus and adenohypophysis. The listed organs, especially the kidneys, require a „technical minimum“ of the blood pressure, below which their effective perfusion is impossible at any output values. This limit is called the critical mean arterial pressure (MAP) and is estimated by normotonics at about 65 mm Hg [16,21].

The second situation, which sets the requirements for the AP, is typical for organs located in intractable anatomical containers. These are the brain located in the cranial cavity, surrounded by a dense capsule of kidneys and skeletal muscles enclosed in inextensible fascial cases. The value of AP becomes critical for these organs when pressure increases inside the case — and then, for example, cerebral perfusion pressure is calculated as the difference between the MAP and intracranial pressure [22].

Therefore, a sufficient level of MAP is also a necessary condition for sound hemodynamics. This logic does not allow limiting „ideal“ blood circulation monitoring only by controlling the cardiac output, it also forces epinephrine (adrenaline) to be administered during arrhythmogenic circulatory arrest, which exacerbates the electrical instability of the myocardium, but has a vasopressor (i.e. vasoconstrictor) effect and thereby increases the blood pressure created by closed heart massage to an effective level [23]. Thus, the dialectic of flow and pressure lies in the fact that both of these parameters are equally necessary conditions for normal tissue perfusion, but only together they form sufficient conditions for it.

2. Fundamentals of biomechanics of systemic circulation

The biomechanics of blood circulation is quite easy for doctors without additional physical, mathematical or engineering training at the macro level (Fig. 1). Four-chamber pump with variable elasticity ($E = dP/dV$, where P — pressure, V —volume) chambers, extremely sensitive to preload by inflow ($Q = dV/dt$, where t — time) at the inlet and almost indifferent to pressure afterload P at the outlet, pumps non-Newtonian fluid through sequentially connected closed circuits of high (large circle of blood circulation) and approximately an order of magnitude lower (small circle) hydraulic resistance ($R = \Delta P/Q$). At the same time, there are individual requirements for the sufficiency of the local flow for each section of these circuits, and there are conditions for sufficient inlet pressure for individual sections of the high-resistance circuit, as noted above („critical value“ AP, cerebral perfusion pressure). The fundamentals of biomechanics of systemic circulation were formed in their modern form by the middle of the 20th century [24] and since then have not undergone revolutionary changes [25].

This relative simplicity tempts further simplification, including the creation of simple physical models. An example of one of the most crude (and generally accepted in the world!) simplifications — the values of the total vascular resistance of both circulatory circles (total peripheral vascular resistance and total pulmonary vascular resistance) are calculated according to Ohm's law for conditions of constant pressure gradients and stationary flow. Meanwhile, real pressures and flows in the arteries pulsate, and, in a strict sense, the instantaneous value of vascular resistance is a function of time with a period equal to the duration of the cardiocycle, the type of which reflects the ratio of active and reactive (i.e., depending on the elasticity of blood vessels

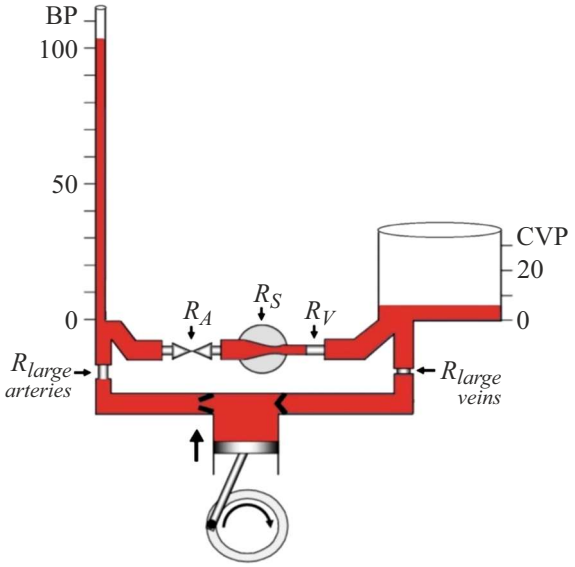

Figure 1. The basic hydraulic scheme of blood circulation. BP — blood pressure, arterial pressure, R — hydraulic resistance: RA — arterioles (represented by a crane, according to the classical metaphor of I.P.Pavlov), RS — capillaries in tissue with non-zero pressure in the interstitial (the so-called Starling resistor), RV — venules, already referred to the capacitive department of the vascular system (reservoir with a scale of central venous pressure, CVP). The small circle is completely omitted for the purpose of simplification, although functionally physiologists also refer it to a low-pressure and high-volume capacitive system lying between the RS and the inlet valve of the pump — LV of the heart (according to [26], with modifications and additions; presumably, the primary source of such technocratic sketches — the second edition of the famous „Applied Physiology of Respiration" John F. Nunn (1977) [27], where a similar but open circuit illustrates the variety of effects on hemodynamics of carbon dioxide).

and inertial characteristics of blood and tissues) components of the impedance of the vascular system [28].

The relationship between cardiac output and the conditions of the external load of the heart is illustrated by two three-dimensional graphs, the first of which (Fig. 2) shows the performance of the heart as a surface function of two variables — preload of the right (MRAP) and afterload of the left (MAP) ventricles. We are talking about pre- and afterloading of different ventricles of the heart, but this simplification is often resorted to for example, in Fig. 1. The graph shows that in the physiological range of MRAP and IDA values, the output depends on preload (as physiologists say, it is the most powerful physiological inotrope!), and afterload has almost no effect on it. The boundaries of the *invariance of the MCV with respect to the average pressure in the aorta* are estimated as 50−150 mm Hg [29], which almost exactly coincides with the boundaries of autoregulation of organ, in particular, cerebral blood flow [22]. Higher MAP figures still cause the output to decrease, and the earlier the higher the MRAP. Thus, an increase in preload above normal values not only does not expand the boundaries of the heart's insensitivity to afterload, but makes the left ventricle (LV) more dependent on resistance in the aorta. At the same time, the absolute output figures for each level of afterload remain proportional to it until the performance plateau is reached. In turn, the higher is the MAP the earlier is the peak of the output dependence curve on MRAP (the classical Frank-Starling curve) is reached.

How does the heart respond to volume overload, is there a „bucket" of the Frank-Starling curve, or is its right side always represented by a plateau [30]? The question is formulated pragmatically in the clinical application: is it possible to decrease the output as a result of an increase of preload, and if so, under what conditions? Let's use Fig. 3 to give a substantive answer, which also shows the surface of the heart function. In contrast to Fig. 2, it is based on data from synchronous measurements of three parameters in real patients — 57 patients with acute myocardial infarction, 11 suffering from chronic forms of coronary heart disease (CHD) and 17 healthy individuals. Of course, this graph cannot be interpreted in the same way as the graph in Fig. 2: it reflects not the reaction of the same heart to changes in pre- and afterloads, but the surface of the real hemodynamic states of various individuals — sick and healthy (this area is designated as an empirical surface), and the extrapolation of empirical data to subnormal values of total peripheral vascular resistance (calculated surface) is also presented. It can be seen from the graph that if, with a low heart rate, the heart confidently fulfills an increase in preload with an increase in ejection, then the application of high

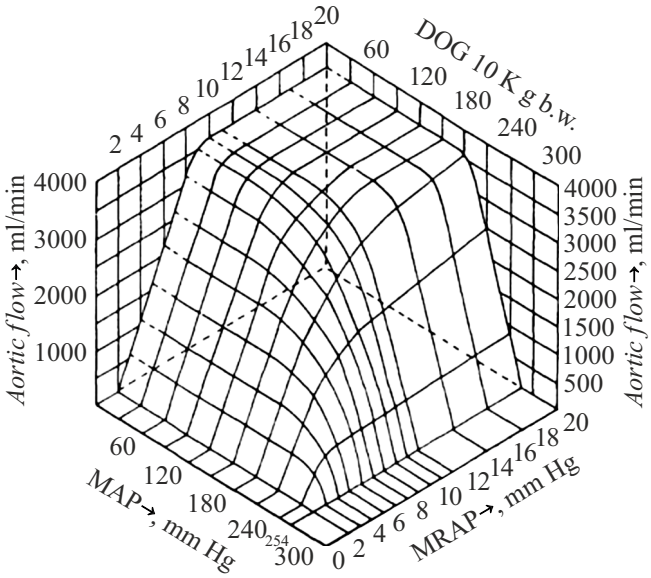

Figure 2. The surface of the heart function of a dog's cardiopulmonary preparation. Axis designations: MAP — Mean arterial pressure, mean blood pressure, mm Hg, MRAP — Mean right atrial pressure, mean pressure in the right atrium, mm Hg, Aortic flow — blood flow in the aorta, ml·min^{-1} (a drawing from the work of C. Herndon and K. Sagawa, 1969 [31]). Explanations in the text.

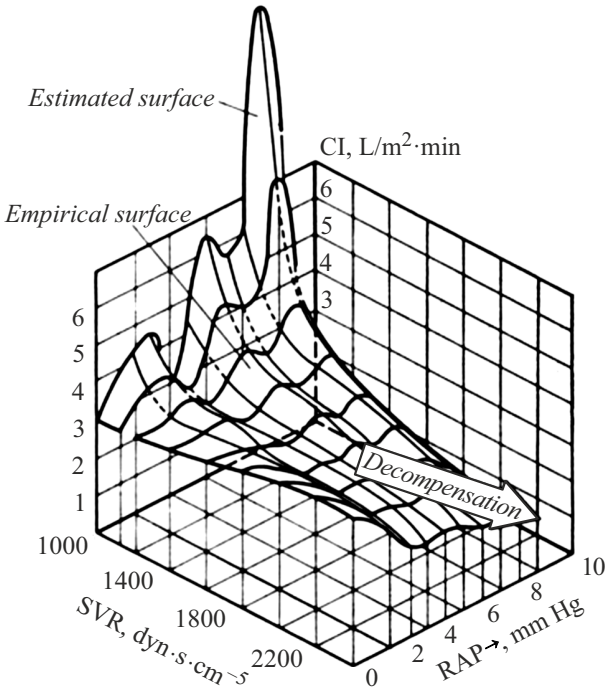

Figure 3. The surface of the heart function in the coordinates of the total peripheral vascular resistance of the large circulatory circle R, SVR — Systemic vascular resistance, dyn·s·cm^{-5}) — RAP (Right atrial pressure, mm Hg) — CI (Cardiac index — output Q, related to body surface area, $l{\cdot}m^{-2}{\cdot}min^{-1}$), „synthesized“ by discrete measurement points in sick and healthy individuals (drawing from the book by L.L. Orlova, A.M. Shilova, G.E. Roitberg, 1987 [32]). Explanations in the text.

preload against a background of high heart rate is associated with a decrease in productivity due to decompensation of contractility. The familiar difference in the relationship between output and afterload at different levels of preload is also striking: if, at zero pressure in the right atrium, heart performance is not related to the value of the heart rate, then, as the preload increases (within its normal values!), higher resistance values correspond to lower and lower ejection figures.

Let's summarize a brief overview of the relationships.

First, when planning to increase the output by increasing the preload through the intravenous infusion of fluids, it is always necessary to take into account the level of afterload: high afterload reduces the likelihood of an increase in heart performance. Conversely, the lower the afterload, the more noticeably the outflow increases in response to volemic support.

Secondly, wishing to increase the output by reducing the total peripheral vascular resistance, we should not forget that this effect is more pronounced the higher the preload, and there is no such effect at low levels of preload.

Finally, thirdly, the more complicated the hemodynamic situation, the more important information about both pre- and afterloading is for making tactical decisions. The real picture is always three-dimensional: no single method of estimating any of the variables individually makes it possible to predict the dynamics of the outlier.

3. Hemodynamic profile, complications and critical incidents

Observing and studying the dynamics of the main indicators of the biomechanics of blood circulation during surgery and anesthesia, we must clearly understand their relationship and the energy side of transitional regimes. Firstly, the output and/or AP drop may be caused by the inability of the LV to ensure the power level required for adequate hemodynamics under new conditions. Secondly, a forced increase of LV power can lead to „Demand ischaemia“ reduced oxygen delivery to the myocardium was sufficient at rest with stable coronary artery stenosis, but, for example, an ischemic damage will occur when necessary to compensate the drop of the total peripheral vascular resistance by an increase of the output. The explanation of these phenomena follows from the requirement to ensure maintaining of adequate AP in conditions of vasodilation (vascular distention). As stated above, since

$$R = \Delta P/Q, \tag{1}$$

then

$$\Delta P = R \cdot Q, \tag{2}$$

and

$$N = \Delta P \cdot Q = R \cdot Q^2, \tag{3}$$

where N — the mechanical power of the LV. The assumption here is that ΔP in all formulas are identical and equal to MAP, i.e. the pressure values at the end of the large circle of blood circulation are ignored (formulas (1)–(2)) and at the entrance to LJ (formula (3)), which are one or two orders of magnitude lower than MAP.

Let us suppose that significant vasodilation occurred as a result of certain effects, i.e. the value of R decreased, for example, by 30%. In this case, we will have to increase the cardiac output Q in the same proportion to maintain stability MAP $= \Delta P$, according to the formula (2). But if MAP does not change, then the LV power, according to the formula (3), will increase by 30%. Therefore, compensation for the drop of the total peripheral vascular resistance by an increase of the output — and the body itself goes exactly this way! — naturally leads to a risk of myocardial damage, which requires the doctor not to infuse fluid, but to use vasopressors (norepinephrine), which return R to values close to the baseline. It is clear from these positions why in experiments with coronary artery clipping in pigs, epidural blockade expands the area of myocardial infarction [33], and intraoperative arterial hypotension today, although prevented by preinfusion of fluid, is compensated almost exclusively by vasopressors [21].

Taking into account these ratios, it is easy to represent the mutually conjugate shifts in cardiac output, vascular

resistance, average arterial pressure and LV power in graphical form [12]. Figure 4 shows a graph reflecting in rectangular coordinates the shifts Q (abscissa axis, ΔQ) and R (ordinate axis, ΔR) from the initial state (origin of coordinates O) — for example, prior to anesthesia. Both scales are linear and graduated as a percentage relative to the initial values of the parameters. The transients in which the levels of mean AP and LV power consumption remain unchanged are represented in such a coordinate system by functions of a fairly simple form.

The hyperbola A represents the line of constancy of the mean AP — the geometric location of the points corresponding to the initial value of MAP on the selected scale. The mean AP does not change in case of the change of the circulatory regime if and only if the point reflecting the new set of parameters lies on the curve A. The area of the graph to the right and above this curve corresponds to higher values of MAP compared to the baseline (at the origin), and to the lower MAP values to the left and below it. Similarly, the curve B represents the line of constant mechanical power of the left ventricle; the maneuver of the circulatory parameters carried out according to the law $N = \text{const}$ assumes that the point reflecting the new state of hemodynamics, as well as the origin, lies on the hyperbola B. The area of the graph located above and to the right of this curve reflects the circulatory regimes with a higher LV power consumption relative to the initial one (at the origin), and the area to the left and below the curve reflects the circulatory regimes with a lower LV power consumption. The equations of the curves -A and B in this coordinate system will be written respectively as

$$\Delta R_A = 10^4 \cdot (\Delta Q + 100)^{-1} - 100, \quad (4)$$

$$\Delta R_B = 10^6 \cdot (\Delta Q + 100)^{-2} - 100. \quad (5)$$

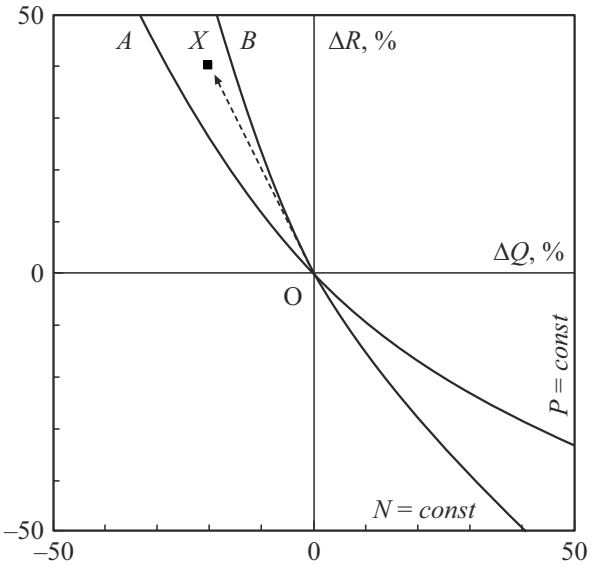

Figure 4. Graphical representation of shifts in indicators of systemic hemodynamics in coordinates $\Delta Q - \Delta R$ (%). A — line of equal mean AP, B — line of equal LV power. Explanations in the text.

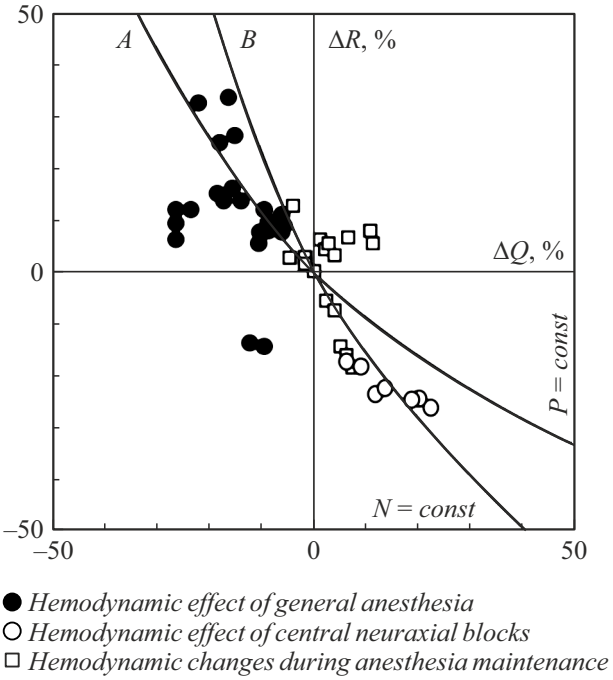

Figure 5. Hemodynamic effects of various methods of general and regional anesthesia [12]. Explanations in the text.

As an example, the graph shows the transition of the circulatory regime from the point O corresponding to the origin of coordinates to the point X, characterized by a decrease of the CI by 20% and an increase of the index of total peripheral vascular resistance by 40% relative to the initial values. It can be seen that the transition $\text{O} \rightarrow X$ is accompanied by an increase of MAP, but at the same time a decrease of LV power consumption. Thus, the graph allows analyzing transients in terms of the four main parameters of systemic hemodynamics.

The analysis of the hemodynamic profiles of anesthesia allows making the following main generalizations (Fig. 5) [12].

For general anesthesia, the primary effect on heart performance is typical, whereas vascular tone adjusts to the dynamics of ejection a second time. At the same time, not the presence of this effect depends on the choice of a specific scheme (i.e., a combination of drugs) of anesthesia — it is constant! — but only the degree of its severity. The introduction of induction drugs is naturally followed by a decrease in cardiac output with a compensatory rise in heart rate. Apparently, the reason for this constancy lies in the constant combination of drugs, leading to a qualitative change in the effects. The common effect, that in the English-language literature is referred as a central sympathetic outflow begin to prevail among these effects, and individual haemodynamic effects are largely mitigated. As a result, the detailed hemodynamic patterns characteristic of individual drugs do not correspond much to the real picture.

At the stage of maintaining anesthesia, fractional administration of hypnotics and analgesics is accompanied by minor hemodynamic effects, and the pattern is determined more by the stage of surgery than by the choice and dosages of drugs. Constant volume-dosed infusion of drugs results in the almost complete disappearance of any significant hemodynamic effects; only a change of the rate of infusion of analgesics leads (and not always!) to a change of the values of individual variables, but never to any radical change of the pattern (the directionality of the deviations of CI and total peripheral vascular resistance in relation to the initial values).

In case of neuroaxial (spinal or epidural) anesthesia, on the contrary, the beginning of the block is always marked by a drop of the total peripheral vascular resistance. This effect is so constant that it can be used to control the effectiveness of the blockade. Cardiac output behaves differently in different patients. The compensated situation is characterized by its increase, sufficient to maintain systemic blood pressure at an acceptable level. Cases of hypotension are explained precisely by the patient's inability to effectively increase the release. Repeated injections of an anesthetic during epidural anesthesia cause a distinct but less pronounced hemodynamic reaction. The dependence of hemodynamics on the stage of surgery is weakly expressed — the weaker, the „the rougher" the patient, i.e., the greater the amplitude of the hemodynamic effect of the anesthesia itself.

Modern anesthesiology not only declares, but has actually achieved a very high level of patient safety, comparable to the safety of passengers on the world's best airlines [34]. This is explained, among other things, by the high level of monitoring equipment: in terms of the quality and quantity of displayed and archived biophysical signals of the patient, the usual operating room today, including in our country, roughly corresponds to the advanced physiological laboratory of the 1970s. It is known that the widespread introduction of only one method of physiological monitoring — pulse oximetry — led from 1982 to 1987 to a twenty-fold (!) decrease of mortality in the UK operating rooms — from 1 case per 10,000 anesthesia to 1 case per 200 000 [35]. And it is even more frustrating when troubles still occur for various reasons during surgery and anesthesia despite these real achievements. They can develop both in the scenario of an obvious catastrophe (the rapid development of an obvious severe violation of one of the main life-supporting functions of the body, including directly on the operating table), and in a less extreme plot, when, certain problems arise in the postoperative period due to known or only suspected, but related to anesthesia reasons. At the same time, only the development of a new nosological form in a patient, causally unrelated to the underlying disease, is today called a *complication* of surgery or anesthesia; the concept of a *critical incident* includes a much wider range of situations of any temporary loss of control of a particular physiological function in addition to complications [34].

Historically, the development of various complications after surgery and anesthesia, including organ failure (cerebral, cardiac, renal, hepatic, etc.), was primarily associated with the toxic effect of anesthesia drugs on organs and systems. And although drugs of older generations (for example, chloroform or barbiturates) often did have significant toxicity, over time it became clear that ischemic organ damage associated with perfusion deficiency due to insufficient cardiac output and/or blood pressure is much more important [12].

Meanwhile, almost every patient during surgery experiences at least one episode of subcritical arterial hypotension with MAP $<$ 65 mm Hg [36]. Randomized studies show that preventing hypotension during surgery and anesthesia reduces the risk of postoperative organ dysfunction by about a quarter, i.e. hypotension — a classic controlled risk factor [37–39]. It is no coincidence that even artificial intelligence technologies are used today to predict these episodes — for example, the so-called hypotension prediction index (HPI) based on the AcumenIQ machine learning algorithm (Edwards Lifesciences, USA) [40,41]. From our point of view, however, the current level of knowledge makes it possible to build discursive models of the development of arterial hypotension during anesthesia based on biomechanical logic instead of studying the „black box" with a priori incomprehensible connections between input and output parameters. The following two sections of the review are devoted to their description.

4. Modeling of the circulatory response to the neuroaxial block

The first model was the systemic vasodilation test, developed by the authors to predict the hemodynamic response to the neuroaxial block [42]. The popularity of spinal and epidural anesthesia (SA and EA) has exacerbated the problem of predicting critical incidents, most often represented by deep arterial hypotension due to severe vasoplegia [43,44]. Compensation in this case depends on the dynamics of the release, rapid fluid infusion is used (not always safe in elderly patients!), and if it is ineffective, vasopressors are required.

The concepts of physiology and pharmacology suggested that a sample with systemic administration of a short-acting vasodilator (i.e. a vasodilator) could become a model of hemodynamic behavior in a neuroaxial block — for example, nitroglycerin. If the patient is predicted to develop deep hypotension, the anesthesiologist has a choice to prepare in advance for the infusion of the vasopressor norepinephrine or to completely abandon the neuroaxial block in favor of general anesthesia. The initial hypothesis was the assumption that the main difference between the groups with optimal (A) or extreme (B) circulatory response to the block is the ability to develop compensatory hyperdynamics (growth Q) during the nitroglycerin test,

the quantitative level of which can be used as the desired prognostic criterion.

This assumption was tested on clinical material from 100 patients aged 18 to 89 years, who underwent spinal and epidural anesthesia for traumatological, general surgical, urological and gynecological interventions at the Samara City Clinical Hospital No.1 named after N.I. Pirogovin 2000–2002. Operations on the lower extremities (48 observations) and urological interventions (26 observations) accounted for the largest share. The group was characterized by a significant incidence of concomitant pathology, amounting to 76% in total, with a predominance of coronary heart disease (43 patients, including one in the acute period of myocardial infarction and one against the background of unstable angina pectoris) and hypertension (23 observations).

The test with systemic vasodilation consisted of taking 500 μg of nitroglycerin under the tongue (on average 7.07 $\mu g \cdot kg^{-1}$). Hemodynamic parameters were recorded in the initial state and at the peak of the reaction to the test for cardiac output deviation. The test was performed on the eve of anesthesia in 21 observations, a day later in one case, a week after anesthesia in another case, and it was performed in the operating room on average for 32 ± 22 min (minimum 13, maximum 170 min) until the moment of puncture in the vast majority of observations (77). We did not subordinate the choice of the time of the test in relation to anesthesia, the method of anesthesia (SA or EA), local anesthetic and the addition of fentanyl to the objectives of the study, but based on the usual clinical criteria — the distribution of patients according to the listed parameters was purposefully given a random character. At the same time, the puncture technique and level remained standard: all anesthesia was performed in the operating room after catheterization of the peripheral vein and infusion of 7–9 $ml \cdot kg^{-1}$ crystalloids in the patients' side position from the puncture at the level of L_3-L_4. If the nitroglycerin test was performed in the operating room, the puncture was performed after mitigation of the hemodynamic reaction to nitroglycerin according to the assessment of the same anesthesiologist. The subarachnoid space was punctured with a Quincke 22G needle. 3 ml of 0.5% isobaric bupivacaine solution or 4 ml of 2% lidocaine solution with the addition of 50 or 100 μg of fentanyl was administered in 31 patients during 1 min after the appearance of liquor. The epidural space was punctured with a Tuohy needle from the median access. A test dose of a local anesthetic was administered (15 mg bupivacaine or 80 mg lidocaine) after verification of the needle position by the resistive method, and the main calculated dose of the same drug was administered after 5 min by adding to it 50–100 mg fentanyl and adrenaline in a dilution of 1:200,000. The patients were slowly moved to a horizontal position on their backs after the local anesthetic was administered. Arterial hypotension was corrected by forcing infusion and — with insufficient effect — bolus administration of ephedrine intravenously at an initial dose of 5 mg.

Hemodynamic monitoring was performed using noninvasive blood pressure measurement and impedance cardiography (complex „Diamant M", St. Petersburg). In dynamics, MAP was measured, heart rate and cardiac index were determined, the total peripheral vascular resistance and the left ventricular power index (LVPI), known in English literature as the cardiac power index (CPI) were calculated:

$$\mathrm{CPI}(\mathrm{W} \cdot \mathrm{m}^{-2}) = 0.0022 \cdot \mathrm{MAP} \cdot \mathrm{CI}, \qquad (6)$$

where 0.0022 — the product of the coefficients of conversion of mm Hg to Pa and $l \cdot \mathrm{min}^{-1}$ to $\mathrm{m}^3 \cdot \mathrm{s}^{-1}$, MAP — mean arterial pressure (MAP) and CI — cardiac index (SI). The data were processed in the „Microsoft Excel-97" and „Statistica 6.0" packages; the reliability of the differences was assessed using the Wilcoxon inversion criterion and the Fisher's method with Yates's correction, the search for the separation point was carried out by an iterative algorithm.

The effect of the nitroglycerin test was manifested by pronounced vasodilation with compensatory hyperdynamics: The index of total peripheral vascular resistance decreased by 36.5% from the initial value, the CI increased by 33.8%. At the same time, the mean LVPI increased by 14.1% (all shifts are reliable). Performing the test in most patients in the operating room immediately before the puncture led to the fact that the parameters before performing the block differ from the initial values before the test by significantly lower values of index of total peripheral vascular resistance and higher values of CI (response plume to nitroglycerin). The massive use of central blocks in emergency work, however, makes it useful to consider this deviation from the „purity of experience": the anesthesiologist cannot always perform the necessary functional tests in advance. Mitigation of the effect of the test according to the doctor's assessment by the time of puncture, fully guaranteeing the patient's safety, seems to be a sufficient limitation: the time interval between the test and the block did not demonstrate any relationship with the development of hypotension.

The circulatory response to the block was characterized by phasing. Vasodilation with a synchronous compensatory „surge" of CI was observed in the first minutes after the administration of a local anesthetic; at the same time, most patients did not experience a sharp decrease of AP. The data of this stage were recorded after 2–3 min after spinal surgery and 4–8 min after epidural anesthesia. The second stage was characterized by a marked decrease of the CI and LVPI, which was clinically manifested by severe arterial hypotension in a number of observations. The development during the block, which does not spread above the level of Th_5, of persistent arterial hypotension (a drop in systolic blood pressure to 75% of working pressure and below), which is not stopped by maximum acceleration of infusion and requires sympathomimetic support. There were 24 such observations, designated hereafter as group B, in the sample. This second stage of block development

corresponded to 5–8 min after SA and 11–18 min after EA; if the administration of ephedrine was necessary, the data were recorded immediately before its start. Finally, the third stage of the reaction was noted in eight patients with EA because of the spread of the block to the level of Th_4 and higher, due to the blockade of sympathetic efferents of the heart. It was characterized by a noticeable decrease of the heart rate (HR) with a further decrease of cardiac output below the initial (background) values. The anesthesiologist's tactics in this situation included the use of atropine at HR of $< 60\,\text{min}^{-1}$ (six observations), and ephedrine administration (four patients) in case of ineffectiveness of the latter or arterial hypotension with the HR of $\geq 60\,\text{min}^{-1}$. Some kind of intervention was required in all eight cases.

We assumed based on the initial hypothesis that the similarity of hemodynamic reactions to the sample and the neuroaxial block is so fundamental that it should manifest itself in the entire population regardless of the type of block and the drug. Therefore, at first the data were analyzed without grouping according to anesthesia techniques, leaving such a selective analysis in case of failure to identify the most common patterns. The differences between the groups of favorable (A) and corrective (B) anesthesia courses were analyzed for all studied parameters. It should be noted that the choice of drugs and the dose of local anesthetic did not show significant differences between the groups of patients. At the same time, it turned out that the groups significantly differ from each other in a significant number of indicators. We would like to highlight the age (patients with hypotension were significantly older) among the general clinical data, as well as the presence of risk factors such as coronary heart disease, hypertension and circulatory insufficiency. Functional differences during the block, as it followed from our initial hypothesis, consisted in the different ability of patients in groups A and B to increase cardiac output in response to vasodilation. In reality, the response of both one-time and minute cardiac work in the groups turned out to be multidirectional: if stable group A was characterized by an increase of these parameters, then the extreme group B demonstrated the decrease of these parameters in response to the block. At the same time, the initial level of the stroke index in the stable group turned out to be significantly higher. At the same time, the LV power index, the average figures of which did not initially differ in both groups, turned out to be significantly higher after the block in the group with stable hemodynamics. We would like to note a higher HR characteristic of the unstable group among other differences in the initial functional state of the cardiovascular system, whereas the total peripheral vascular resistance between the groups did not significantly differ.

As expected, the differences between the groups in the response to the nitroglycerin test turned out to be significant. First of all, the index of total peripheral resistance after the test turned out to be significantly higher in the disadvantaged group B. Despite this, not only the percentage shifts in systolic, diastolic and mean AP, but also the absolute figures of diastolic blood pressure in this group demonstrated a significant tendency to hypotension. The reason for such sharp differences, as expected, was the different ability of patients in the two groups to increase stroke volume in response to vasodilation: if in the well-off group A, the stroke index increased by an average of 25%, then in the extreme group it increased only by 12%. Since there were no significant differences in HR dynamics between the groups, the increase in minute heart work in the stable group also turned out to be about twice as high.

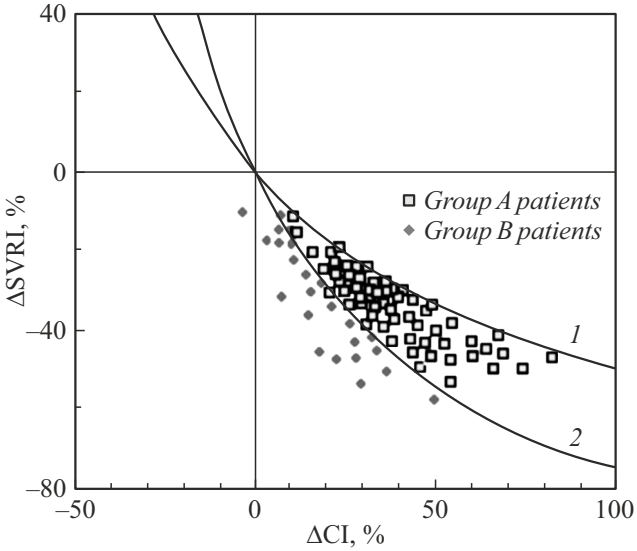

Figure 6. Shifts in hemodynamic parameters during the nitroglycerin test [12]. SVRI — Systemic vascular resistance index, CI — Cardiac index. *1* — curve of equal MAP, *2* — curve of equal LV power. Explanations in the text.

If the differences in the dynamics of AP and emission between the groups were quantitative, whereas the shifts themselves were unidirectional, then the dynamics of the LV power index turned out to be qualitatively different in the groups. LVPI increased by an average of 24% during the test in patients of the stable group, whereas, on the contrary, its decrease by an average of 7% turned out to be typical for patients of the disadvantaged group ($p < 0.001$). The optimal point of separation between the groups was the shift of the LVPI during the test, equal to +2.55% of the initial value.

A visual representation of the difference between the groups is given by the graph $\Delta Q - \Delta R$ (Fig. 6): it can be seen that the changes in the sample in both groups correspond in the vast majority of observations to a decrease in MAP, whereas with respect to the line of equal power, the groups are separated. If the majority of patients in group A are characterized by an increase in the LVPI, then group B shows a tendency to its decline. This pattern turned out to be so significant that even 4 observations of high EA, in which the use of ephedrine was required, significantly differed from 4 „favorable" cases: their LVPI decreased by an average of 0.97%, whereas LVPI increased by an average

of 16.8% during the testing in the group with the optimal reaction.

The importance of LV power resource for patient safety prompted us to study the relationship between changes in LVPI during the test and during the block. The abscissa axis of this graph (Fig. 7) reflects the percentage shift of the LVPI during the sample (ΔN_{test}), and the ordinate axis — the same parameter but against the background of the block (ΔN_{block}). It turned out that the dependence reflected by the point cloud, with linear approximation (straight line *1*), gives a correlation coefficient $R = 0.63$, whereas the parabola approximation (curve *2*) demonstrates a better correlation with $R = 0.73$. Differentiation of the latter function showed that its maximum corresponds to an increase in LVPI at the sample by 50.25% of the initial value.

By virtue of the laws of statistics, the evidence of the results obtained is the greater the higher the incidence of complications. Fortunately, our analysis is almost entirely based on successfully treated critical incidents in the form of severe hypotension. Therefore, the case of the most severe complication of the central neuroaxial block that occurred in the hospital during the study, which was included in the sample retrospectively, is of particular interest. We are talking about a 76-year-old patient who suffered a circulatory arrest after spinal anesthesia (in Fig. 7, this point is visible at the level of $\Delta N_{block} = -100\%$). A nitroglycerin test performed a week after successful resuscitation of the patient showed a drop in LVPI by 23%, which makes it possible to confidently classify her as a prognostically unfavorable group.

Thus, a decrease of heart LVPI during a test with nitroglycerin makes it possible to predict the development of severe arterial hypotension during the block. Obviously, the reserve of mechanical power of the ventricle, determined by a breakdown with nitroglycerin, characterizes the ability of the heart to adapt to new operating conditions requiring a rapid increase in energy costs. At the same time, there seems to be a certain „reaction norm“, a deviation from which in any direction can serve as a marker of an increased

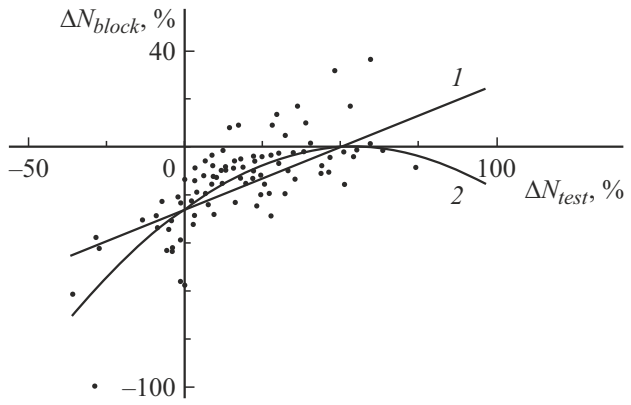

Figure 7. Changes in LVPI in case of nitroglycerin test (abscissa) and neuroaxial block (ordinate) [12]. Explanations in the text.

risk of complications. An increase of the power index in case of testing by at least 2.5% of the initial level can be considered a limit of patient safety for the development of hypotension, and 50% turned out to be the optimal level of the increase of the parameter in the authors' paper. The dynamics of the output turns out to be less demonstrative in comparison with the LVPI. The similarity of hemodynamic reactions during the test and the neuroaxial block, which require the mobilization of LV power reserve, emphasizes the need to carefully and differentially approach the use of central blockades in patients with compromised LV function, using general anesthesia in serious doubt.

5. Simulation of the circulatory response to induction of general anesthesia

Inspired by the successful experience of modeling the response to the neuroaxial block, we decided to explore the possibility of modeling the hemodynamic response to the induction of general anesthesia using the same principle — using a drug that selectively causes a similar primary deviation of blood circulation parameters. The most convenient test agent for this task was esmolol — a short-acting cardioselective β_1-adrenoblocker, the negative inotropic effect of which is not accompanied by a noticeable effect on vascular tone. The first attempt in this direction was made in 2004–2007 by V.V. Stadler (Samara) at our suggestion [45]. However, at that moment it was not possible to find a parameter of the biomechanics of blood circulation that would allow, based on the result of the esmolol test, to reliably identify a group of patients with the development of subcritical hypotension after induction of anesthesia [46,47] — perhaps due to the heterogeneity of induction schemes in the group he studied. Therefore, V.V. Stadler et al. proposed to use the response not to the esmolol test but *post hoc* to induction per se as a prognostic model of „unstable hemodynamics during anesthesia“ [48,49].

The task of evaluating the results of the esmolol test was solved using a more homogeneous group and a different biomechanical criterion for evaluating the response. The clinical material of this study was collected from 104 patients aged 22 to 80 years (mean age 64.6 years, 73 women and 31 men) who underwent elective oncosurgical interventions under general anesthesia at the Leningrad Regional Oncologic Dispensary in 2011–2016. 89 patients had coronary heart disease, 82 patients had hypertension. The study did not include patients with contraindications to the use of esmolol.

Hemodynamic monitoring included noninvasive blood pressure measurement and impedance cardiography (system „Rheoanalyzer-monitor KM-AR-01“, St. Petersburg). MAP was measured, HR and CI were determined, total peripheral vascular resistance, LVPI and Left Vetricular Peak Rower Index (LVPPI) were calculated:

$$\mathrm{LVPPI}(\mathrm{W}\cdot\mathrm{m}^{-2}) = 0.000133 \cdot V_{peak} \cdot \mathrm{MAP} \cdot \mathrm{BSA}^{-1}, \quad (7)$$

where 0.000133 — the product of coefficients of conversion of ml in m^3 and mm Hg in Pa, V_{peak} — the peak rate of blood ejection into the aorta, $ml \cdot s^{-1}$, and BSA (Body Surface Area) — the surface area of the patient's body, m^2, calculated using the formula D. DuBois and E.F. DuBois (1916). Critical arterial hypotension after induction was considered at least a single result of measuring the average blood pressure below 60 mm Hg. Data archiving and statistical processing were performed in „Microsoft Excel" and „Statistica 6.0".

The esmolol test was performed in the operating room before induction of general anesthesia. A patient lying on a horizontally positioned operating table was injected intravenously with a bolus of $500\,\mu g \cdot kg^{-1}$ for 1 min which is a standard loading dose of the drug. The induction of anesthesia was performed after mitigation of the effect of the test according to the assessment of the same anesthesiologist. It included intravenous administration of $2.5\,mg \cdot kg^{-1}$ of propofol and 0.1 mg fentanyl in 54 patients, $4\,mg \cdot kg^{-1}$ of sodium thiopental and 0.1 mg fentanyl in 50 patients; trachea was intubated after standard preoxygenation against the background of $1.5\,mg \cdot kg^{-1}$ of succinylcholine.

The hemodynamic response to the esmolol test did indeed have obvious similarities to the response to induction of general anesthesia. In both cases, a marked decrease of output to varying degrees was the first and main change of the circulatory regime, and the degree of its compensation for MAP depended on the dynamics of vascular tone. The linear correlation between the reactions of the same parameters to the test and to induction turned out to be significant for CI ($R = 0.8$), LVPPI ($R = 0.7$), HR ($R = 0.6{-}0.7$), total peripheral vascular resistance (0.6). At the same time, however, patients with adequate hemodynamics and with the development of subcritical arterial hypotension could be reliably distinguished by the esmolol test either by CI drop, or by the dynamics of total peripheral vascular resistance, or even by changes in LVPI neither in the propofol induction subgroup nor in the thiopental sodium induction subgroup. The best discriminator was LVPPI: its decrease by 26% in the propofol induction subgroup, by 29% in the thiopental sodium induction subgroup and by 27% in the group as a whole became the optimal points of separation of stable and unstable groups. A more significant decrease of LVPPI with high reliability foreshadowed the development of an episode of subcritical hypotension after induction of general anesthesia.

The sensitivity of the test was 94% for the propofol subgroup, and the specificity was 81%, and it was 75% and 92%, respectively, for the thiopental sodium subgroup. When analyzing groups together, excluding hypnotics, the sensitivity of the sample is 86%, and the specificity is 89%. ROC analysis (Receiver Operation Curve) of the esmolol test quality using the numerical trapezoid method showed the $AUC = 0.885$ for the entire group, $AUC = 0.915$ for the propofol subgroup, $AUC = 0.802$ for the thiopental-sodium subgroup. $AUC \geq 0.8$ characterizes the quality of the predictive model as „very good" according to the expert scale [50]. This made it possible to protect the developed „Method for predicting intraoperative arterial hypotension during anesthesia" with a patent of the Russian Federation [51]. The method makes it possible to use alternative induction drugs such as benzodiazepines or ketamine in patients with a high probability of development of hypotension.

We would like to note the difference in the physical meaning of LVPI and LVPPI, which is emphasized by the difference in their normal values — $0.5{-}0.7$ and $3{-}5\,W \cdot m^{-2}$, respectively. If the first parameter characterizes the average LV power throughout the entire cardiocycle, then the second parameter characterizes the peak power developed by it, the value of which is given by the impendance calculation of the maximum value of the instantaneous rate of blood ejection into the aorta. It is logical to believe that the conditions of external ventricular load play a large „forcing" role in the formation of LVPI, whereas LVPPI is more directly influenced by the state of myocardial contractility: the attempts to assess myocardial contractility by the steepness of the leading edge of various pulse waves (pressure, linear flow velocity, photoplethysmograms, etc.) are widespread although the contractility criteria which is a „reference" for a physiologist — ratio of dP/dt in the phase of isometric contraction ventricle and is not available in clinical settings [28].

Anticipating the next section, we would like to note that attempts in the framework of the same study using changes in body position (postural tests) to simulate the circulatory response to blood loss before anesthesia, and after induction to stop pronounced hypotension, were unsuccessful. The response of hemodynamics before anesthesia to lowering the foot end of the operating table by 30° was completely different from the reaction to volume loss against the background of general anesthesia by preserving the compensatory response of vascular tone, and the lifting the foot end of the table by 45° with the development of subcritical arterial hypotension after induction of anesthesia did not compensate for it, which underscores the need for decisive application of vasopressor support in such situations [52].

6. Simulation of the circulatory response to volumetric infusion

Volumetric infusion remains one of the most effective and popular methods of increasing cardiac output (CO). At the same time, there are categories of patients in whom infusion does not cause an increase in CO or even leads to its decrease with the development of acute heart failure, and the analysis of the initial indicators of pre- and afterload (sec. 2) does not always allow them to be highlighted. There is a task of predicting the hemodynamic response to the volume load as accurately as possible, which boils down to reliably distinguishing those patients who will respond to the infusion with an increase of output (Responders) from

Table 1. Variants of performing and evaluating the fluid challenge

Authors, year [link]	Fluid challenge			Response criteria
	Solution	Dose	Time	
Tousignant C.P. et al., 2000 [56]	HES 6%	500 ml	15 min	$\Delta SBV \geq 20\%$
Berkenstadt H. et al., 2001 [57]		100 ml	2 min, via 5 min — repeatedly	$\Delta SBV \geq 5\%$
Wiesenack C. et al., 2003 [58]		7 ml/kg	7 min	CI changes, SBV variability
Reuter D.A. et al., 2003 [59]		10 ml/BMI	5 min	$\Delta SBV \geq 5\%$
Kramer A. et al., 2004 [60]	Donated blood	500 ml	–	$\Delta CI \geq 12\%$
Van Tulder L. et al., 2005 [61]	HES 6%	7 ml/kg	30 min	Increase of glucose consumption rate
Monnet X. et al., 2005 [62]	NaCl 0.9%	500 ml	10 min	Δ of blood flow in the aorta $> 15\%$
Preisman S. et al., 2005 [63]	Gelatin 3.5%	250 ml	5–7 min	$\Delta SBV \geq 15\%$
Tokuda Y. et al., 2007 [64]	Albumin 5%; FFP; HES 6%	480–500 ml	30–60 min	$\Delta SBV \geq 10\%$
Osman D. et al., 2007 [65]	HES 6%	500 ml	20 min	$\Delta CI \geq 15\%$
Mahjoub Y. et al., 2012 [66]	NaCl 0.9%			$\Delta SBV \geq 15\%$
Soliman R.A. et al., 2015 [67]	HES 6%		10 min	$\Delta CI \geq 15\%$
Airapetian N. et al., 2015 [68]	NaCl 0.9%		15 min	$\Delta CO \geq 10\%$
Xu B. et al., 2017 [69]		250 ml	10 min	$\Delta SBV \geq 10\%$
Pouska J. et al., 2018 [70]		5 ml/kg	20 min	$\Delta SI \geq 15\%$
Si X. et al., 2018 [71]	Albumin	250 ml	30 min	
Gavaud A. et al., 2019 [72]	NaCl 0.9%	500 ml	15 min	$\Delta CO \geq 15\%$
Dépret F. et al., 2019 [73]			10 min	$\Delta CI \geq 15\%$
Beurton A. et al., 2019 [74]				
Taccheri T. et al., 2021 [75]				$\Delta CI \geq 10\%$

Note. HES — Hydroxyethyl Starch; FFP — Fresh Frozen Plasma; BMI — Body Mass Index, $kg \cdot m^{-2}$; SBV — Stroke Blood Volume; CO — Cardiac Output; CI — Cardiac Index; SI — Shock Index.

those who will respond to it in a different manner (Non-responders).

R.D. Weisel et al. [53] described the fluid challenge test in 1975 which was a scalable biomechanical model suggesting that the introduction of a low dose of liquid causes a small amplitude circulatory response of the same orientation as the subsequent volumetric infusion. For several decades, this test was considered as the „gold standard“ of prediction of the response to the volume used for verification of other criteria [54]. Analysis of numerous test protocols presented in the literature (Table. 1), however, led us to understand the fact that the complete lack of uniformity in the choice of the infusion medium, its dose and rate of administration, as well as in assessing the criteria for hemodynamic response does not allow us to consider the fluid challenge as a normalized test and, therefore, makes questionable any comparison of the results of studies. However, a convergence of techniques has been observed in the last ten years: a crystalloid solution with a fixed volume of 500 ml administered in less than 20 min is most often used in adult patients, an increase of the output by $\geq 15\%$ is considered as a positive response [55]. However, the reversibility of the increase of intravascular volume in patients with a negative response is more doubtful the higher the dose of the trial infusion.

Therefore, the search for less risky and more standardized alternatives continues. One of them is the variability of the stroke volume of blood and its derivatives (in particular, pulse AP) in patients on artificial ventilation

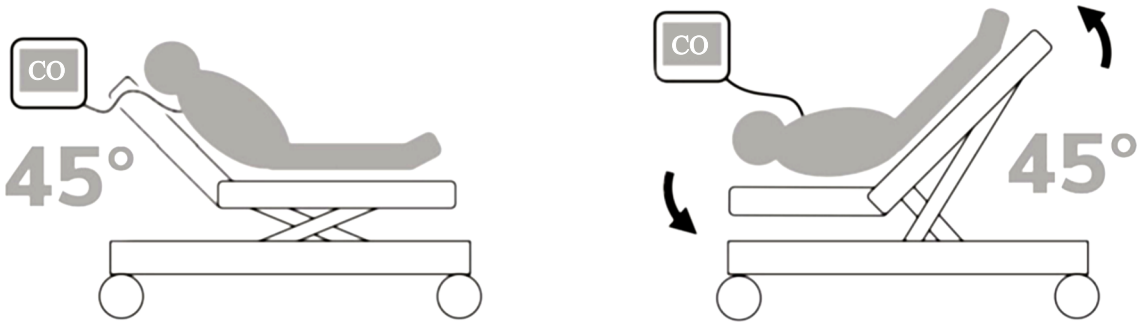

Figure 8. Scheme for performing the passive leg lift test using a functional bed. CO — cardiac output (figure from the publication of Monnet X. et al., 2006 [82]).

without attempts of self-respiration: it was shown that the range of variation in values of parameters over 13% well predicts the response to trial infusion [54]. The physical modeling of the LV output response to variable preload is achieved here due to the phase displacement of blood from a limited volume of lungs by gas injected into them [76]. An unspecified condition of the test, which introduces a random error, are the values of pressures in the alveoli during the respiratory cycle, on which the amplitude of preload fluctuations depends in the process of cardiopulmonary interaction [77].

An article by T. Boulain, J.M. Achard, J.-L. Teboul et al. appeared in the journal „Chest“ in 2002 [78] with a description of a simple alternative to the fluid challenge: the authors proposed a test with passive rising of legs by 45° (passive leg rising, PLR). In essence, the Teboul test, as it is often called today, was the development of a long-standing idea to use the Trendelenburg position for the treatment of shock (F. Trendelenburg, 1885): a patient in a semi-sitting position is transferred using a functional bed to a position with the lower extremities raised by 45° and the horizontal position of the trunk and the head (Fig. 8). Such a change in posture leads to a temporary limitation of venous capacity and gravitational autotransfusion of 300−500 ml of blood from the lower extremities to the inferior vena cava, right heart and small circle [79,80]. Preload increases without the use of artificial infusion solutions, and physiological changes are transient and easily reversible by returning the patient to the initial position, which eliminates the risk of fluid overload. The easily reproducible PLR test is not without drawbacks, however: it also does not yet have a standardized protocol (Table 2), it is rarely performed in the operating room, it is contraindicated in deep vein thrombosis of the legs, traumatic brain injury, intra-abdominal hypertension, and evaluation of its result requires one or another method for output measurement.

Meanwhile, a technically simple, safe and standardized biomechanical model of the hemodynamic response to volumetric infusion seems to be an important „everyday tool“ for a doctor today. The well-documented linear relationship between stroke blood volume and pulse AP with a proportionality factor determined by the current value of vascular impedance [28] suggests that it may be possible to reliably identify increase of SVB based on the increase of the pulse AP measured by an affordable and noninvasive oscillometric method.

7. Monitoring of the viability of surgical hemostasis

An extremely simple and pragmatic example of the model can be considered a long-known test in practice for the reliability of the surgeon's final stop of bleeding (hemostasis) in a surgical wound. Indeed, a potentially dangerous situation often arises: the surgeon controls hemostasis before completing the operation at a time when anesthesia is still deep enough, and the traumatic nature of manipulations with tissues is minimal, which is reflected in the normal or subnormal AP level. Since it is AP, and not cardiac output, that determines the bleeding of blood vessels in the wound [97,98], the surgeon does not see potential sources of bleeding at this moment. But when AP increases as a result of the recovery of consciousness, pharyngeal and laryngeal reflexes, reactions to the endotracheal tube, muscle tremors, etc., vessels that are not bandaged in a timely manner begin to bleed, sometimes requiring repeated surgical revision of the wound.

The solution is known from practice — this is a hemodynamic test for the viability of surgical hemostasis, which consists in a short-term increase of the AP above the working level by intravenous administration of a vasopressor. This technique is used in neurosurgery, otorhinolaryngology, abdominal surgery and other branches of operative medicine. However, to our surprise, we found no mention of this technique in the literature. The method involves obvious risks, and yet no one has proven its effectiveness and a uniform protocol has never been published, which is necessary in such situations.

Often using a hemodynamic test, the authors decided to develop and work out a safe algorithm for its implementation, and then use it to test the effectiveness of the test. Proposed and published protocol [99] includes rules for selecting patients and performing a test involving slow

Table 2. Options for performing and evaluating the result of the passive leg lift test

Authors, year [link]	Initial position of the head and trunk/leg lift	Response evaluation	Criteria response
Lafanechére A. et al., 2006 [81]	0°_/45°	Maximum in 4 min	$\Delta CI \geq 15\%$
Monnet X. et al., 2006 [82]	45° ∨ 45°	Maximum in 5 min	$\Delta CI \geq 15\%$
Maizel J. et al., 2007 [83]	0°_/30°	After 2 min	ΔCO or $\Delta SBV \geq 12\%$
Biais M. et al., 2009 [84]	45° ∨ 45°	Maximum in 1.5 min	ΔSBV15%
Benomar B. et al., 2010 [85]	45° ∨ 45°	Maximum in 10 min	$\Delta CI \geq 9\%$
Lakhal K. et al., 2010 [86]	0°_/30°	After 1 min	$\Delta CI \geq 10\%$
Preau S. et al., 2010 [87]	30° ∨ 45°	After 5 min	$\Delta SBV \geq 15\%$
Guinot P.G. et al., 2011 [88]	45° ∨ 45°	Maximum in the first 5 breathing cycles	$\Delta SBV \geq 15\%$
Dong Z.Z. et al., 2012 [89]	45° ∨ 45○	After 2 min	$\Delta SBV \geq 15\%$
Monge Garcia M.I. et al., 2012 [90]	45° ∨ 45°	Maximum in 5 min	$\Delta CO \geq 15\%$
Kupersztych-Hagege E. et al., 2013 [91]	45° ∨ 45°	Maximum in 6 min	$\Delta CI \geq 15\%$
Marik P.E. et al., 2013 [92]	45° ∨ 45°	Maximum in the first 3 breathing cycles	$\Delta SBV \geq 10\%$
Silva S. et al., 2013 [93]	45° ∨ 45°	Maximum in 6 min	$\Delta CI \geq 15\%$
Kang W.S. et al., 2014 [94]	0°_/45°	Maximum in 5 min	$\Delta CO \geq 7\%$
Yu T. et al., 2015 [95]	45° ∨ 45°	Maximum in 1 min	$\Delta CI \geq 10\%$
Giraud R. et al., 2021 [96]	45° ∨ 45°	Maximum in 1 min	Δ of integral of linear velocity of flow in the aorta $\geq 15\%$

intravenous administration of $250-500\,\mu$g of phenylephrine (mezaton). The protocol was tested on the material from 54 patients of the St. Petersburg Center for Endocrine Surgery (Professor A.F. Romanchishen), operated under general anesthesia for toxic goiter in 2009–2010. Thyroidectomy was the most common operation (37 cases), 11 patients underwent subtotal resection of the gland, hemithyroidectomy was performed in six cases. The control group, where no hemodynamic test was performed, included 35 patients comparable to the main group in terms of demographic indicators, diagnoses of underlying and concomitant pathology and the structure of interventions. All pulse oximetry, heart rate and AP was monitored in all patients by noninvasive oscillometric method using monitors Life Scope (Nihon Kohden, Japan) or M69 (Biolight, China).

Systolic AP in the study group as a result of a hemodynamic test at the time of final hemostasis was 180 ± 13.6 mm Hg, diastolic AP was 105 ± 9.2 mm Hg, heart rate was $54.4 \pm 8.4\,\mathrm{min}^{-1}$, while the control group values were 123 ± 12.7 mm Hg, 84.7 ± 8.3 mm Hg and $86 \pm 16\,\mathrm{min}^{-1}$ respectively (for all three parameters $P < 0.001$). The additional time spent by the surgeon on correcting hemostasis during the test was about 3 min. The effect of the test was evaluated a day after the operation by the total volume of discharge through the active drainage system. It turned out to be 2–3 times less in the main group than in the control group — 25.3 ± 12 ml versus 53.4 ± 22.8 ml ($P < 0.0001$). There were no bleeding from the bed of the removed gland that required revision in the patients of the study group, whereas two bleeds were recorded in the control group in the volume of 150 ml in 6 h after subtotal resection of the gland and in the volume of about 500 ml in 20 h after thyroidectomy. A retrospective analysis of anesthesia charts showed that hemostasis in both cases was performed at a blood pressure level of 120–130/80 mm Hg [100].

Thus, a hemodynamic test at the stage of surgical hemostasis control can significantly reduce the volume of blood loss in the immediate postoperative period and, ultimately, reduce the risk of life-threatening bleeding after thyroid surgery for toxic forms of goiter. However, a hydraulic sample is potentially unsafe, and therefore

requires a careful approach to the selection of patients, special attention from a doctor and compliance with a strict protocol, a version of which was published by us.

8. Titration of the optimal level of finite expiratory pressure

In contrast to the previous extremely simple example, this approach, described in detail in our papers [76,101,102], is based on a more complex biomechanics of the formation of the diffusion surface area of the lungs. The latter, as the pressure in the alveoli increases to a certain limit, increases due to the opening of the closed alveoli, but then begins to decrease due to the displacement of blood flow by intraalveolar pressure from the capillaries entwining the ventilated alveoli. The threshold and the rate of this decrease depend on the degree of filling of the vessel capacity of the small circle. As a result, the analysis of the dynamics of oxygen absorption and carbon dioxide release by the lungs as the pressure values change at the end of the respiratory cycle during mechanical ventilation allows today to select the optimal balance between the coupling of ventilation with perfusion and the volemic status of the patient.

Conclusion

The idea of predicting dangerous reactions of systems based on modeling their responses to weak disturbances similar in physical nature would seem to be self-explanatory. Nevertheless, it has been developed in clinical biomechanics of blood circulation only in recent decades. But even today, no simple, reliable and safe (non-invasive) models have been created for many destabilizing hemodynamic effects — for example, there is no such model for intraperitoneal hypertension-causing carboxyperitoneum during laparoscopic operations, a reliable test for the possibility of radical elimination of large ventral hernias has not been developed, the possibility of a completely non-invasive assessment of the result of the Teboul test is waiting for its researchers and etc. There is still much to be done in this field for a targeted functional study of patients before surgery and anesthesia to provide very specific tactical recommendations on functional operability, the choice of anesthesia and intensive care methods, and biophysical „titration“ of our impacts on organs and systems, often quite crude. The authors will consider their task accomplished if this review contributes to such a development.

Conflict of interest

The authors declare that they have no conflict of interest.

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