Reflex regulation and the functional assessment possibility of the cardiorespiratory system in pregnancy: a systematic review

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Abstract

INTRODUCTION: Anesthesia planning for cesarean section requires knowledge of physiological and functional features a pregnant patient has in her gestational age. Proper planning reduced the perioperative critical incidents risk. **OBJECTIVE:** Search for data on the methods and results of assessing the cardiorespiratory status of pregnant women using methods that involve such key mechanisms of arterial baroreflex (ABR) and peripheral chemoreflex (PCR) mechanisms. **MATERIAL AND METHODS:** We performed a systematic review of the literature in accordance with the PRISMA guidelines. The bibliographic search was performed in December 2022 in the Medline (Pubmed), RSCI (eLibrary.ru) and Cochrane Library databases. The search keywords were: “pregnancy breath holding test”, “pregnancy chemoreflex”, “pregnancy baroreflex”, “Valsalva test pregnancy”. **RESULTS:** 110 documents were found, after deleting 68 papers for various reasons 42 full-text sources were analyzed, including a detailed comparative analysis of 8 sources that met totally the inclusion criteria. The design, objectives, methods, data availability, and outcomes of the studies were heterogeneous, so a meta-analysis was not performed. Were extracted and summarized data on functional changes in the work of cardiorespiratory system during pregnancy and changes in the sensitivity of the baroreflex and chemoreflex.

Особенности рефлекторной регуляции кардиореспираторной системы при беременности: систематический обзор литературы

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Реферат

АКТУАЛЬНОСТЬ: Врачу — анестезиологу-реаниматологу при составлении плана анестезиологического обеспечения операции кесарева сечения необходимо знать о том, какие физиологические и функциональные особенности имеет беременная пациентка в том или ином сроке гестации. Правильное составление плана анестезии и тактики ведения пациенток в периоперационном периоде помогает снизить риск гемодинамических, респираторных и других критических инцидентов. **ЦЕЛЬ ИССЛЕДОВАНИЯ:** Поиск данных о способах и результатах оценки кардиореспираторного статуса беременных с использованием методов, задействующих такие ключевые механизмы рефлекторной регуляции, как артериальный барорефлекс (АБР) и периферический хеморефлекс (ПХР). **МАТЕРИАЛЫ И МЕТОДЫ:** Мы провели систематический обзор литературы в соответствии с рекомендациями PRISMA. Поиск был проведен в декабре 2022 г. в базах Medline (Pubmed), «Российский индекс научного цитирования» (РИНЦ, eLibrary.ru) и Cochrane Library. Поиск производился по запросам: «произвольное пороговое апноэ беременность», «хеморефлекс беременность», «барорефлекс беременность», «проба Вальсальвы беременность», «pregnancy breath holding test», «pregnancy chemoreflex», «pregnancy baroreflex», «Valsalva test pregnancy». **РЕЗУЛЬТАТЫ:** Было найдено 110 работ,

CONCLUSIONS: The sensitivity of PCR in pregnant women can be assessed by inhalation of hyperoxic, hypercapnic and isooxic-hypercapnic gas mixtures (rebreathing test). The sensitivity of ABR in pregnant can be assessed by phenylephrine test, Valsalva test, orthostatic test, and spectral analysis of the sequences of blood pressure values and the R-R interval. The sensitivity of PCR in full-term pregnancy increases. The sensitivity of ABR in pregnant progressively decreases from the beginning of pregnancy to the end of the second trimester and increases in the postpartum period to initial level; in the third trimester of pregnancy, changes in ABR sensitivity are individual and do not have a single trend.

KEYWORDS: pregnancy, functional tests, cardiorespiratory system, arterial baroreflex, chemoreflex, breath holding test, Valsalva maneuver, systematic review

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после удаления по различным причинам 68 работ было проанализировано 42 полнотекстовых источника, в том числе проведен подробный сравнительный анализ 8 источников, полностью соответствующих критериям включения. Дизайн, цели, методы, доступность данных и конечные результаты исследований были неоднородными, поэтому метаанализ данных не проводился. Были извлечены и обобщены данные о функциональных изменениях в работе кардиореспираторной системы, происходящих при беременности и отражающихся в изменении чувствительности АБР и ПХР. **ВЫВОДЫ:** Чувствительность ПХР у беременных можно оценивать с помощью вдыхания гипероксической, гиперкапнической и изооксически-гиперкапнической газовой смеси (варианты пробы с возвратным дыханием). Чувствительность АБР у беременных можно оценивать с помощью фенилэфринового теста пробы Вальсальвы, ортостатической пробы, а также спектрального анализа последовательностей значений артериального давления и интервала R–R. Чувствительность ПХР при доношенной беременности увеличивается. Чувствительность АБР у беременных прогрессивно снижается от начала беременности до конца II триместра и повышается в послеродовом периоде до исходного уровня; в III триместре беременности изменения чувствительности АБР носят индивидуальный характер и не имеют единой тенденции.

КЛЮЧЕВЫЕ СЛОВА: беременность, функциональные тесты, кардиореспираторная система, артериальный барорефлекс, хеморефлекс, произвольное пороговое апноэ, проба Вальсальвы, систематический обзор

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Introduction

Many patients may experience various adverse events in the perioperative period, associated with impaired normal functioning of the cardiorespiratory system (CRS), such as arterial hypotension, hypertension, tachycardia, bradycardia, extrasystole, desaturation, etc. With a significant deviation of the parameters from the norm and longtime of existence, these situations can become critical incidents (CI), and then complications of the perioperative period. These CIs are not always directly related to anesthesia, but their severity and the duration of persistence are directly related to the reflex regulation of the cardiorespiratory system, with the level of sensitivity of regulatory reflexes [1, 2].

Reflex regulation of CRS is a set of reflexes that provide rapid hemodynamics stabilization and respiratory function when exposed to factors that disturb the physiological balance. The most important reflexes that form the basis of this regulation are arterial baroreflex (ABR) and peripheral chemoreflex (PCR) [3, 4].

Pregnancy, although not a pathological condition, causes significant changes in the work of CRS. In pregnant women cardiac output and minute inspiratory volume have been increases, and the trigger points of reflex regulation of key parameters of respiration and hemodynamics also differ from the general population of patients [5, 6].

Each gestational age is unique in its own way in terms of such changes, and therefore unique in terms of the risk of CI and compensatory capabilities in the perioperative period. Anesthesiologist, drawing up a plan for the anesthetic management of a caesarean section, needs to know the physiological and functional characteristics of pregnant patients. Proper planning of anesthesia helps to reduce the risk of CI and complications in the perioperative period [7].

The purpose of this systematic review was to search for data on methods for assessing the cardiorespiratory status of pregnant women, involving such key mechanisms of reflex regulation as ABR and PCR, as well as on the possibility of safe use of these methods in pregnant women.

Materials and methods

During this review, the following questions were asked:

1. What are the ways to safely and effectively assess the sensitivity of ABR and PCR in pregnant women?
2. How does the sensitivity of ABR and PCR change in pregnant women at different gestational ages and in the postpartum period compared with the initial state?

The study was performed in accordance with the guidelines for writing systematic reviews and meta-analyses “Preferred Reporting Items for Systematic Reviews and Meta-Analyzes” (PRISMA) [8, 9] (see Figure 1). At the first stage (in November 2022), a search was made for lit-

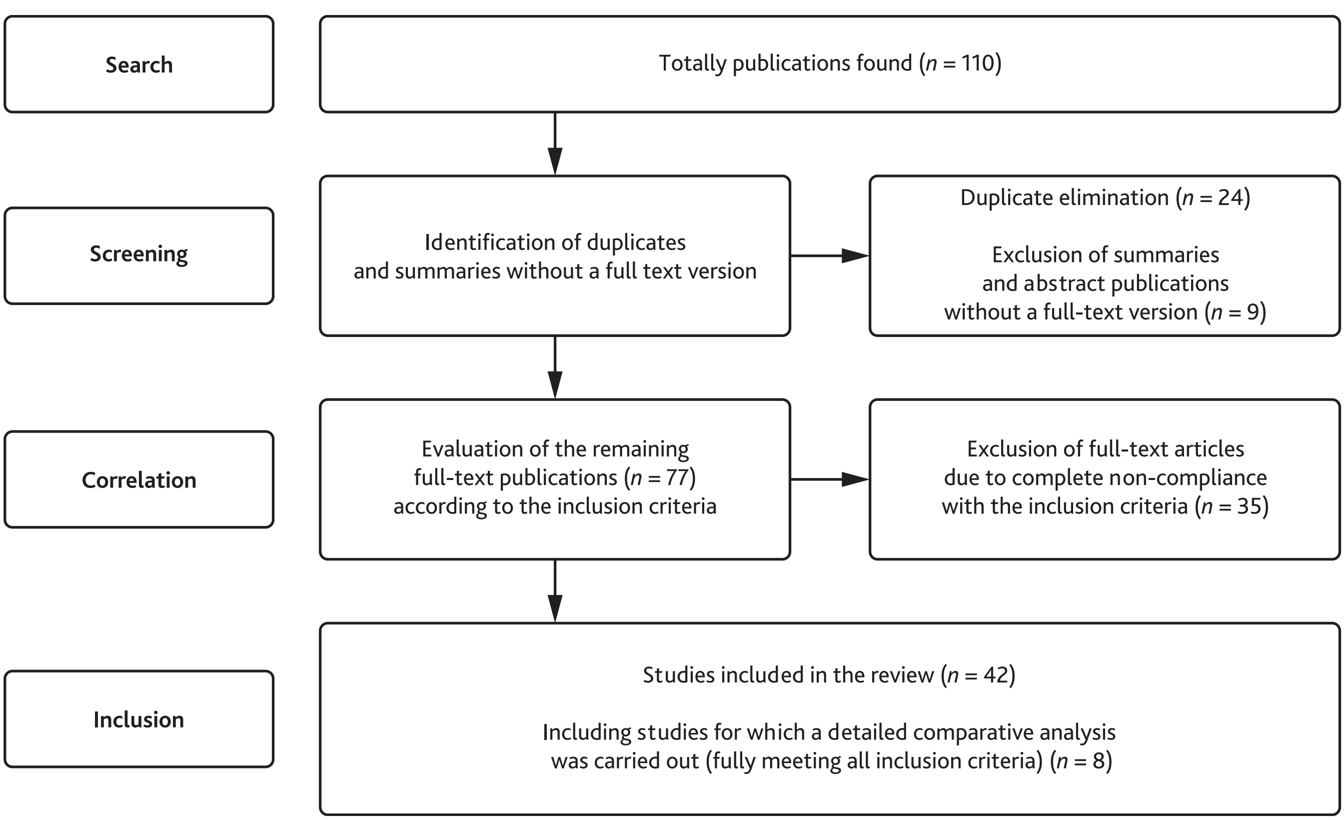

Fig. 1. Literature search algorithm (PRISMA)

erature sources in the Medline (Pubmed), Cochrane Library and Russian Science Citation Index (RSCI, eLibrary) databases. In the Pubmed and Cochrane Library databases, the search was carried out on queries: "pregnancy breath holding test", "pregnancy chemoreflex", "pregnancy baroreflex", "Valsalva test pregnancy". In the eLibrary database, the search was performed on the queries: "произвольное пороговое апноэ беременность", "хеморефлекс беременность", "барорефлекс беременность", "проба Вальсальвы беременность". The search included studies of any design published and indexed in the specified databases for the period from 1982 to 2022. Initially, 110 studies were found. After removing duplicates, abstract publications and abstracts of articles, 77 papers remained without an accessible full-text version.

The second stage consisted of reviewing abstracts of articles and excluding publications that did not meet the study criteria.

The criteria for inclusion in the review were:

1) the object of the study were pregnant women at any gestational age;
2) the sensitivity of ABR was assessed in pregnant women by one or more of the methods described in the literature for the general population of patients (phenylephrine test, Valsalva test, orthostatic test, spectral analysis of sequences of blood pressure (BP) values and R-R interval, as well as modifications and combinations of these ways);
3) in pregnant women, the sensitivity of PCR was assessed by one or more of the methods described in the literature for the general population of patients (inhalation of a hypoxic gas mixture, inhalation of a hyperoxic gas mixture, inhalation of a hypercapnic gas mixture, rebreathing, breath holding test, as well as modifications and combinations specified methods);
4) publication language Russian or English.

After removing 35 articles that did not fully meet the inclusion criteria, 42 remaining full-text articles were analyzed, including a detailed comparative analysis of 8 literature sources that fully met the inclusion criteria.

Research results

As a result of the search and subsequent phased screening of literary sources according to the above algorithm, 8 sources were identified that fully met the inclusion criteria. Of these, 6 were devoted to assessing the sensitivity of ADB [10–15]; 2 sources — assessment of the sensitivity of PCR [16, 17].

Comparative characteristics of two studies assessing the sensitivity of PCR in pregnant women [16, 17] are shown in Table 1.

Table 1. Comparative characteristics of clinical studies aimed at determining changes in the sensitivity of PCR during pregnancy

Authors, year of study	Study design, sample size	Research features	Method(s) for monitoring indicators; method(s) for assessing the sensitivity of PCR	Research results, conclusions
Jensen D. et al, 2005 [16]	Prospective comparative cohort study (*n* = 22)	A study of two cohorts of patients: 1) pregnant women at 36.5 ± 0.4 weeks of gestation (*n* = 11); 2) a control group of non-pregnant women with similar physical and demographic parameters (*n* = 11)	Repeated rebreathing in two ways: 1) hyperoxic-hypercapnic gas mixture (CCR sensitivity assessment) and 2) isooxic-hypercapnic gas mixture (PCR sensitivity assessment)	Increased sensitivity of both PCR and CCR in pregnant women compared with non-pregnant controls
Reyes L.M. et al, 2020 [17]	Prospective comparative cohort study (*n* = 36)	A study of two cohorts of pregnant patients in the third trimester of pregnancy: 1) pregnant women with gestational diabetes mellitus (GDM) (*n* = 18) and 2) a control group of pregnant women with normoglycemia (*n* = 18)	Determination of muscle sympathetic nerve activity (peroneal microneurography) during a test with hyperoxia (breathing 100 % oxygen through a mask for 3 minutes)	A more pronounced decrease in muscle sympathetic nerve activity during the test with hyperoxia in women with GDM, but not in women with normoglycemia, which indicates an increased sensitivity of PCR in women with GDM compared with the control group of pregnant women with normoglycemia

CCR — central chemoreflex.

Table 2. Comparative characteristics of clinical studies aimed at determining the sensitivity of ABR in pregnancy

Authors, year of study	Study design, sample size	Research features	Method(s) for monitoring indicators; method(s) for assessing ADB sensitivity	Research results, conclusions
Leduc L. et al, 1991 [10]	Prospective cohort study ($n = 9$)	Study of the same cohort of patients at 38 ± 0.3 weeks of gestation and 6–8 weeks after delivery, patients without hypertensive disorders	Spectral analysis of sequences of changes in heart rate and mean arterial pressure (ΔHR/ΔBPmean); phenylephrine test, Finapres — monitoring	An increase in the sensitivity of ABR at full-term pregnancy compared with 6-8 weeks of the postpartum period (during pregnancy — a decrease in hweart rate by 0.9 beats / min with an increase in blood pressure by 1 mm Hg, in the postpartum period — a decrease in heart rate by 0.5 beats/min with an increase in BPmean by 1 mmHg, $p < 0.007$). Attenuated pressor response to phenylephrine during pregnancy compared with 6–8 weeks postpartum ($p < 0.05$)
Blake M.J. et al, 2000 [11]	Prospective comparative cohort study ($n = 26$)	Study group of pregnant women ($n = 16$, study during each trimester of pregnancy) and control group of non-pregnant women ($n = 10$), patients without hypertensive disorders	Spectral analysis of ΔHR/ΔBPsyst sequences; orthostatic test, Finapres — monitoring	Decreased sensitivity of ABR compared with the control group at 16 to 36 weeks' gestation, measured in the supine position ($p < 0.001$)
Lucini D. et al, 1999 [12]	Prospective comparative cohort study ($n = 14$)	Study of the same cohort of patients up to 6 weeks of gestation and then at 32–34 weeks of gestation, patients without hypertensive disorders	Spectral analysis of ΔHR/ΔBPsyst sequences, Finapres monitoring	Decreased sensitivity of ABR in late pregnancy compared to early
Gugova F.K. et al., 2008 [13]	Prospective cohort study ($n = 23$)	Study of the same cohort of patients at 12–14 weeks of gestation and then again at 26–30 weeks of gestation, patients without hypertensive disorders	Spectral analysis of ΔHR/ΔBPsyst sequences, orthostatic test, Finapres monitoring	In the early stages of pregnancy — preservation or increase in the sensitivity of ABR in the supine position and its pronounced decrease in orthostasis, with further progression of pregnancy — a decrease in the sensitivity of ABR and simultaneous restoration of orthostatic tolerance ($p < 0.05$)
Visontai Z. et al, 2002 [14]	Prospective cohort study ($n = 23$)	Study of the same cohort of patients during each trimester of pregnancy and in the postpartum period, patients without hypertensive disorders	Spectral analysis of ΔHR/ΔBPsyst sequences, Finapres — monitoring; additionally, an ultrasound assessment of the extensibility coefficient of the carotid arteries was carried out (in % of the original)	ABR sensitivity decreased significantly from the 1st to 2nd trimester of pregnancy, then continued to decrease slightly from the 2nd to 3rd trimester. In the postpartum period, ABR sensitivity returned to values comparable to those in the first trimester of pregnancy. In addition, it was found that in pregnant women there is a local decrease in the extensibility of the wall of the carotid arteries, while the extensibility of the entire arterial bed as a whole increases in them
Silver H.M., et al, 2001 [15]	Prospective comparative cohort study ($n = 80$)	A study of 4 subgroups of patients: 1) 20 pregnant women with normotension; 2) 20 pregnant women with gestational hypertension; 3) 20 pregnant women with preeclampsia; 4) 20 non-pregnant women. Gestational terms in all pregnant women corresponded to the 3rd trimester	Spectral analysis of sequences ΔR–R interval /ΔBPsyst, Finapres — monitoring; Valsalva test; slow deep breathing test	The sensitivity of ABR in normotensive pregnant women was lower than in non-pregnant women (ΔR–R/ΔBPsyst = 15.8 ± 7.2 *vs.* 10.8 ± 4.1 ms/mm Hg; $p = 0.001$). The sensitivity of ABR decreased even more in pregnant women with preeclampsia (ΔR–R/ΔBPsyst = 10.8 ± 4.1 *vs.* 7.2 ± 2.6 ms/mm Hg; $p = 0.003$) and in gestational hypertension (10.8 ± 4.1 *vs.* 6.5 ± 2.7 ms/mmHg; $p = 0.001$) compared with normal pregnancy

The data obtained indicate that the sensitivity of PCR in the third trimester of pregnancy is significantly higher than in non-pregnant patients, and with concomitant GDM, the increase in the sensitivity of PCR is most pronounced.

Comparative characteristics of six studies assessing the sensitivity of ABR in pregnant women [10–15] are shown in Table 2.

The table shows that ABR sensitivity, if we take the state before pregnancy as a starting point, progressively decreases from the beginning of pregnancy, reaching its minimum values by the end of the second trimester. From the end of the second trimester to full-term pregnancy, ABR sensitivity behaves heterogeneously (it can either slowly decrease or remain at the same level or increase), but in the postpartum period, ABR sensitivity gradually increases in all patients and reaches the initial values. At the same time, the decrease in ABR sensitivity is more pronounced in the presence of hypertensive disorders (gestational hypertension, preeclampsia) than in normotensive pregnancy [15].

The discussion of the results

The results obtained are consistent with the data described for the general patient population, which suggest that there is defined antagonism between ABR and RCR [18, 20]. An increase in the sensitivity of one of the reflexes is often accompanied by a decrease in the sensitivity of the other, and if this antagonism may not be observed in acute conditions, then in chronic, long-term persistent conditions (including pregnancy) it is most often present [18]. This feature is due to the fact that during its implementation, ABR mainly activates parasympathetic physiological mechanisms, while PCR uses sympathetic ones.

The afferent link of the ABR consists in the flow of nerve impulses from the baroreceptors of the aortic arch and carotid bodies to the vasomotor center of the medulla oblongata [4]. These impulses affect both the tone of the vasomotor center itself and the tone of the nuclei of the vagus nerves. The efferent link of ABR is realized in two ways — vascular (changes in the tone of peripheral vessels) and chronotropic (changes in heart rate) [19]. Thus, in general, ABR is implemented according to two possible scenarios:

An external factor causing a decrease in blood pressure → reflex tachycardia and an increase in arterial tone → an increase in blood pressure to the initial level

An external factor causing an increase in blood pressure → reflex bradycardia and a decrease in arterial tone → a decrease in blood pressure to the initial level

Peripheral chemoreflex is the second most important regulatory mechanism of CRS. Peripheral chemoreceptors, like baroreceptors, are located mainly in the carotid bodies and in the area of the aortic arch. They respond to changes in the concentration of hydrogen ions (estimated through the pH index), oxygen tension (PaO_2), and carbon dioxide tension ($PaCO_2$) of arterial blood, namely, to acidosis, hypoxia, and hypercapnia [20]. The afferent pathway of PCR passes along the fibers of Hering's nerve (part of the IX pair of cranial nerves) and the fibers of the aortic branch of the vagus nerve (X pair) to the respiratory center in the medulla oblongata. Activation of the neurons of the respiratory center increases the frequency and depth of respiration, that is, it causes an increase in the minute volume of respiration, proportional to the shift in pH, PaO_2 and $PaCO_2$, which is aimed at compensating the values of these parameters in the opposite direction, up to certain equilibrium points [21].

Individual patient characteristics, in particular the presence of comorbidities and conditions, may change the balance of default settings for the sensitivity of ABR and RCR. Available literature data suggest that arterial hypertension, chronic heart failure, diabetes mellitus, chronic obstructive pulmonary disease, obstructive sleep apnea increase the sensitivity of PCR and decrease the sensitivity of ABR [22–25]. In acute conditions, the high sensitivity of PCR is rather a favorable factor that helps to start compensatory mechanisms faster in response to hypoxia and hypercapnia and to quickly reach the state of compensation. But with long-term persistent diseases, a constant increase in the sensitivity of PCR leads to chronic hyperactivation of the sympathetic part of the autonomic nervous system, which contributes to the progression of bovine diseases and, as a result, worsens the compensatory capabilities of the body [26–32].

A normal pregnancy is characterized by an increase in the minute volume of respiration (mainly due to an increase in the depth of respiration, and not due to the respiratory rate), a concomitant decrease in CO_2 tension ($PaCO_2$) in arterial blood by 5–10 mm Hg, as well as a decrease in the level of plasma bicarbonate and blood pH [5]. At the same time, such parameters as inspiratory effort (inspiratory drive), airway resistance, peak expiratory flow rate, forced expiratory volume in the first second, and functional lung capacity in pregnant women usually do not have significant differences from those in the general patient population [33].

A test with voluntary inspiratory breath holding causes transient hypoxia and hypercapnia, activating PCR, and the duration of breath holding in seconds correlates inversely with the sensitivity of PCR: the longer the time, the lower the sensitivity of PCR. In addition, hypercapnia itself increases the activity of the respiratory center (activates the central chemoreflex), dilates the brain vessels, and increases cerebral blood flow [34]. The peculiarity of these processes during pregnancy is a decrease in the threshold of the chemoreflex response and, thus, an increase in the sensitivity of PCR [16].

Jensen et al. in a retrospective analysis of data from pregnant patients [5, 35] found that the $PaCO_2$ equilibrium point, which is a trigger for PCR triggering and a subsequent increase in cardiac output, shifts downward during pregnancy, towards values corresponding to hypocapnia for nonpregnant women. Thus, the variability in the respiratory response to exercise and the accompanying subjective sensation of dyspnea in healthy pregnant women may also be associated with individual changes in PCR sensitivity.

The concentration of progesterone in the blood of a pregnant woman has a strong inverse correlation with the level of $PaCO_2$ at rest [36, 37]. Female sex hormones not only increase the sensitivity of central and peripheral chemoreceptors to the concentration of hydrogen ions, but also increase the minute volume of breathing in pregnant women through the activation of estrogen-dependent progesterone receptors in the CNS, while the second mechanism does not depend on blood pH [37]. The neuroactive progesterone steroids (allopregnanolone) are involved in the increase in the sensitivity of PCR (and the concomitant decrease in the sensitivity of ABR) in pregnant women [38].

The sensitivity of PCR during pregnancy is also affected by other concomitant factors, such as disorders of carbohydrate metabolism [17] and smoking [39]. Reyes et al [17], comparing sympathetic nerve activity in 18 pregnant patients with GDM and 18 pregnant women with normoglycemia, found that in women with GDM, basal sympathetic nerve activity was similar to that in the control group, but the sensitivity of PCR in patients with GDM was higher. than in the control group. Conversely, prenatal exposure to nicotine in pregnant women reduces the sensitivity of PCR [39].

Due to the reduced sensitivity of ABR, pregnant women are more prone to orthostatic hypotension than non-pregnant women [40, 41]. The same mechanism can provoke the development of CI during neuraxial anesthesia during caesarean section, in particular, arterial hypotension.

There are several ways to assess the sensitivity of ABR, but they either require medical intervention (phenylephrine test), or require special equipment to monitor and calculate the variability of spontaneous fluctuations in blood pressure and R–R intervals (sequence method, spectral method). The most non-invasive and available method for determining the sensitivity of ABR is the Valsalva test, modified versions of which have been successfully used in pregnant patients [42–45].

The physiological essence of the classic Valsalva test is as follows: as a result of tension against the background of a fixed expiratory resistance, intrathoracic pressure increases, which is transmitted to the heart and great vessels and causes a transient increase in blood pressure. As expiratory resistance continues, venous return to the right side of the heart decreases, resulting in a decrease in pulse pressure. Baroreceptors of blood vessels react to the drop in pulse pressure, which is manifested by an increase in heart rate; at the same time, peripheral vasoconstriction occurs. After a sharp exhalation, there is an equally sharp increase in venous return to the right heart and an increase in left ventricular output. Increased cardiac output entering the arterial bed causes a significant increase in blood pressure and reflex bradycardia. Then hemodynamics is restored, and the parameters reach the initial values [42–45].

Souma et al performed a series of Valsalva maneuvers on 282 pregnant and 37 non-pregnant patients (slow exhalation through resistance, i.e. through a mercury manometer with a narrow exhalation port, maintaining pressure at 40 mmHg for 30 seconds, and subsequent sharp exhalation past the manometer) [42]. The Valsalva ratio in this study was calculated as the ratio of the maximum recorded tachycardia to the maximum pronounced bradycardia, expressed in beats / min. The Valsalva ratio can also be calculated as the ratio of the longest RR interval between 1 and 20 heartbeats after the test is stopped, to the shortest RR interval during the test. The value of the obtained ratio characterizes not only the sensitivity of ABR, but also the degree of influence of the parasympathetic divisions of the nervous system on the heart. The mean Valsalva ratio in the control group (non-pregnant) was higher than in any of the subgroups of pregnant women (divided by gestational age), while there was a clear trend towards a decrease in the Valsalva ratio from 29 to 32 weeks of gestation [42]. Thus, the Valsalva test can be used instead of the classic phenylephrine test for non-invasive assessment of ABR sensitivity in pregnancy without hypertensive disorders, while the value of the Valsalva coefficient directly correlates with ABR sensitivity.

The onset of pregnancy is associated with a relative hyperreactivity of the sympathetic part of the autonomic nervous system, while the second half of pregnancy is characterized by an increase in hemodynamic stability with orthostatic stress. The response of the heart rate to the Valsalva test in the middle of pregnancy is blunted (until the 29th week of gestation, then the sensitivity increases again and by the full term is compared with that in non-pregnant women), which is associated with an increase in the volume of circulating blood and directly correlates with the dynamics of ABR sensitivity described earlier and measured in other, more complex ways. Heart rate variability decreases significantly in the second trimester of pregnancy [42].

In general, cardiovascular reflex testing can be used to non-invasively study the effect of drugs on maternal circulation [43]. Ekholm et al conducted a study in 1998 to evaluate the feasibility of a non-invasive measurement of ABR sensitivity in pregnant women using the Valsalva maneuver [45]. ABR sensitivity was measured in nine pregnant women (gestational age from 24 to 33 weeks, no concomitant hypertensive disorders and cardiovascular diseases) in two ways: 1) by the reflex response to an injection of 150 μg of phenylephrine and 2) using the Valsalva test. In this study, the Valsalva test was performed as a slow exhalation through a pressure gauge with a narrow exhalation port, maintaining the pressure at around 40 mm Hg within 15 seconds. Both tests gave similar sensitivity estimates for ABR: 9.3 (4.1) ms/mm Hg. in the phenylephrine test against 8.0 (5.2) ms/mm Hg. with Valsalva maneuver, Pearson's correlation coefficient $r = 0.81$, $p < 0.008$. Both tests showed comparable changes in heart rate and blood pressure. The authors summarized that the Valsalva maneuver can be used to non-invasively measure ABR sensitivity during pregnancy.

When comparing data obtained from the same patients at different gestational ages, the Valsalva coefficient was significantly lower in the second trimester than before pregnancy ($p = 0.02$) and than in the first trimester of pregnancy ($p = 0.004$) [45]. This suggests that ABR sensitivity gradually decreases from the start of pregnancy to the end of the second trimester.

The revealed patterns of ABR and PCR sensitivity make further studies in pregnant women relevant to identify risk factors for critical incidents during caesarean section in a high-risk group of patients. In addition, a significant difference in the dynamics of ABR sensitivity in patients with normotension and hypertensive disorders of pregnancy makes it relevant to search for early predictors of the risk of developing preeclampsia, which can help identify these disorders before their clinical manifestation.

Conclusion

Generalization of the extracted and analyzed data allows us to draw the following conclusions:

- PCR sensitivity in pregnant women can be assessed using methods such as inhalation of a hyperoxic gas mixture, inhalation of a hypercapnic gas mixture, inhalation of an isooxic-hypercapnic gas mixture (rebreathing test variant);
- the sensitivity of ABR in pregnant women can be assessed using methods such as phenylephrine test, Valsalva test, orthostatic test, spectral analysis of sequences of blood pressure values and R–R interval;
- the sensitivity of PCR during pregnancy increases, while the equilibrium point of $PaCO_2$ shifts towards hypocapnia compared to the initial state before pregnancy;
- sensitivity of ABR in pregnant women always progressively decreases from the beginning of pregnancy to the end of the second trimester and always increases in the postpartum period to the initial level; in the third trimester of pregnancy, changes in ABR sensitivity are individual and do not have a single trend.

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References

[1] *Ferré F., Martin C., Bosch L., et al.* Control of Spinal Anesthesia-Induced Hypotension in Adults. Local Reg Anesth. 2020; 13: 39–46. DOI: 10.2147/LRA.S240753

[2] *Kinsella S.M., Tuckey J.P.* Perioperative bradycardia and asystole: relationship to vasovagal syncope and the Bezold-Jarisch reflex. Br J Anaesth. 2001; 86(6): 859–68. DOI: 10.1093/bja/86.6.859

[3] *Sleight P., La Rovere M.T., Mortara A., et al.* Physiology and pathophysiology of heart rate and blood pressure variability in humans: is power spectral analysis largely an index of baroreflex gain? Clin Sci (Lond). 1995; 88(1): 103–9. DOI: 10.1042/cs0880103

[4] *Bernardi L., Gabutti A., Porta C., et al.* Slow breathing reduces chemoreflex response to hypoxia and hypercapnia, and increases baroreflex sensitivity. J Hypertens. 2001; 19(12): 2221–9. DOI: 10.1097/00004872-200112000-00016

[5] *Jensen D., Webb K.A., O'Donnell D.E.* The increased ventilatory response to exercise in pregnancy reflects alterations in the respiratory control systems ventilatory recruitment threshold for CO2. Respir Physiol Neurobiol. 2010; 171(2): 75–82. DOI: 10.1016/j.resp.2010.03.009

[6] *Fu Q., Levine B.D.* Autonomic circulatory control during pregnancy in humans. Semin Reprod Med. 2009; 27(4): 330–7. DOI: 10.1055/s-0029-1225261

[7] *Gaba D.M.* Anaesthesiology as a model for patient safety in health care. BMJ. 2000; 320(7237): 785–8. DOI: 10.1136/bmj.320.7237.785

[8] *Liberati A., Altman D.G., Tetzlaff J., et al*. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. J Clin Epidemiol. 2009; 62(10): 1–34. DOI: 10.1016/j.jclinepi.2009.06.006

[9] *Page M.J., Moher D., Bossuyt P.M., et al*. PRISMA 2020 explanation and elaboration: updated guidance and exemplars for reporting systematic reviews. BMJ. 2021; 372: n160. DOI: 10.1136/bmj.n160

[10] *Leduc L., Wasserstrum N., Spillman T., et al*. Baroreflex function in normal pregnancy. Am J Obstet Gynecol. 1991; 165(4 Pt 1): 886–90. DOI: 10.1016/0002-9378(91)90433-r

[11] *Blake M.J., Martin A., Manktelow B.N., et al*. Changes in baroreceptor sensitivity for heart rate during normotensive pregnancy and the puerperium. Clin Sci (Lond). 2000; 98(3): 259–68. DOI: 10.1042/cs0980259

[12] *Lucini D., Strappazzon P., Dalla Vecchia* L., *et al*. Cardiac autonomic adjustments to normal human pregnancy: insight from spectral analysis of R–R interval and systolic arterial pressure variability. J Hypertens. 1999; 17(12 Pt 2): 1899–904. DOI: 10.1097/00004872-199917121-00019

[13] *Гугова Ф.К., Мамонтов О.В., Богомолова О.А. и др*. Неинвазивная оценка чувствительности барорефлекса при беременности. Артериальная гипертензия. 2008;14(1):49–52. [*Gugova F.K., Mamontov O.V., Bogomolova O.A., et al*. Non-invasive assessment of baroreflex sensitivity during pregnancy. Arterial'naya gipertenzya. 2008; 14(1): 49–52. (In Russ)]

[14] *Visontai Z., Lenard Z., Studinger P., et al*. Impaired baroreflex function during pregnancy is associated with stiffening of the carotid artery. Ultrasound Obstet Gynecol. 2002; 20(4): 364–9. DOI: 10.1046/j.1469-0705.2002.00820.x

[15] *Silver H.M., Tahvanainen K.U., Kuusela T.A., et al*. Comparison of vagal baroreflex function in nonpregnant women and in women with normal pregnancy, preeclampsia, or gestational hypertension. Am J Obstet Gynecol. 2001; 184(6): 1189–95. DOI: 10.1067/mob.2001.112871

[16] *Jensen D., Wolfe L.A., Slatkovska L., et al*. Effects of human pregnancy on the ventilatory chemoreflex response to carbon dioxide. Am J Physiol Regul Integr Comp Physiol. 2005; 288(5): R1369–R1375. DOI: 10.1152/ajpregu.00862.2004

[17] *Reyes L.M., Khurana R., Usselman C.W., et al*. Sympathetic nervous system activity and reactivity in women with gestational diabetes mellitus. Physiol Rep. 2020;8(13):e14504. DOI: 10.14814/phy2.14504

[18] *Francis D.A. Coats J.S., Ponikowski P*. Chemoreflex-baroreflex interactions in cardiovascular disease. In: Sleep apnea. Implication in cardiovascular and cerebrovascular disease. Bradley T.D., Floras J.S., editors. New York: Marcel Dekker, 2000: 261–83.

[19] *Parati G., Omboni S., Fratolla A., et al*. Dynamic evaluation of baroreflex in ambulant subjects. In: Blood pressure and heart rate variablity. Ed by M. Di Rienzo *et al*. Amsterdam: IOS Press, 1992: 123–37.

[20] *Покровский В.М.* Физиология человека. Под ред. В.М. Покровского, Г.Ф. Коротько. 3-е изд. М.: Медицина, 2011. [*Pokrovskyj V.M.* Human physiology. Ed. by V.M. Pokrovskyj, G.F. Korot'ko. 3rd Ed. M.: Medicine, 2011. (In Russ)]

[21] *Gonzalez C., Almaraz L., Obeso A., et al*. Carotid body chemoreceptors: from natural stimuli to sensory discharges. Physiol Rev. 1994; 74(4): 829–98. DOI: 10.1152/physrev.1994.74.4.829

[22] *Coats A.J., Clark A.L., Piepoli M., et al*. Symptoms and quality of life in heart failure: the muscle hypothesis. Br Heart J. 1994; 72(2 Suppl): S36–S39. DOI: 10.1136/hrt.72.2_suppl.s36

[23] *Piepoli M.F., Coats A.J.* The skeletal muscle hypothesis in heart failure revised. Eur Heart J. 2013; 34(7): 486–8. DOI: 10.1093/eurheartj/ehs463

[24] *Frattola A., Parati G., Gamba P., et al*. Time and frequency domain estimates of spontaneous baroreflex sensitivity provide early detection of autonomic dysfunction in diabetes mellitus. Diabetologia. 1997; 40(12): 1470–5. DOI: 10.1007/s001250050851

[25] *Ducher M., Cerutti C., Gustin M.P., et al*. Noninvasive exploration of cardiac autonomic neuropathy. Four reliable methods for diabetes? Diabetes Care. 1999; 22(3): 388–93. DOI: 10.2337/diacare.22.3.388

[26] *Schultz H.D., Sun S.Y.* Chemoreflex function in heart failure. Heart Fail Rev. 2000; 5(1): 45–56. DOI: 10.1023/A:1009846123893

[27] *Schultz H.D., Marcus N.J., Del Rio R*. Mechanisms of carotid body chemoreflex dysfunction during heart failure. Exp Physiol. 2015; 100(2): 124–9. DOI: 10.1113/expphysiol.2014.079517

[28] *Schultz H.D., Marcus N.J., Del Rio R*. Role of the Carotid Body Chemoreflex in the Pathophysiology of Heart Failure: A Perspective from Animal Studies. Adv Exp Med Biol. 2015; 860: 167–85. DOI: 10.1007/978-3-319-18440-1_19

[29] *Somers V.K., Dyken M.E., Clary M.P., et al*. Sympathetic neural mechanisms in obstructive sleep apnea. J Clin Invest. 1995; 96(4): 1897–904. DOI: 10.1172/JCI118235

[30] *Paton J.F., Sobotka P.A., Fudim M., et al*. The carotid body as a therapeutic target for the treatment of sympathetically mediated diseases. Hypertension. 2013; 61(1): 5–13. DOI: 10.1161/HYPERTENSIONAHA.111.00064

[31] *Porzionato A., Macchi V., De Caro R*. Role of the carotid body in obesity-related sympathoactivation. Hypertension. 2013; 61(6): e57. DOI: 10.1161/HYPERTENSIONAHA.113.01248

[32] *Del Rio R., Andrade D.C., Toledo C., et al*. Carotid Body-Mediated Chemoreflex Drive in The Setting of low and High Output Heart Failure. Sci Rep. 2017; 7(1): 8035. DOI: 10.1038/s41598-017-08142-3

[33] *Kolarzyk E., Szot W.M., Lyszczarz J.* Lung function and breathing regulation parameters during pregnancy. Arch Gynecol Obstet. 2005; 272(1): 53–8. DOI: 10.1007/s00404-004-0691-1

[34] *van Veen T.R., Panerai R.B., Haeri S., et al*. Effect of breath holding on cerebrovascular hemodynamics in normal pregnancy and preeclampsia. J Appl Physiol (1985). 2015; 118(7): 858–62. DOI: 10.1152/japplphysiol.00562.2014

[35] *Jensen D., O'Donnell D.E.* The impact of human pregnancy on perceptual responses to chemoreflex vs exercise stimulation of ventilation: a retrospective analysis. Respir Physiol Neurobiol. 2011; 175(1): 55–61. DOI: 10.1016/j.resp.2010.09.007

[36] *Jensen D., Webb K.A., O'Donnell D.E.* Chemical and mechanical adaptations of the respiratory system at rest and during exercise in human pregnancy. Appl Physiol Nutr Metab. 2007; 32(6): 1239–50. DOI: 10.1139/H07-120

[37] *Jensen D., Duffin J., Lam Y.M., et al*. Physiological mechanisms of hyperventilation during human pregnancy. Respir Physiol Neurobiol. 2008; 161(1): 76–86. DOI: 10.1016/j.resp.2008.01.001

[38] *Brooks V.L., Fu Q., Shi Z., et al.* Adaptations in autonomic nervous system regulation in normal and hypertensive pregnancy. Handb Clin Neurol. 2020; 171: 57–84. DOI: 10.1016/B978-0-444-64239-4.00003-5

[39] *Campos M., Bravo E., Eugenín J.* Respiratory dysfunctions induced by prenatal nicotine exposure. Clin Exp Pharmacol Physiol. 2009; 36(12): 1205–17. DOI: 10.1111/j.1440-1681.2009.05214.x

[40] *Brooks V.L., Cassaglia P.A., Zhao D., et al.* Baroreflex function in females: changes with the reproductive cycle and pregnancy. Gend Med. 2012; 9(2): 61–7. DOI: 10.1016/j.genm.2012.02.004

[41] *Brooks V.L., Dampney R.A., Heesch C.M.* Pregnancy and the endocrine regulation of the baroreceptor reflex. Am J Physiol Regul Integr Comp Physiol. 2010; 299(2): R439–R451. DOI: 10.1152/ajpregu.00059.2010

[42] *Souma M.L., Cabaniss C.D., Nataraj A., et al.* The Valsalva maneuver: a test of autonomic nervous system function in pregnancy. Am J Obstet Gynecol. 1983; 145(3): 274–8. DOI: 10.1016/0002-9378(83)90710-x

[43] *Ekholm E.M., Erkkola R.U.* Autonomic cardiovascular control in pregnancy. Eur J Obstet Gynecol Reprod Biol. 1996; 64(1): 29–36. DOI: 10.1016/0301-2115(95)02255-4

[44] *Ekholm E.M., Vesalainen R.K., Tahvanainen K.U., et al.* Valsalva manoeuvre can be used to study baroreflex sensitivity in pregnancy. Eur J Obstet Gynecol Reprod Biol. 1998; 76(2): 153–6. DOI: 10.1016/s0301-2115(97)00179-6

[45] *Ekholm E.M., Piha S.J., Erkkola R.U., et al.* Autonomic cardiovascular reflexes in pregnancy. A longitudinal study. Clin Auton Res. 1994; 4(4): 161–5. DOI: 10.1007/BF01826181