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Safety and effectiveness of volumetric computed tomography of the heart in combination with a pharmacological test with adenosine triphosphate in the diagnosis of coronary heart disease

Aim	To evaluate safety and efficacy of sodium adenosine triphosphate (ATP) as a vasodilator in assessment of left ventricular (LV) myocardial perfusion and in verification of ischemia by cardiac volumetric computed tomography (CT).
Material and methods	The study included 58 patients with suspected ischemic heart disease (IHD). For all included patients, cardiac volumetric CT with a pharmacological ATP test was performed. The rate of adverse effects was analyzed during the ATP infusion. Results of the study were compared with data from using other noninvasive methods for IHD diagnosis by calculating Cohen's kappa, the measure of agreement between two variables.
Results	The test performed during CT showed good tolerability of the ATP infusion, a low rate of moderate adverse reactions (8.6%), and the absence of severe side effects. Results of diagnosing IHD with cardiac volumetric CT with the ATP pharmacological test were comparable with data from using other methods for noninvasive verification of LV myocardial ischemia (bicycle ergometry, treadmill test, stress echocardiography) in combination with coronarography or CT coronarography.
Conclusion	ATP appears a safe pharmacological agent for diagnosing transient LV myocardial ischemia. ATP can be recommended as a vasodilator for evaluation of perfusion using cardiac volumetric CT.
Keywords	Sodium adenosine triphosphate; cardiac volumetric computed tomography; left ventricular myocardial perfusion; ischemic heart disease
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Coronary heart disease (CHD) continues to be the leading cause of death worldwide [1], with only 40–50% of all CHD patients being aware of their disease and receiving appropriate treatment, while 50–60% of cases remaining undiagnosed. Almost 50% of CHD patients have myocardial infarction (MI) as the first manifestation of the disease [2]. Thus, the timely non-invasive diagnosis of left ventricular (LV) ischemia remains a relevant issue. The step-by-step performance of multiple non-invasive tests is not cost-effective: e.g., non-invasive tests amount to about 40% of the national health insurance cost in the United States, i.e., $ 17 billion annually [3], and less than 50% of patients with positive stress tests have obstructive changes in coronary arteries at invasive coronary angiography (CA) [4]. International scientific associations (AHA, ESC) have developed guidelines for selecting examinations in suspected CHD [5, 6].

Computed tomography (CT) of coronary arteries is recommended as the first imaging technique in the diagnosis of CHD as an alternative to non-invasive stress tests [5]. It should obviously be supplemented by an estimation of LV myocardial perfusion using volumetric cardiac CT and pharmacological stress test. Adenosine and its derivatives, e.g., sodium adenosine triphosphate (ATP), are commonly used to identify LV myocardial ischemia and assess perfusion. According to the literature, there is experience of the safe use of ATP to assess coronary fractional flow reserve and LV myocardial perfusion by single-photon emission computed tomography (SPECT) [7–9]. However, ATP infusion safety has not been assessed with the simul-

taneous administration of a radiopaque contrast agent (RCA) and volumetric cardiac CT (640 slices, 1 cardiac cycle).

Objective

To assess the safety and efficacy of a pharmacological stress test with ATP-mediated vasodilatation and the simultaneous administration of RCA and volumetric cardiac CT in CHD diagnosis.

Material and methods

The study was conducted in accordance with the Declaration of Helsinki. The Ethics Committee of the Russian National Cardiology Research Center approved the study protocol. All subjects signed informed consent. From March 2017 to December 2019, 58 patients were included in the study. All were examined to verify myocardial ischemia and to choose between invasive or conservative management. Inclusion criteria: age over 18 years, probable CHD or hypertensive heart disease (HHD) stage II–III, type 2 diabetes mellitus (DM) was allowed.

In order to clarify the diagnosis of CHD, patients were subjected to comprehensive non-invasive examination (stress echocardiography, electrocardiographic stress tests, volumetric cardiac CT, including CT-CA and LV myocardial perfusion at rest and with ATP stress test), and invasive CA was performed at the final stage.

The criteria for LV myocardial ischemia based on ECG stress test were horizontal or downsloping ST-segment depression of more than 1 mm (>1 mV) in two or more leads, when submaximal heart rate (HR) was attained and pain appeared behind the sternum, or signs of a local reduction in LV myocardial contractility at stress echocardiography when the submaximal HR is attained. Exclusion criteria were: contraindications to ATP infusion (atrial fibrillation and/or atrial flutter, acute MI, decompensated heart failure, left coronary artery stenosis more than 50%, chronic obstructive pulmonary disease, bronchial asthma); or nonionic iodine-containing RCA (glomerular filtration rate less than 30 mL/min/1.73 m^2 according to the MDRD formula, allergic reactions); and pregnancy.

The study was performed during the gradual withdrawal of antianginal therapy (including beta-blockers, 48 hours before the trial), in accordance with two-phase protocol (rest and stress), in breath-holding spells, and with intravenous bolus administration of 60–80 mL (depending on the patient's body weight) of nonionic iodide-containing RCA (iodine 370 mg/mL) at the rate of 4–5 mL/s using an automatic syringe in the rest phase. First, topograms were made, then volumetric cardiac CT was performed in native and arterial phases. The second examination was carried out 20 minutes after the first injection of RCA with the simultaneous infusion of ATP 1% solution using an infusion syringe pump at the rate of 0.16 mg/kg/min. The infusion did not exceed 5 minutes. The administration was stopped early if chest pain, negative ECG trends, or moderate to severe adverse reactions appeared. Without interrupting the ATP infusion, the intravenous bolus of RCA was injected into a cubital catheter placed in the other arm, while volumetric cardiac CT was performed in the arterial contrast phase. After completion of the ATP infusion, the patient was left on the scanner table and monitored for 5 minutes under ECG control.

Since there is a wide range of phenomena associated with adenosine receptor stimulation, the examination was performed with ECG monitoring throughout the time of the ATP infusion and within 5 minutes after its completion. This allowed for the timely detection of heart rhythm and conduction disorders, as well as monitoring heart rate gains. The tomography unit in which the examination was performed was equipped with a defibrillator in good working order. A 10% solution of aminophylline, an ATP antagonist, was prepared for each patient before examination and administered intravenously at the dose of 4 mg/kg to manage severe side effects. Blood pressure (BP) was registered before the examination and after the end of the ATP infusion.

The safety of the volumetric CT with ATP stress test was assessed by the rates of the following side effects: mild (not requiring withdrawal or special treatment, resolving spontaneously: headache, dyspnea, chest discomfort without changes in ECG); moderate (requiring discontinuation of infusion or special treatment: symptomatic arterial hypotension, extra heartbeats, stress-induced atrial fibrillation, PQ interval prolongation, and atrioventricular block), and severe (life-threatening: ventricular tachycardia, ventricular fibrillation, MI, bronchospasm).

The imaging data was processed using the Vitrea Advanced suite on a Vitrea workstation by evaluating a series of volumetric CT images acquired at rest, and after ATP stress test. 3D and multiplanar reconstructions were undertaken in order to view coronary arteries. Defects of LV myocardial perfusion were determined visually and by automatic calculation of semi-quantitative measurements: LV myocardial tissue density drop (DD), LV myocardial perfusion index (PI), and transmural perfusion rate (TPR), at rest and during reactive hyperemia, using the following formulas:

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Table 1. Interpretation of Cohen's kappa coefficient

κ value (Cohen's kappa coefficient)	Consistency
<0.20	Very weak
0.21–0.40	Weak
0.41–0.60	Moderate
0.61–0.80	Good
0.81–1.00	Very good

Table 2. Clinical characteristics of the examined patients (n = 58)

Parameter	Value
Sex	Female 41 (71); male 17 (29)
Age, years	58.5 [51; 64]
Body mass index, kg/m^2	29 [26; 32]
Smoking	12 (21)
Significant family history of cardiovascular diseases	29 (50)
Systolic BP, mmHg	130 [120; 140]
Diastolic BP, mmHg	80 [72; 90]
HR, bpm	68.5 [64; 74]
Dyslipidemia	44 (76)
Total cholesterol, mmol/L	5.22 [4.14; 5.7]
LDL cholesterol, mmol/L	3.295 [2.225; 3.84]
Glomerular filtration rate (MDRD), mL/min/1.73m^2	85 [77; 97]
CHD+HHD	38 (65.5)
CHD+DM type 2	15 (25.9)
Postinfarction cardiosclerosis	3 (5.17)
Coronary atherosclerosis	
• single vessel	22 (38)
• two vessels	30 (51.7)
Intact coronary arteries	6 (10.3)
HHD	5 (8.6)

The data is presented as the absolute and relative values or the median and the interquartile range [25th percentile; 75th percentile]. BP, blood pressure; HR, heart rate; LDL, low-density lipoproteins; CHD, coronary heart disease; HHD, hypertensive heart disease; DM, diabetes mellitus.

DD = mean density of contrast-enhanced myocardium (HU) – density of native myocardium (baseline, HU)

PI = mean myocardial DD/mean LV DD

TPR = subendocardial PI (single segment)/ subepicardial PI (entire layer).

Perfusion defect was determined as the hypodense LV myocardial segment detected at stress and undetectable at rest. It is most commonly located in the subendocardial layer, and identified in one or more segments in three consecutive images when comparing the radiological density of the adjacent LV myocardial areas. TPR at stress should be less than 0.99 in the hypoperfusion area.

This paper presents the final result, which is the presence or absence of a transient defect in LV myocardial perfusion. If a subendocardial defect in LV myocardial perfusion was detected, this sign was coded as «1», if not as «0». The same codes were used after a comprehensive examination to identify the presence or absence of CHD. These results were subsequently matched by calculating consistency between two Cohen's kappa variables. The presence of ischemic defects in LV myocardial perfusion shown by the volumetric cardiac CT, combined with the ATP stress test was compared as a variable with CHD verification following comprehensive examination as a second variable. After this Cohen's kappa consistency between these variables was calculated. Cohen's kappa consistency was interpreted in accordance with Table 1. Thus, the examination's efficacy was assessed by the comparability of confirmed cases of ATP-induced LV myocardial perfusion defects with the definitive clinical diagnosis of CHD.

In this study, the Statistica 5.1 suite was used to calculate statistical data (clinical characteristics of the examined patients, the incidence of side effects during the use of ATP, frequency of the administration of aminophylline solution). The median and interquartile interval were defined for each of the above parameters. In order to determine consistency between the two Cohen's kappa variables, the MedCalc 11.5 suite was used.

Results

The study included 58 patients whose clinical characteristics are presented in Table 2. Coronary atherosclerotic changes are described based on CT-CA and invasive CA findings, which were identical.

Safe pharmacological use of ATP in volumetric CT

The incidence of mild, moderate, severe side effects of the administration of ATP was determined. Systolic blood pressure decreased from 132±12.9 to 128±16.3 mmHg (p>0.05) during ATP infusion. Diastolic blood pressure decreased from 85±5.7 to 77±16.3 mmHg (p=0.02). The decrease in systolic and diastolic blood pressure was not accompanied by a worsening course or hemodynamic disorders. Mean HR increased from 66±6 to 90±16 bpm (p<0.0002) during ATP administration.

Headache (64%), chest pain of various types without changes in ECG (69%), dyspnea (90%) were

the most common adverse events of ATP infusion. Administration of ATP was accompanied by single extra (supraventricular or ventricular) heartbeats in 10 patients, which did not require an aminophylline solution. There were no extra heartbeats after the examination was completed.

One patient had PQ interval prolongation from 162 to 220 ms. In 2 minutes after the administration of the aminophylline solution, the duration of the PQ interval normalized.

The above phenomena resolved within 1 to 2 minutes after the end of ATP administration or regressed after intravenous administration of 10% solution of aminophylline, used to manage adverse events in 10 (17%) patients: 5 to 10 mL were administered after volumetric cardiac CT at stress (one cardiac cycle). Patients stopped complaining 84 ± 22 seconds after its administration.

There were no deaths, stress-induced ventricular tachycardia or ventricular fibrillation, atrial fibrillation, MI, bronchospasm, clinically significant arterial hypotension.

Table 3 presents the incidence of side effects associated with ATP administration and the frequency of using the aminophylline solution to manage side effects.

Efficacy of volumetric cardiac CT with ATP stress test in the diagnosis of LV myocardial ischemia

The images acquired by volumetric CT with ATP stress test were analyzed. Figure 1 contains images showing the presence of a subendocardial LV perfusion defect at stress.

According to Table 1, the consistency of the results of the two examinations was calculated: the presence of an ischemic defect in LV myocardial perfusion shown by volumetric CT with ATP stress test and results of the comprehensive examination to verify the diagnosis of CHD. Cohen's kappa was 0.83, i.e., the consistency of results was excellent.

Discussion

ATP, a derivative of adenosine, purine nucleoside, non-selective agonist of adenosine receptors, inducing vasodilation of coronary microvessels [10] and epicardial coronary arteries [11] is an effective vasodilator used to study LV myocardial perfusion. In atherosclerotic epicardial coronary arteries and in the case of atherosclerosis of vascular walls or abnormal vascular tone of the microcirculatory vessels, the steal effect is expected due to the redistribution of blood flow when ATP is administered. This induces LV myocardial ischemia. Due to the heterogeneous blood supply of different LV myocardial layers, it is possible to verify transient perfusion disorders caused by atherosclerosis or abnormal microcirculation.

ATP produces a non-selective effect on adenosine receptors, purinergic receptors, which are transmembrane proteins when coupled with G-protein. Like adenosine, ATP has a pronounced effect on organs and tissues, including the heart, by activating two families of purinergic receptors, P1 and P2 [12].

The P1 receptor family is represented by subtypes A1, A2A, A2B, A3 [13], detected in almost all tissues. Activation of the Al and AZ receptors decreases the levels of intracellular cyclic adenosine monophosphate (cAMP). Activation of the A2A and A2B receptors when coupled with GS-protein mediates cAMP synthesis [14]. The P2 receptor family includes subtypes P2X and P2Y [15]. The R2X receptors include seven subtypes of ion channels. The R2Y receptors combine eight subtypes of G-protein coupled structures [16]. The systemic effects of adenosine and the non-selective agonist of adenosine receptors ATP are manifested due to several factors and depend on the characteristics of a receptor, type of tissue, presence or absence of tissue damage, and adenosine levels.

Administration of ATP may be accompanied by short-term episodes of sinus bradycardia, exacerbated atrial-ventricular conduction, arterial hypotension (reduced systolic and diastolic BP by 10–15 mmHg), chest pain, dyspnea [17]. In our study, ATP-induced increase in mean HR from 66±6 to 90±16 bpm was

Table 3. Incidence of side effects during the use of ATP; the rate of administration of aminophylline solution

Adverse events	Number of side effects, n (%)	Aminophylline, n (%)
Dyspnea	52 (90)	3 (5)
Chest discomfort without changes in ECG	40 (69)	5 (8.6)
Headache	37 (64)	0
Extra heartbeats	10 (17)	1 (1.7)
Atrioventricular block/ PQ interval prolongation	1 (1.7)	1 (1.7)

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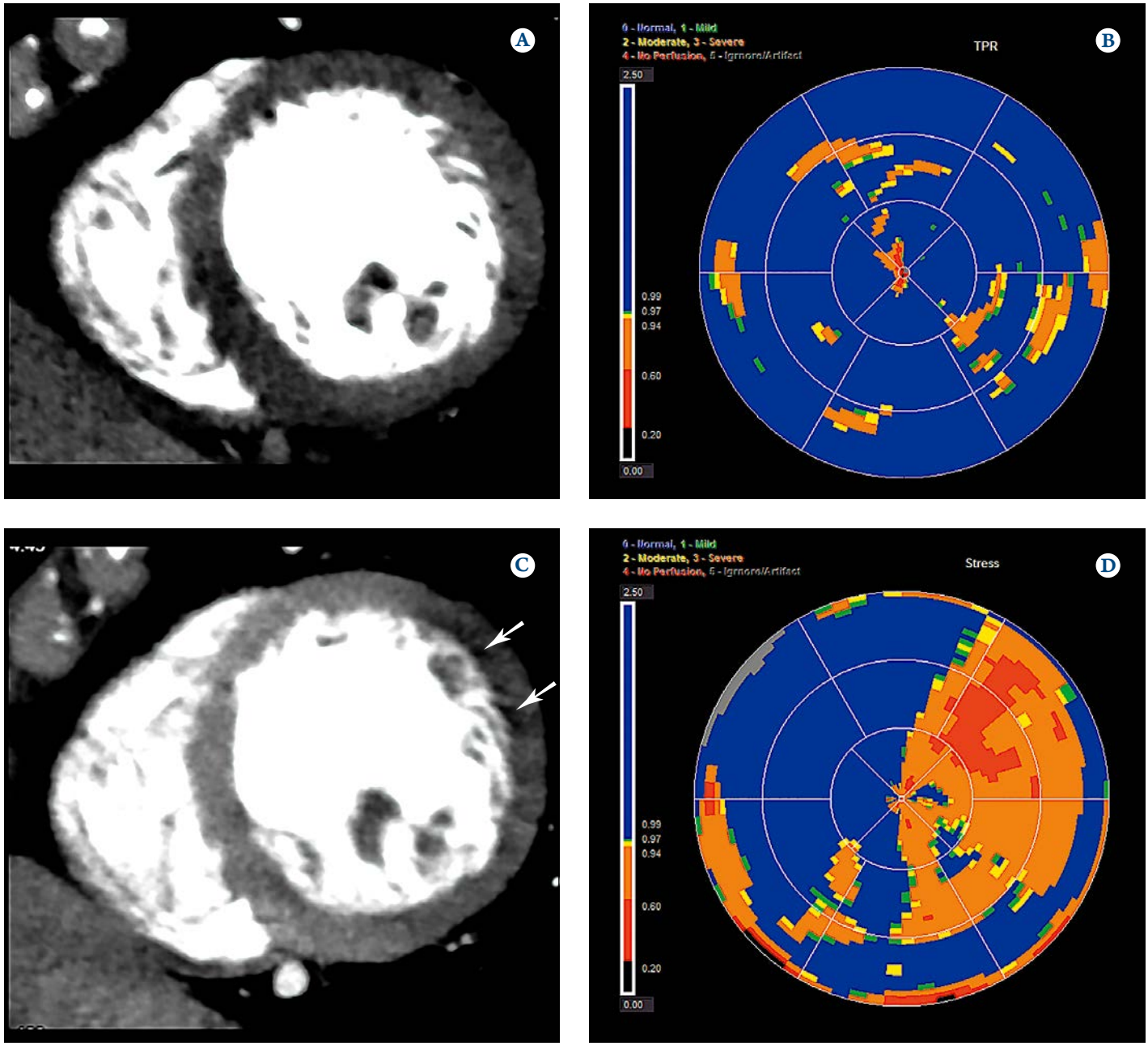
Figure 1. Detection of subendocardial perfusion defect in the LV lateral wall



A is the image of LV myocardium in the arterial contrast phase at rest, multiplanar reconstruction, cross-sectional slice at the level of middle segments of LV myocardium, no LV myocardial contrast defects detected;
B is a detailed polar map of the distribution of transmural perfusion ratio across all segments with TPR >0.99;
C is LV myocardium in the arterial contrast phase at ATP-induced stress, multiplanar reconstruction, transverse slice at the level of middle segments of LV myocardium, myocardial contrast-enhancement defect detected in the LV lateral wall projection (white arrows)
D is a detailed polar map of the distribution of transmural perfusion ratio in all LV lateral wall segments with TPR <0.99 (orange-red area). LV, left ventricle.

not accompanied by a deterioration in the patient's wellbeing and was caused by baroreflex-mediated activation of the sympathetic vegetative nervous system [18, 19].

The effects of stimulating A1 receptors, including bronchospasm, are directly proportional to the levels of adenosine. We calculated an ATP dose based on the patient's body weight, in order to attain the drug's best-possible blood levels without causing bronchospasm.

The low rate of side effects and their rapid resolution within 1 to 2 minutes from the end of ATP infusion are due to fast ATP metabolism and a short half-life period (T½ 0.5–1.5 s) [15]. Only 1% of the administered volume of ATP solution was found in whole blood in 40 seconds after bolus injection [20, 21].

Our findings on the safe use of ATP as a vasodilator when estimating LV myocardial perfusion by volumetric cardiac CT are consistent with the safety of

adenosine receptor agonists in the detection of LV myocardial perfusion abnormalities using SPECT [9] or cardiac magnetic resonance imaging (MRI) [22]. The administration of ATP as a vasodilator to view LV myocardial ischemia in cardiac CT has previously been compared to invasive CA data in 21 patients. The high diagnostic accuracy of combined CT-CA with ATP stress test has been demonstrated in the detection of ischemic defects of LV myocardial perfusion [23]. Multispiral cardiac CT with ATP stress test and myocardial perfusion scintigraphy and invasive CA have been shown to be highly comparable in detecting ischemic defects in LV myocardial perfusion [24]. In our study, the capabilities of the ATP stress test in the diagnosis of CHD were studied for the first time during volumetric CT. This is able to obtain simultaneously 6400.5 mm slices in a single cardiac cycle, capture the entire heart and determine the anatomical location of LV myocardial perfusion defects.

Our findings confirmed the high level of consistency between the results of volumetric CT in combination with the ATP stress test and comprehensive examination used to diagnose CHD. The high accuracy of determining the hemodynamic significance of coronary stenoses by volumetric cardiac CT with the ATP stress test was demonstrated earlier when compared with the invasive determination of the coronary fractional flow reserve [25].

This innovative method is also useful in verifying LV myocardial ischemia in normal coronary arteries and requires no other diagnostic methods. The female predominance of our study population was due to the low baseline probability of having CHD. This was of particular interest in demonstrating the diagnostic capabilities of volumetric cardiac CT combined with the ATP stress test. We have previously published a case study of a typical clinical picture of exertional angina and ischemic changes in ECG during the treadmill test, in which CHD with normal coronary arteries was diagnosed, taking into account ischemic defect in LV myocardial perfusion and intact coronary arteries according to volumetric cardiac CT in combination with ATP stress test [26]. Perfused cardiac CT using adenosine stress test to detect CHD was also highly informative in multi-center international trial CORE-320. In this case, perfused CT-320 was studied by assessing the hemodynamic significance of coronary stenosis in 381 patients. Invasive CA and SPECT were used as reference methods. The combination of CT-CA and CT perfusion with adenosine has been shown to be more specific (70% vs. 86%) and accurate (79%) than isolated CT-CA in the assessment of the hemodynamic significance of coronary stenosis [27].

Conclusion

The use of sodium adenosine triphosphate in the diagnosis of transient left ventricular myocardial ischemia, despite a wide range of processes stimulated, seems to be safe when used in combination with simultaneous volumetric cardiac computed tomography. This is due to the short half-life of the drug, the possibility of early diagnosis of adverse reactions and their rapid management. The administration of a 1% solution of sodium adenosine triphosphate may be recommended as a vasodilator when assessing left ventricular myocardial perfusion by volumetric cardiac computed tomography.

The analysis of the scans for the left ventricular hypoperfusion area after administration of sodium adenosine triphosphate identified them as stress-induced ischemia zones. The high level of comparability of the results of volumetric cardiac computed tomography with the sodium adenosine triphosphate stress test in detecting coronary heart disease with stress tests and invasive coronary angiography makes it possible to conclude that volumetric computed tomography with the sodium adenosine triphosphate stress test is an effective, innovative non-invasive method for the diagnosis of coronary heart disease. It meets this critical clinical challenge in a single examination without the need for invasive coronary angiography.

No conflict of interest is reported.

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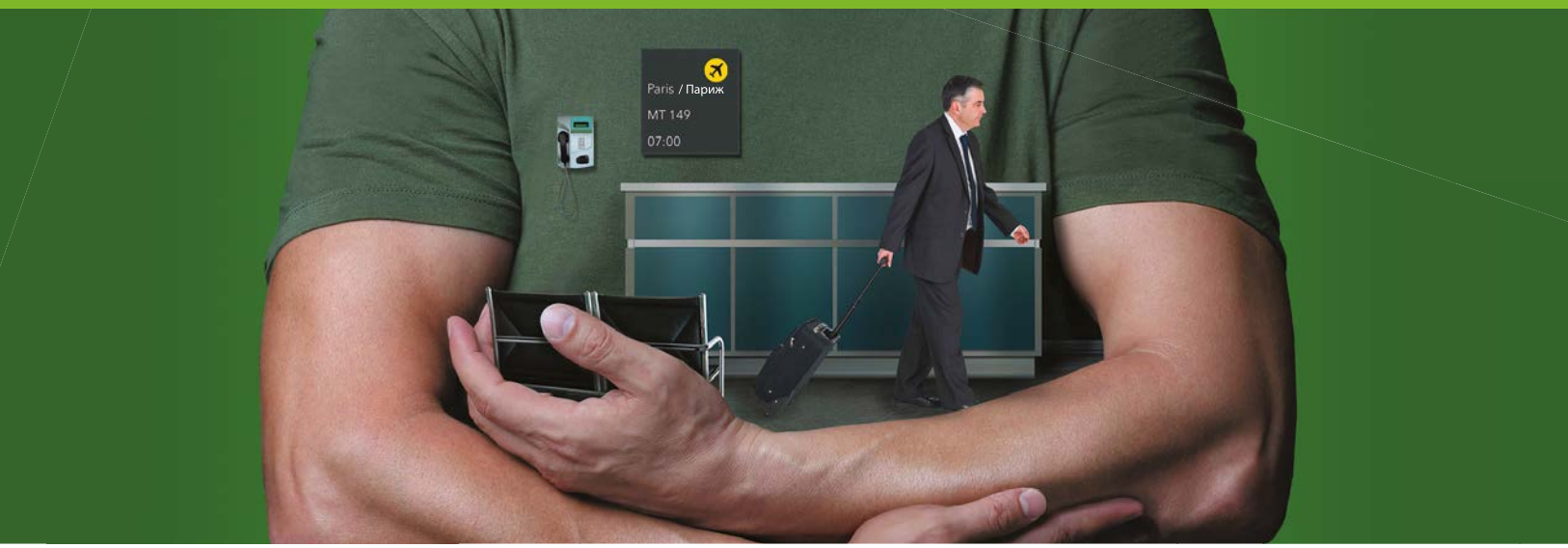
ФАРМАКОТЕРАПИЯ ОКС/ЧКВ С ПОЗИЦИИ АНТИАГРЕГАНТА 1-Й ЛИНИИ[1]



Для предупреждения тромботических осложнений у пациентов с ОКС, которым проводится ЧКВ[3]

Более выраженное действие по сравнению с клопидогрелом в снижении частоты ПКТ и ВКТ с 3-го дня и до 450 дней[2]

Среди пациентов, которым показан прасугрел (Эффиент®) 10 мг, нет отличий от терапии клопидогрелом 75 мг по риску «больших» по классификации TIMI, не связанных с АКШ кровотечений[2]

КРАТКАЯ ИНСТРУКЦИЯ ПО ПРИМЕНЕНИЮ*

Состав*. Прасугрела гидрохлорид 5,49/10,98 мг соответствует прасугрелу (основанию) 5,00/10,00 мг. **Показания к применению***. Для предупреждения тромботических осложнений у пациентов с острым коронарным синдромом (ОКС), которым проводится чрескожное коронарное вмешательство (ЧКВ): пациентам с нестабильной стенокардией (НС) или инфарктом миокарда (ИМ); без подъема сегмента ST (ИМБПСТ), которым проводится ЧКВ. Пациентам с ИМ с подъемом сегмента ST (ИМСПСТ), которым проводится первичное или отложенное ЧКВ. Для предупреждения тромбоза стента при ОКС. **Способ применения и дозы***. Внутрь, независимо от приема пищи. Недопустимо ломать таблетку перед приемом. Прием начинают с однократной нагрузочной дозы 60 мг. Далее принимают ежедневную поддерживающую дозу 10 мг. Пациенты с НС/ИМБПСТ, которым проводится коронарная ангиография в течение 48 часов после госпитализации, должны принимать нагрузочную дозу только во время ЧКВ. Пациенты, принимающие прасугрел, также должны ежедневно принимать ацетилсалициловую кислоту (75-325 мг). У пациентов с ОКС, которым было проведено ЧКВ, преждевременное прекращение терапии любым антиагрегантом, включая Эффиент®, может привести к повышенному риску тромбоза, ИМ или смерти вследствие основного заболевания. Рекомендуется лечение продолжительностью до 12 месяцев, если не возникнут показания для отмены препарата. *Пациенты с массой тела <60 кг:* прием начинают с однократной нагрузочной дозы 60 мг. Далее принимают ежедневную поддерживающую дозу 5 мг. Поддерживающая доза 10 мг не рекомендуется. *Пациенты в возрасте ≥75 лет:* применение лекарственного препарата Эффиент®, как правило, не рекомендуется, если лечение считается необходимым, то прием начинают с однократной нагрузочной дозы 60 мг, далее назначается ежедневная поддерживающая доза 5 мг. *Пациенты с почечной недостаточностью:* коррекция дозы не требуется. *Пациенты с печеночной недостаточностью:* для пациентов с умеренной печеночной недостаточностью коррекция дозы не требуется (класс А и В по шкале Чайлд-Пью). *Дети и подростки:* не рекомендуется, так как данные об эффективности и безопасности недостаточны. **Противопоказания***. Установленная повышенная чувствительность к прасугрелу или к любому компоненту, входящему в состав препарата; состояния с повышенным риском кровотечения (патологические кровотечения, например при пептической язве); транзиторная ишемическая атака или инсульт в анамнезе; тяжелая печеночная недостаточность (класс С по шкале Чайлд-Пью); дефицит лактазы, непереносимость лактозы, глюкозо-галактозная мальабсорбция; период грудного вскармливания; возраст до 18 лет; планируемое срочное аортокоронарное шунтирование (АКШ), поскольку это связано с более высоким риском послеоперационного кровотечения. При проведении планового АКШ рекомендована предшествующая (за 7 дней до планируемой операции) отмена прасугрела. **Особые указания***. *Тромботическая тромбоцитопеническая пурпура (ТТП)* может возникнуть менее чем через 2 недели после начала приема препарата. ТТП – серьезное заболевание, которое может привести к летальному исходу и требующее срочного лечения, включая плазмаферез. ТТП характеризуется тромбоцитопенией, неврологическими нарушениями, нарушением функции почек и лихорадкой. *Хирургические вмешательства:* пациентам рекомендуется сообщать врачам, в том числе стоматологам, о применении прасугрела при планировании хирургических вмешательств или назначении новых лекарственных препаратов. Увеличение частоты кровотечений в 3 раза и их тяжести может наблюдаться у пациентов с АКШ в течение 7 дней после отмены прасугрела. *Риск кровотечения:* у пациентов с ИМБПСТ, принимавших нагрузочную дозу прасугрела в среднем за 4 часа перед диагностической коронарной ангиографией, увеличивался риск больших и малых кровотечений по сравнению с пациентами, принимавшими нагрузочную дозу прасугрела во время ЧКВ. Пациентов следует предупреждать о возможном увеличении времени кровотечения на фоне приема прасугрела (в комбинации с АСК) и о необходимости информировать врача о любых возникших кровотечениях. *Гиперчувствительность, включая ангионевротический отек:* сообщалось о случаях у пациентов, принимавших прасугрел, в том числе у пациентов с реакцией гиперчувствительности к другим тиенопиридинам в анамнезе. *Лактоза.* Пациентам с редкими наследственными проблемами непереносимости галактозы, дефицитом лактазы, глюкозо-галактозной мальабсорбцией принимать препарат не следует. **Взаимодействие с другими лекарственными средствами***. *Варфарин:* с особой осторожностью в связи с возможностью увеличения риска кровотечения. *Нестероидные противовоспалительные препараты (НПВП):* в связи с возможностью увеличения риска кровотечения применение прасугрела на фоне постоянной терапии НПВП (включая ингибиторы ЦОГ-2) должно проводиться с особой осторожностью. *Лекарственные средства, метаболизирующиеся изоферментом CYP2B6:* прасугрел – слабый ингибитор изофермента CYP2B6. У здоровых субъектов прасугрел на 23% снижал эффект гидроксибупропиона – метаболита бупропиона, образованного изоферментом CYP2B6. Такой эффект может быть клинически выраженным, только когда прасугрел применяется совместно с препаратами, имеющими узкое терапевтическое окно и метаболизирующимися исключительно изоферментом CYP2B6 (например, циклофосфамид или эфавиренз). *Другие виды сочетанного применения препаратов:* можно одновременно применять с препаратами, метаболизируемыми изоферментами цитохрома Р450, включая статины, или с препаратами, являющимися индукторами или ингибиторами изоферментов цитохрома Р450. Также можно одновременно применять с АСК, гепарином, дигоксином и препаратами, повышающими pH желудочного сока, включая ингибиторы протонной помпы, и с блокаторами Н2-гистаминовых рецепторов. **Беременность* и период грудного вскармливания***. Неизвестно, выделяется ли прасугрел с грудным молоком. В период грудного вскармливания применение препарата не рекомендовано. Прасугрел может назначаться во время беременности, только если потенциальная польза для матери оправдывает потенциальный риск для плода. **Влияние на способность управлять автомобилем и выполнять работы, требующие высокой скорости психических и физических реакций***. Не установлено. **Побочное действие***. Побочные эффекты, выявленные в ходе клинических исследований (при лечении ОКС). *Кровотечения, не связанные с АКШ:* «большие» кровотечения по классификации TIMI (угрожающие жизни, в том числе фатальные; клинически выраженные внутричерепные кровотечения; требующие инотропных препаратов; требующие хирургического вмешательства; требующие переливания крови (≥4 единиц)); «малые» кровотечения по классификации TIMI. *Кровотечения, связанные с АКШ:* «малые» кровотечения по классификации TIMI, большие кровотечения по классификации TIMI (фатальные, повторная операция, переливание ≥5 единиц крови, кровоизлияние в мозг). *Побочные реакции геморрагического характера. Часто:* гематома, носовое кровотечение, желудочно-кишечное кровотечение, экхимозы, гематурия, гематома в месте пункции сосуда, кровотечение в месте пункции, ушиб. *Нечасто:* внутриглазное кровоизлияние, кровохарканье, ректальное кровотечение, кровотечение из десен, кровянистый стул (гематохезия), забрюшинное кровотечение, подкожная гематома, кровотечение после проведения процедуры. *Нежелательные реакции негеморрагического характера. Часто:* анемия, кожная сыпь. *Редко:* тромбоцитопения. При использовании стандартных режимов дозирования прасугрела пациенты, перенесшие ранее инсульт или транзиторную ишемическую атаку, имеют больший риск развития инсульта или ТИА, чем пациенты с отсутствием этих заболеваний в анамнезе. *Нежелательные реакции, выявленные методом сбора спонтанных сообщений. Редко:* реакции гиперчувствительности, включая ангионевротический отек. *Очень редко:* тромбоцитопеническая пурпура. **Передозировка***. **Фармакологические свойства***. Антиагрегантное средство; является антагонистом рецепторов класса P2Y12 к аденозиндифосфату и ингибирует активацию и агрегацию тромбоцитов. **Форма выпуска***. Таблетки, покрытые пленочной оболочкой, 5 мг, 10 мг. **Номер регистрационного удостоверения:** ЛП-000675.

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* Для получения полной информации, пожалуйста, обратитесь к инструкции по медицинскому применению лекарственного препарата.
**Исследование Тритон-Тими 38.

АКШ – аортокоронарное шунтирование, ВКТ – вторичные конечные точки (выявленный/возможный тромбоз стента, смерть от сердечно-сосудистой причины, нефатальный инфаркт миокарда, нефатальный инсульт, экстренная реваскуляризация целевого сосуда в течение 30 дней или повторная госпитализация по причине коронарно-ишемических событий). ОКС – острый коронарный синдром, ПКТ – первичные конечные точки (нефатальный инфаркт, нефатальный инсульт, смерть от сердечно-сосудистой причины), ЧКВ – чрескожное коронарное вмешательство.

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