COMPARATIVE EVALUATION OF THE EFFECTIVENESS OF RESVERATROL AND QUERCETIN IN PATIENTS WITH CORONARY HEART DISEASE ACCORDING TO DAILY HOLTER MONITORING OF ELECTROCARDIOGRAM

Abstract. The leading cause of death in the world remains Coronary Heart Disease (CHD), despite the many treatments being developed. Therefore, the search for new effective methods of treating CHD is extremely relevant. One of the pathogenetic mechanisms of atherosclerosis progression, which is the morphological basis of CHD, is chronic systemic inflammation. Anti-inflammatory activity at different levels of pro-inflammatory signaling has polyphenols of plant origin, which determined the direction of our scientific search.

A prospective open-label randomized controlled trial was conducted in 108 people with CHD, I-II functional class (FC), with heart failure I-II FC. After analyzing the results of daily Holter monitoring (HM) of electrocardiogram (ECG), patients were randomized to 2 study groups and a comparison group. Along with the basic therapy of CHD, study group I prescribed 100 mg of resveratrol per day, group II -120 mg of quercetin per day. At 2 months, the electrocardiogram (ECG) was evaluated.

After the treatment, the total daily duration of depression episodes of the ST segment and the number of ST episodes decreased in patients of all study groups. However, under the influence of resveratrol, the total daily duration of depression episodes of the ST segment decreased by 43 % and significantly differed from the values of the comparison group and the group of patients taking quercetin. The maximum depth of depression significantly decreased only under the influence of resveratrol – by 15%. The number of premature atrial complexes in patients of all groups after treatment was also probably less. The number of premature ventricular complexes was significantly influenced only by therapy with resveratrol and quercetin: a decrease in the daily amount was 40% and 18%, respectively, which proves the superiority of the effectiveness of resveratrol.

It is determined that the use of resveratrol and quercetin in the complex therapy of patients with coronary artery disease had a positive effect on the
indicators of daily myocardial ischemia with the advantage of the effectiveness of resveratrol, which makes it possible to recommend it for wide use in the complex therapy of coronary artery disease.

**Keywords:** coronary heart disease, resveratrol, quercetin, daily Holter electrocardiogram monitoring, myocardial ischemia, extrasystoles.

**Poriv'nya otsivka efektivnosti resveratrolu ta kvercetinu u xvorikh na ischemic'nu xvorobu sercja za dannymi dobovogo Holteriv'skogo monituruvannya elektrokardiogramichy**

**Anotatsiya.** Prowadnoy primyno smerntnosti v sviti zalishaetsya'i sememichna xvoroba sercya (IXC), popri chislenno metodiy likuvannya, cho rozrobylayutsya. Tomu pozuy noviyh efektivnych metodiy likuvannya IXC vkray aktuallych. Odinom z patogenetichnych mekhaniizmov progresuvannya aterosklerozu, cho je morfolohichnoy osnovoyu IXC, vhihnoh sistemnye zapaleniya. Protizapalnoy aktivnosti na riznyh rivenakh probalnoy signalizatsii voldoyt' polifenoly roslinnoy poxodzhennya, cho y viznachilo napryamok nashho naukovogo pozuy.

Prowadnoy prospektivnoy v'akrte ranodomizovane kontorlyuvane doslidzheniya za uchastvo 108 osib, xvorih na IXC, I-III funktsionalnyy klass (FK), iz sercveyy nedostatnyst'yu ne vyche II FK. Pisla analizu rezultatov dobovogo Holteriv'skogo monituruvannya (XM) elektrokardiogramiy (EKG), xvorhi ranodomizovani v 2 grupi doslidzheniya ta grupu porivnya. Porяд z bazysnoy terapiyu IXC, grupi doslidzheniya I porivno 100 mg resveratrolu na doby, grupi II – 120 mg kvercetiny na doby. Cheress 2 miaschiy oqineno rezultaty (XM) elektrokardiogramiy (EKG).

Pisla provedenoy likuvannya u xvorikh usi doslidzuvanych grup zmenyshil'sya sumarna dobowa trivalist' epizoidiv depressii segmentu ST ta k'yl'kist' epizoidiv ST. Prute, pisla v'akrym resveratrolu sumarna dobowa trivalist' epizoidiv depressii segmentu ST zmenyshil'sya na 43 % y dostovirno vidr'izval'sya vidi nombrej grupy porivnya ta grupy xvorih, yki priyimali kvercetiu. Maksimal'na glibina depressii dostovirno zmenyshil'sya lishe pisla v'akrym resveratrolu – na 15 %. K'yl'kist' nashlyuchovykh ekstrastol u xvorikh usi grup p'iesla likuvannya, takoz, bua virogdno men'sho. Na k'yl'kist' nashlyuchovykh ekstrastol dostovirno v'akryl'na lihe terapiia iz zaostovuvannya reseveratrolu i kvercetiny: zmenyshennia dobovoy k'yl'kosti
Problem statement. Coronary heart disease (CHD) for many years in a row remains the leading cause of death from all causes in the world. Almost a third in the composition of cardiovascular diseases is disability due to CHD, while about 37 percent is disability in people of working age. Factors that cause an increase in cardiovascular diseases are mental stress, high-calorie nutrition, hypodynamia, environmental pollution, and an excess of xenobiotics [1,2]. In Ukraine, in conditions of war, the problem of chronic stress, which often causes post-traumatic stress disorder, is a particularly significant trigger and basis for the development of cardiovascular pathology [3].

The morphological basis of CHD is atherosclerosis (AS) [4]. Despite numerous scientific studies and the development of various methods of correction, the problem of AS treatment remains unresolved. That is why the search for new effective pathogenetically justified means of correction of AS and CHD is extremely relevant.

Analysis of recent research and publications. The pathogenesis of AS is complex and multicomponent, including chronic systemic inflammation (CHD) [5]. Proinflammatory molecules that produce immunocompetent cells involved in the process cause modification of low-density lipoproteins, endothelial dysfunction, etc. CD4+ T cells in the affected areas of blood vessels by activating nuclear factor kappa B (NF-kB) cause the formation of pro-inflammatory cytokines (CK) [6]. Therefore, the effect on chronic systemic inflammation (CSI) is appropriate in the treatment of CHD. Agents with proven anti-inflammatory activity are, in particular, polyphenols – substances of plant origin, which are widely used in clinical medicine. Among the representatives of polyphenols are stilbenes, flavonoids, lignins, phenolic acids [7]. The study of the effectiveness of polyphenols in CHD is a promising direction of scientific research.

Purpose of the article: to assess the effect of polyphenols – resveratrol and quercetin – on myocardial ischemia according to Holter ECG monitoring in patients with CHD.

Presentation of the main material. To fulfill the task, a prospective open randomized controlled trial was conducted with the participation of 108 persons of both sexes aged 53 + 6.1 years, patients with CHD: stable angina pectoris, II FC, HF 0-I. 30 healthy individuals constituted the control group.
On the eve of the examination, all patients personally signed an informed consent to participate in the study, in accordance with the requirements of the Helsinki Declaration of 1975, Order of the Ministry of Health of Ukraine No. 690 of 23.09.2009 "On Approval of the Procedure for Conducting Clinical Trials of Medicines and Examination of Clinical Trial Materials" and "Model Regulation on Ethics Commissions."

The criteria for inclusion in the study were the age of men and women of 40-75 years, the presence of CHD: angina pectoris of II FCTension, a stable course of at least 2 months and the patient's willingness to cooperate.

The exclusion criteria were a history of myocardial infarction, the presence of hypertension above the second stage of rhythm disturbance. (permanent form of atrial fibrillation or extrasystole of high gradations according to Lown), nodular blockades above grade II, complete bundle branch block, rheumatic diseases, heart defects, anemia, diabetes mellitus and other endocrine diseases, including obesity, chronic liver and kidney failure, oncological diseases, arthritis in the stage of exacerbation.

Patients underwent a comprehensive examination in accordance with the Unified Clinical Protocol of primary, secondary (specialized) and tertiary (highly specialized) medical care "Stable coronary heart disease" [8]. All study participants underwent Holter electrocardiogram monitoring (HM ECG).

Daily HM ECG was performed using the diagnostic complex "Beecardia" (Ukraine) version 8.3.0 (Diagnostic Systems LLC, Kharkiv). Three bipolar leads were used: Sky A leads (reflecting the anterior parts of the LV myocardium), modified thoracic SM-6 leads (anterior-lateral part of the myocardium), and Frank Y leads (posterior-diaphragmatic parts of the LV myocardium).

Episodes of ischemia were recorded, the criteria of which were horizontal depression of the ST > 100 μV segment and a minimum duration of depression of 60 s. The patient noted the pain component or its equivalents in the diary. The episodes of depression of the ST segment, which occurred asymptomatic, were also taken into account. The depression depth of the ST segment was determined 60 ms from point J after the QRS. The number of episodes of depression of the ST segment (ST depr), their total duration (Σ t) with counting in all three leads combined with the maximum depth (max) were estimated [9]. The number of extrasystoles – premature atrial complexes (PACs) and premature ventricular complexes (PVCs) was counted.

During the study, all patients with CHD received standard therapy – β blockers, statins, acetylsalicylic acid – for 2 months to stabilize the clinical state [8]. At the end of this period, patients were randomized by envelopes. 28 patients constituted study group I, which was additionally prescribed resveratrol at a dose of 100 mg per day per os before standard treatment. Study group II (28 people) prescribed quercetin at a dose of 120 mg per day per os. 50 patients made up the comparison group. 2 months after the start of therapy with resveratrol and quercetin, all three groups of patients underwent repeated HM ECG.
Statistical processing of the study results was carried out using the KyPlot program (version 6.0). The hypothesis of distribution normality was tested using the Shapiro-Wilk test, the belonging of each sample to one population was determined using the Kraskel-Wallis test. Using the paired Student's t-test, patient examination data were comparable before and after treatment. For comparison of three independent groups, the odd Student's t-test with Bonferoni correction was used. The data were indicated as $X + \sigma$, where $X$ is the average value, $\sigma$ is the average quadratic deviation. Differences in data were considered significant at a significance level of $p < 0.05$.

**Study results and discussion.**

After the treatment, the daily total depression ST (duration and number of episodes) decreased in patients of all study groups (Table 1). In patients who were on standard treatment, the $\Sigma t$ ST depr decreased by 19%, in patients who additionally took quercetin – by 26%, and under the influence of resveratrol – by 43% and probably differed from the values of the study group II and the comparison group and ($p < 0.05$).

**Table 1**

<table>
<thead>
<tr>
<th>Group / Parameter, X+σ</th>
<th>Comparison group, n=50</th>
<th>Study group I, n=28</th>
<th>Study group II, n=28</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before treatment</td>
<td>After treatment</td>
<td>Before treatment</td>
</tr>
<tr>
<td>ST depr, episodes.</td>
<td>12,4+2,9</td>
<td>9,0+2,9*</td>
<td>11,3+3,0</td>
</tr>
<tr>
<td>$\Sigma t$ ST depr, min</td>
<td>52,3 +11,2</td>
<td>40,3+12,2*</td>
<td>52,1+14,1</td>
</tr>
<tr>
<td>ST depr max, μV</td>
<td>235,4+47,4</td>
<td>225,5+35,5*</td>
<td>234,9+52,5</td>
</tr>
<tr>
<td>PAC, quantity, beats.</td>
<td>56,3 +40,3</td>
<td>39,0+29,4*</td>
<td>58,1+36,4</td>
</tr>
<tr>
<td>PVC, quantity, beats.</td>
<td>28,4+15,60</td>
<td>23,6+14,2</td>
<td>25,3+15,6</td>
</tr>
</tbody>
</table>

Note: * – Reliable difference before and after treatment ($p<0.05$),
• – reliable difference before and after treatment ($p<0.001$).
# – reliable difference between I and II study groups after treatment ($p<0.05$).

In the comparison group, the number of episodes of ST depr decreased by 15%, in the study group I – by 33%, in the study group II – by 27%. There was no significant difference in values between the groups after treatment. In the comparison group and study group II, ST depr max decreased by 7% and 11%, respectively, but there was no statistically significant difference before and after treatment in these groups, in contrast to study group I, where the difference after treatment was significant ($p < 0.05$).
The number of PACs in patients of all study groups after a two-month treatment period was less (p < 0.05): in the conditions of standard therapy – by 29%, in study group I – by 45%, in study group II - 38%. (Table 1). The number of PVCs significantly decreased only under the influence of resveratrol and quercetin, which amounted to 40% and 18%, respectively.

Various scientific studies have determined the positive effects of quercetin and resveratrol on the vascular wall and microcirculation. Quercetin is known to have a ruthin-like membrane stabilizing effect. In the experiment, quercetin increased the bioavailability of nitric oxide (NO). Due to the activation of the phosphorylation process, which ensured vasodilation [10]. Quercetin modulates mitochondrial activity, which activates cellular respiration during the formation of adenosine triphosphate [11]. It has also been found that quercetin has the ability to resist the activity of the angiotensin-converting enzyme, and, accordingly, to reduce vasoconstriction and systemic inflammation [12]. In our study, quercetin less effectively than resveratrol affected the ectopic activity of the myocardium, which may be due to its low bioavailability [13].

Our data on the anti-ischemic action of resveratrol are consistent with previous studies. Resveratrol, according to Cruz M.N. [14], promotes NO synthesis, stimulates estrogen receptors, providing vasodilation and cardioprotection. Also, resveratrol showed an antioxidant and endothelioprotective effect on blood vessels, in particular, coronary arteries [15].

The anti-ischemic properties of resveratrol can also be realized through its participation in preconditioning by activating the A1- and A3-receptors of adenosine, a number of intracellular kinases, and adenosine diphosphate-dependent K+ channels [16, 17]. According to the results of the study Lina Y. And colleagues, resveratrol showed the ability to block the channel of transient receptor potential (TRP) A1, which determines its antinociceptive, anti-inflammatory and antioxidant properties [18]. Improvement of microcirculation in the myocardium can also be due to blocking of platelet activation and aggregation by resveratrol [19].

Under the conditions of ischemia, under the influence of reactive oxygen species and cytokines, the formation of pain mediators increases and vagal nociceptive impulse increases [20,21]. Reduction of pro-inflammatory signal transduction by resveratrol and quercetin is, in our opinion, one of the determining mechanisms of their anti-ischemic action with a predominance of the effectiveness of resveratrol, which is also consistent with the results of our previous studies [22].

**Conclusions.** Thus, the use of both polyphenols studied in the complex therapy of patients with stable CHD had a positive effect on the electrical stability and myocardial ischemia, with the advantage of the effectiveness of resveratrol.

The obtained data allow us to recommend the active introduction of resveratrol in the treatment regimens of patients with CHD.

**References:**


**Література:**


