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Platelet aggregation and von Willebrand factor in patients with artherial hypertension combined with osteoarthritis

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Abstract

Objective: To investigate the platelet aggregation and level of von Willebrand factor in patients with hypertension and knee osteoarthritis.

Methods: The study involved 102 people: 29 patients with hypertension stage II combined with osteoarthritis stage II – main group; 29 patients with hypertension stage II – first group of comparison, 24 patients with osteoarthritis stage II – second group of comparison. The control group consisted of 20 almost healthy persons. Methods: ambulatory blood pressure monitoring, optical platelet aggregation test (inducers of platelet aggregation – adenosine diphosphate, collagen, thrombin, ristocetin (2 micromole)).

Results: Von Willebrand factor was higher in patients with hypertension combined with osteoarthritis and in patients with isolated hypertension (182.6 [171.6 – 201.7] %, 184.8 [171.6 – 207.7] % respectively), compared to patients with osteoarthritis (167 [144.6 – 181.6] %) and the control group (163.4 [151.7 – 172.3] %) ($p<0.05$). The degree of platelet aggregation with adenosine diphosphate in patients with hypertension combined with osteoarthritis and in patients with hypertension had significant correlations with level of total cholesterol and daily index of systolic blood pressure ($p <0.05$)).

Conclusion: Von Willebrand factor, degree platelet aggregation induced by adenosine diphosphate, collagen and thrombin were higher in patients with hypertension combined with osteoarthritis and in patients with hypertension compared to both the group of patients with osteoarthritis and control group ($p <0.05$). The degree of platelet aggregation with adenosine diphosphate was influenced by the level of total cholesterol and daily index of systolic blood pressure, the degree of platelet aggregation with collagen was influenced by daily index of systolic blood pressure and daily index of diastolic blood pressure ($p<0.05$).

Keywords: hypertension – osteoarthritis – platelet aggregation – von Willebrand factor – ambulatory blood pressure monitoring.

ОСТЕОАРТРОЗБЕН ҚОСАРЛАНҒАН АРТЕРИАЛДЫ ГИПЕРТЕНЗИЯСЫ БАР НАУҚАСТАРДАҒЫ ТРОМБОЦИТТЕР АГРЕГАЦИЯСЫ ЖӘНЕ ВИЛЛЕБРАНД ФАКТОРЫ

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ТҰЖЫРЫМДАМА

Мақсаты: Тізе буындарының остеоартрозыменен қосарланған артериалды гипертензиясы бар науқастардағы тромб түзілу қызметін және тамыр эндотелиінің жағдайын тромбоциттер агрегациясы деңгейі мен Виллебранд факторына байланысты бағалау.

Зерттеудің әдістері: 102 адам зерттелген:остеоатроздың II дәрежесімен қосарланған артериалды гипертензияның II стадиясы, 2 дәрежесімен 29 науқас – негізгі топ; артериалды гипертензияның II стадиясымен 29 науқас – салыстыратын бірінші топ, остеоартроздың II дәрежесімен 24 науқас – салыстыратын екінші топ. Бақылау тобы - жастары бойынша сәйкес келетін 20 сау адамдар. Артериалды қысымның тәуліктік мониторингі, тромбоциттер агрегациясының индукторларын қолданумен оптикалық агрегатометрия – аденозиндифосфат, коллаген, тромбин, ристомицин (2 мкмоль).

Нәтижелері: Остеоартрозбен қосарланған артериалды гипертензиясы бар науқастарда және артеиалды гипертензиясы бар науқастарда аденозинфосфатпен тромбоциттер агрегациясының дәрежесі жалпы холестерин көрсеткішінің жоғарлауына және систолалық артериалды қысымның түнгі уақытта төмендеу (p<0,05) дәрежесіне байланысты. Остеоартрозбен қосарланған артериалды гипертензиясы бар науқастарда және оқшауланған артериалды гипертензиясы бар науқастарда Виллебарнд факторы (182,6 [171,6 – 201,7] %, 184,8 [171.6 – 207.7] % тиісінше) остеоартрозы бар нуақастарға (167 [144.6 – 181.6] %) және бақылау тобына 163.4 [151.7 – 172.3]%) (p<0,05) қарағанда жоғары.

Қорытынды: Остеоартрозбен қосарланған артериалды гипертензиясы бар науқастарда және қосарланған патологиясы жоқ артериалды гипертензиясы бар науқастарда Виллебранд факторы, индукторлармен тромбоциттер агрегациясы деңгейінің көрсеткіші осеоартрозбен науқастардың және бақылау тобының көрсеткіштерімен салыстырғанда айтарлықтай жоғары (p<0,05). Аденозиндифосфатпен тромбоциттердің агрегациясының дәрежесіне жалпы холесериннніің жоғары деңгейі және систолалық артериалды қысымның түнгі уақытта томендеу деңгейі, коллагенмен тромбоциттердің агрегация дәржесінің жоғарлауына систолалық артериалды қысымның түнгі уақытта төмендеу деңгейі және диастолалық артериалды қысымның түнгі уақытта төмендеу деңгейі әсер еткен.

Маңызды сөздер: артериалды гипертензия – остеоартроз – артериялды қысымның тәуліктік мониторингі – тромбоцит тер агрегациясы – Виллебранд факторы.

АГРЕГАЦИЯ ТРОМБОЦИТОВ И ФАКТОР ВИЛЛЕБРАНДА У БОЛЬНЫХ АРТЕРИАЛЬНОЙ ГИПЕРТЕНЗИЕЙ В СОЧЕТАНИИ С ОСТЕОАРТРОЗОМ

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РЕЗЮМЕ

Цель исследования: оценить функцию тромбообразования и состояние сосудистого эндотелия у больных артериальной гипертензией в сочетании с остеоартрозом коленных суставов по уровню агрегации тромбоцитов и фактора Виллебранда.

Методы: Обследовано 102 человека: 29 больных артериальной гипертензией II стадии, 2 степени, в сочетании с остеоартрозом II ст. – основная группа; 29 пациентов с артериальной гипертензией II стадии – первая группа сравнения, 24 пациента с остеоартрозом II ст. – вторая группа сравнения. Группа контроля – 20 практически здоровых лиц сопоставимых по возрасту. Проводилось суточное мониторирование артериального давления, оптическая агрегатометрия с применением индукторов агрегации тромбоцитов – аденозиндифосфат, коллаген, тромбин, ристомицин (2 мкмоль).

Результаты: Степень агрегации тромбоцитов с аденозиндифосфатом у больных артериальной гипертензией в сочетании с остеоартрозом и у больных артериальной гипертензией достоверно связана с повышением показателя общего холестерина и степенью ночного снижения систолического артериального давления (p<0,05)). Фактор Виллебранда был повышен у больных артериальной гипертензией в сочетании с остеоартрозом и у больных с изолированной артериальной гипертензией (182,6 [171,6 – 201,7] %, 184,8 [171.6 – 207.7] % соответственно), по сравнению с больными остеоартрозом (167 [144.6 – 181.6] %) и с группой контроля (163.4 [151.7 – 172.3]%) (p<0,05).

Выводы: У больных артериальной гипертензией в сочетании с остеоартрозом и у больных с больных с артериальной гипертензией без сочетанной патологии фактор Виллебранда, показатель степени агрегации тромбоцитов с индукторами были достоверно выше по сравнению с показателями как в группе больных остеоартрозом, так и в группе контроля (p<0,05). На повышение степени агрегации тромбоцитов с аденозиндифосфатом влиял повышенный уровень общего холестерина и степень ночного снижения систолического артериального давления, на повышение степени агрегации тромбоцитов с коллагеном влияли степень ночного снижения систолического артериального давления и степень ночного снижения диастолического артериального давления (p<0,05).

Ключевые слова: артериальная гипертензия – остеоартроз – суточное мониторирование артериального давления – агрегация тромбоцитов – фактор Виллебранда.

Introduction

Hypertension remains the most prevalent and preventable cause of cardiovascular and cerebrovascular disease. [1]. The presence of high blood pressure enlarges probability of myocardial infarction in 2 times, heart failure in 4 times, stroke in 3.7 times [2]. The World Health Organization (WHO) defines hypertension as “the leading global risk of increasing of death from cardiovascular disease in the world” [3, 4]. According to the WHO, 1.5 billion people, including 30–45% of European population, have high blood pressure (BP) for today [5].

Cardiovascular diseases are the reason of about 17 million death cases in a year at the global level, it is nearly one third of total number of deaths [3]. Complications of HT causes 9.4 million deaths worldwide each year [4]. Not less than 45% of the deaths caused by heart troubles and 51% of the cases of death caused by a stroke fall to the share of HT [6].

In Ukraine, every third adult suffers from HT [7]. Thus, in 2012 in Ukraine there were 12286.8 cases, while the prevalence of HT was 32780.9 per 100 thousand of population [8].

Ukraine ranks first in mortality due to complications of HT among the European countries [5]. Also, there causes concern the fact that mortality from cardiovascular diseases in working age people in Ukraine is 3-5 times higher than those in other European countries, with a tendency to increase of mortality [7].

It is necessary to mark that the frequency of HT origin increases with age, at the same time HT even more often is accompanied by associated diseases, first of all - joint pathology [9]. So, in Europe where exist a problem of aging of the population (25.6% are people ≥55 years), osteoarthritis (OA) is one of the most frequent forms ofjoints diseases, which accounts for 60-70% of all diseases of the joints [9, 10]. European researchers pay attention to the high incidence of HT in patients with diseases of the joints [11]. And it is noted that joint disease in combination with HT is the most common chronic condition in the elderly persons, because about 36% of patients with HT suffer from joint diseases and 50% of patients with diseases of the joints have concomitant cardiovascular disease [12].

About 20% of elderly population need to take analgetic drugs because of chronic pain, often non-steroidal anti-inflammatory drugs (NSAIDs) at high doses and without any control, which can cause the development of multiple side effects and, in particular, creates pathogenic conditions for progression and complication of HT because promotes reducing the synthesis of prostaglandin E2 and prostacyclin, which have vasodilatative effect, while the synthesis of thromboxane A2, which causes vasoconstriction, doesn’t change [13].

Lots of clinical trials, such as ALLHAT, ACCOMPLISH, ASCOT-LLA, APOLLO, CHHIPS are aimed to find out the

most appropriate, safe and effective therapy for hypertension and prediction of the development of cardiovascular disorders, in which not the least role is played by thrombosis and endothelial dysfunction [5]. Hemodynamic changes that lead to the disturbance of hemostasis and thrombolysis occur in the early stages of HT. Inflammation and subsequent intake of NSAIDs in patients with OA also contribute to the imbalance between thromboxane synthesis in platelets, which have prothrombogenic action and "antithrombogenic" eicosanoids (prostacyclin), which ultimately leads to increased risk of thrombosis [14]. This problem necessitates studying the platelet aggregation and level of von Willebrand factor in patients with HT combined with OA [14].

Objectives: to investigate the platelet aggregation induced by adenosine diphosphate, collagen and thrombin, and level of von Willebrand factor in patients with HT combined with knee OA.

Materials and methods

Our prospective study included 102 people. They were divided in 3 groups: main group included 29 male patients with HT stage II, 2nd degree combined with knee OA stage II according to Kellgren-Lawrence, with dysfunction of joints (JDF) of the 1-2 degree, age 40-65 years (mean age – 54.33±1.82 years). The first comparison group consisted of 29 patients with HT stage II, degree 1–2, the second comparison group consisted of 24 patients with OA stage II according to Kellgren–Lawrence, with JDF 1–2 degree (mean age – 53.64±1.71 years and 55.81±1.67 years respectively). The average duration of the HT in patients with HT combined with OA was 10.08±0.72 years, in patients with isolated HT – was 10.17±0.61 years. The duration of OA – in patients with HT combined with OA was 7.64±0.83 years, in patients with isolated OA was 8.31±0.91 years. Control group included 20 almost healthy individuals. This study was a part of the PhD research, which was approved by the ethics committee of SE "Dnipropetrovsk medical academy of Health Ministry of Ukraine" protocol № 1 from 18.01.2015.

All patients of all groups were comparable with the main group in age, sex, duration of diseases. Diagnosis of "Arterial hypertension" was put according to the recommendations of the Ukrainian Association of Cardiology (2012), the Order of the Ministry of Health of Ukraine № 384 from 24.05.2012 [15, 16]. Diagnosis "Osteoarthritis" was put according to clinical and radiological criteria of the American College of Rheumatology, EULAR recommendations from 2009 and formulated as required by the Ministry of Health of Ukraine according to the Order № 676 "On approving the protocols of care in specialty «Rheumatology»" from 12.10.2006 [17, 18, 19].

Criteria for inclusion in research: presence of verified diagnosis of HT of the II stage, 2nd degree, combined with verified diagnosis of knee OA of the II stage with JDF 1–2 degree; age of patients is 40–65 years; receiving the voluntary informed consent to participation in research.

Exclusion criteria: age less than 40 years and more than 65 years; established and verified diagnosis of ischemic heart disease; HT of the III stage and/or 3rd degree; chronic heart failure of the III–IV functional class; cardiac arrhythmia that causes a violation of hemodynamics and requires correction with the use of antiarrhythmic drugs; diabetes mellitus; hyper- and hypothyroidisms; chronic renal insufficiency (glomerular filtration rate (GFR) <60 ml / min / 1,73 m2); obesity of the III–IV degree; tuberculosis, cancer, any chronic disease exacerbation.

Body mass index, waist size was defined in all patients, also there were held general clinical studies (complete blood count, urinalysis, blood chemistry, including total cholesterol, uric acid, C–reactive protein).

To confirm the presence and nature of HT, patients had 24–hour ambulatory blood pressure monitoring with "AVR–01" («Solveig», Ukraine). Measurements were carried out every 15 minutes during daytime activity and every 30 minutes during the night.

We analyzed the average values of systolic and diastolic blood pressure (SBP and DBP). Data were assessed daily and in day and night time. Previous calculations of average values for blood pressure in night time sleep and daytime hours were used in order to reveal the adequacy of daily (circadian) rhythm of blood pressure, which was estimated according to the degree of reduction of SBP and DBP at night.

According to the degree of nocturnal BP reduction there were distinguished the following groups of patients and types of daily blood pressure curves: patients with normal blood pressure reduction at night (degree of reduction = 10–20%) – type «dippers», patients with insufficient nocturnal reduction of blood pressure (degree of reduction <10%) – «non-dippers», patients with nocturnal increase of blood pressure (degree of reduction has a negative value) – «night-peakers», patients with excessive nocturnal reduction of blood pressure (degree of reduction > 20%) – «over-dippers».

In order to assess the platelet aggregation properties there was held optical platelet aggregation test with determination of degree, time and velocity of platelet aggregation. There were used adenosine diphosphate (ADP), collagen, thrombin (2 micromole) as inducers of platelet aggregation. Also, level of von Willebrand factor was determined using platelet aggregation with ristocetin (2 mM) (platelet aggregation analyzer AR 2110, SEC "Solar").

For confirming the diagnosis of OA there were used data of anamnesis, physical examination and x–ray examination of joints.

Statistical analysis of the research results was performed using the software package STATISTICA (6.1). There were analyzed a type of quantitative data distribution using W–test of Shapiro–Wilk. Average values were determined with averages (M) and standard error (± m) for normal type of distribution and median (Me) with upper and lower quartiles ([25% – 75%]) for abnormal type of distribution. Authenticity of differences between the determined data was carried out with t–criterion of Student for normal type of distribution and U–Mann–Whitney criterion for abnormal type of distribution and number of patients less than 30 in each group. Dependence between variables was estimated using Spearman correlation coefficient (R). The results were considered as statistically significant at $p < 0.05$.

Results

Patients with HT mostly complained about periodical headache – 58 (100%), dizziness, flickering flies in front of the eyes – 8 (13.8%), periodical blood pressure increase – 36 (62 %).

Patients with OA most often complained about joint pains – 53 (100%), impaired walking – 34 (64.2%), limitation of movement in knee joints – 36 (68%). On examination, there were also determined: pain in the joint projection – in 33 patients (62.2%), limiting flexion – in 29 (54.7%), crunching and crackling during movement – in 21 (39.6%). X–ray examination determined exacerbation and prolongation of intercondylar

tuberosity in 40 patients (75.5%), sclerosis of the articular surfaces –in 25 patients (47.2%), joint space narrowing – in 18 patients (34%), osteophytes – in 7 patients (13.2%).

The average body mass index in patients with HT in combination with OA was 31.2 [26.18 – 35.1] kg/m2, in patients with HT was 26.6 [23.2 – 31.2] kg/m2, in patients with OA was 29.88 [27.4 – 35] kg/m2. Waist size in main group was 94 [85 – 104] cm, in patients with HT – 87 [80 – 99] cm, in patients with OA – 92 [86 – 100] cm.

Average daily pressure level in patients with HT in combination with OA was 144.3 [131.4 – 154.8] / 98.5 [91.7 – 106.5] mm Hg, in patients with HT – 142 [138.4 – 148.8] / 94.8 [85.0 – 102.8] mm Hg, in patients with OA was 121.6 [106.4 – 138.2] / 74 [65.2 – 83.3] mm Hg.

While analyzing the circadian rhythm of blood pressure in patients with HT combined with OA there was found that in 4 (13.8 %) patients a sufficient level of nocturnal reduction of blood pressure (normal type of BP daily curve – dippers) was determined, in 16 (55.2 %) patients was identified insufficient degree of blood pressure reduction (non-dippers), in 6 (20.7 %) was revealed an excessive blood pressure reduction at night (over-dippers), and in 3 (10.3 %) patients – increased blood pressure at night (night-peakers). SBP daily index was 8 [6 – 17], DBP daily index was 6 [0 – 18].

While analyzing the circadian rhythm of blood pressure in patients with isolated HT there was found that in 7 (24.1 %) patients was determined a sufficient level of nocturnal reduction of blood pressure (normal type of daily curve – dippers), in 14 (48.3 %) patients was identified insufficient degree of BP reduction (non-dippers), in 6 (20.7 %) was revealed an excessive blood pressure reduction at night (over-dippers). SBP daily index was 11 [5 – 19], DBP daily index was 11 [6 – 19].

While analyzing the circadian rhythm of blood pressure in patients with OA there was found that in 16 (66.7 %) patients was determined a sufficient level of nocturnal blood pressure reduction (normal type of BP daily curve – dippers), in 7 (29.2 %) patients was identified insufficient degree of blood pressure reduction (non-dippers). SBP daily index was 15 [6 – 21], DBP daily index was 14 [5 –20].

When analyzing biochemical parameters, attention was paid to the indicators of total cholesterol, uric acid and C-RP (Table 1).

Table 1 Average values of total cholesterol, uric acid and C–RP (Med [25% – 75%])

Indicator	Main group (Hypertension in combination with Osteoarthritis), n=29	1st group of comparison (Hypertension), n=29	2nd group of comparison (Osteoarthritis), n=24	Control group, n=20
Total cholesterol, mmol/l	5,54 [4,46 – 6,14]	5,44 [4,54 – 6,28]	5,17 [4,47 – 6,02]	4,44 [4,14 – 4,83]
Uric acid, μkmol/l	368 [319 – 434]	344 [261 – 351]	344 [301 – 368]	336 [282 – 379]
C-reactive protein, g/l	less than 6,0	less than 6,0	less than 12,0	less than 6,0

The tendency to increase of C-RP in OA patients in remission may indicate the presence of indolent inflammation that requires continuing treatment with NSAIDs and may increase the risk of further defeats of cardiovascular system in patients of this group.

When comparing the platelet aggregation induced by ADP, collagen and thrombin there were obtained the following data: (Table 2)

Table 1 Average values of platelet adhesion and aggregation induced by ADF, collagen and thrombin (Med [25% – 75%])

Indicator	Main group (Hypertension in combination with Osteoarthritis), n=29	1st group of comparison (Hypertension), n=29	2nd group of comparison (Osteoarthritis), n=24	Control group, n=20	p
Degree of aggregation with adenosine diphosphate,%	66.9 [57.9 – 79.4]*	63.5 [53.2 – 70.3] *	44.5 [39.7 – 52.9]	41.2 [35.0 – 48.0]	p1-2 = 0.19 p1-3 = 0.001 p2-3 = 0.002
Response time of aggregation, sec	386 [330 – 446]	426 [354 – 518]	451 [346 – 544]	462 [244 – 498]	p1-2 = 0.12 p1-3= 0.07 p2-3 = 0.86
Velocity of aggregation in 30 seconds	52.4 [42.4 – 66.4]*	54.9 [44.6 – 66.7]*	37.1 [25.1 – 43.8]	33.1 [25.9 – 42.1]	p1-2 = 0.84 p1-3 = 0.004 p2-3= 0.018
Degree of aggregation with collagen,%	63.4 [54.8 – 73.1]*	61.8 [55.7 – 70.8]*	44.9 [33.0 – 45.7]	42.7 [33.0 – 45.7]	p1-2 = 0,98 p1-3 = 0.007 p2-3=0,002
Response time of aggregation, sec	384 [324 – 446]	415 [349 – 498]	385 [313 – 484]	347 [283 – 431]	p1-2 = 0,27 p1-3 = 0,76 p2-3= 0,19
Velocity of aggregation in 30 seconds	39.4 [29.4 – 49.0]	41.6 [40.8 – 55.7]	44.0 [33 – 58.0]	35.5 [28.3 – 41.6]	p1-2 = 0.68 p1-3 = 0.37 p2-3=0.33
Degree of aggregation with thrombin, %	70,9 [59.8 – 86.7]*	70,3 [50.6 – 92.4]*	58.8 [44.5 – 76.4]*	38.3 [35.6 – 45.3]	p1-2 = 0,9 p1-3 = 0,019 p2-3= 0,049
Response time of aggregation, sec	448 [340 – 551]	458 [355 – 551]	521 [282 – 579]*	436 [322 – 519]	p1-2 = 0.85 p1-3 = 0.36 p2-3= 0.36
Velocity of aggregation in 30 seconds	49.8 [42.6 – 56.8]*	51 [36 – 68.8]*	42.4 [29.2 – 47.2]	36.5 [21.8 – 43.8]	p1-2 = 0.58 p1-3 = 0.028 p2-3=0.022
Von Willebrand Factor, %	182.6 [171.6 – 201.7]*	184.8 [171.6 – 207.7]*	167 [144.6 – 181.6]	163.4 [151.7 – 172.3]	p1-2 = 0,72 p1-3 = 0,01 p2-3= 0,004

Note: * – reliability of distinctions between results in comparison with group of control < 0.05

Von Willebrand factor, as an indirect indicator of vascular endothelium damage, was significantly higher in patients with HT combined with OA and increased in patients with isolated HT (182.6 [171.6 – 201.7] %, 184.8 [171.6 – 207.7] % respectively) in comparison with OA patients (167 [144.6 – 181.6] %) and the control group (163.4 [151.7 – 172.3] %), which may indicate more expressed endothelial damage with further development of its dysfunction ($p<0.05$).

At the same time, patients with HT combined with OA and patients with isolated HT had significantly higher degree of platelet aggregation with ADP (66.9 [57.9 – 79.4] %, 63.5 [53.2 – 70.3] % respectively) in comparison with OA patients (44.5 [39.7 – 52.9] %) and the control group (41.2 [35.0 – 48.0] %) ($p<0.05$). Also these patients had increased velocity of platelet aggregation with ADP for 30 sec (patients with HT combined with OA – 52.4 [42.4 – 66.4], patients with isolated HT – 54.9 [44.6 – 66.7]) in comparison with OA patients (37.1 [25.1 – 43.8] %) and the control group (33.1 [25.9 – 42.1] %) ($p<0.05$). So, it is possible to consider that increased initiation of irreversible aggregation of circulating platelets takes place.

Also, patients with HT combined with OA and patients with isolated HT had significantly higher degree of aggregation with collagen (63.4 [54.8 – 73.1] %, 61.8 [55.7 – 70.8] % respectively) comparing to patients with OA and control group (44.9 [33.0 – 45.7] %, 42.7 [33.0 – 45.7] % respectively), what indicates an increased adhesion of platelets to collagen of the injured vascular endothelium ($p<0.05$).

Also, a significant increase in degree of thrombin aggregation in all groups of patients was observed (HT combined with OA – 70.9 [59.8 – 86.7%, HT – 70.3 [50.6 – 92.4] %, OA – 58.8 [44.5 – 76.4] % in comparison with the group of control – 38.3 [35.6 – 45.3]. But patients with HT combined with OA and patients with isolated HT also had a significantly increased velocity of aggregation with thrombin in 30 seconds (49.8 [42.6 – 56.8] %, 51 [36 – 68.8] % respectively) comparing to patients with OA and control group (42.4 [29.2 – 47.2] %, 36.5 [21.8 – 43.8] % respectively). These data indicate the stimulation of endothelin–1 synthesis with subsequent disturbance of procoagulants and anticoagulants ratio and can promote further endothelial dysfunction in vessels ($p<0.05$).

When determining the correlative relationships according to Spearman there was revealed that degree of platelet aggregation with ADP in patients with HT combined with OA and in patients with HT had reliable connections with level of total cholesterol ($r = 0.44$; $p <0.05$) and SBP daily index ($r = -0.53$; $p<0.05$).

At the same time, there was found a significant correlation between the degree of platelet aggregation with collagen and SBP daily index ($r = -0.58$; $p<0.05$) and DBP daily index ($r = -0.56$; $p <0.05$). Also, in patients with isolated HT was found correlative relationship between values of von Willebrand factor and level of total cholesterol ($r = 0.49$; $p<0.05$) (Figure 1).

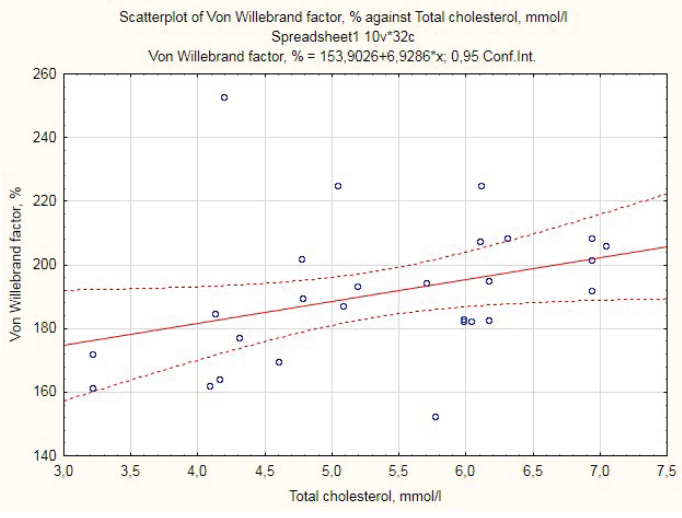

Figure 1- Correlation between the degree of von Willebrand factor and level of total cholesterol in hypertensive patients.

Discussion

In our study we revealed, that patients with HT combined with OA and patients with isolated HT mostly had insufficient degree of blood pressure reduction (non-dippers), but patients with HT combined with OA have more decreased SBP daily index and DBP daily index. In 29.1 % of patients with OA, despite the fact of absence of complains which are characteristic for HT, was identified insufficient degree of blood pressure reduction (non-dippers) and in 4.1 % was identified an excessive blood pressure reduction at night (over-dippers), which indicates the further possible occurrence of cardiovascular disease in these patients.

The tendency to increase of C-RP in OA patients in remission may indicate the presence of indolent inflammation that requires continuing treatment with NSAIDs and may increase the risk of further injury of cardiovascular system in patients of this group.

Von Willebrand factor, as an indirect indicator of vascular endothelium damage, was significantly higher in patients with HT combined with OA and increased in patients with isolated HT compared to patients with OA, which may indicate more expressed endothelial damage with further development of its dysfunction. At the same time, patients with HT combined with OA and patients with isolated HT had significantly higher degree and velocity of platelet aggregation with ADP. So, it is possible to consider that increased initiation of irreversible platelet aggregation takes place. Also, patients with HT combined with OA and patients with isolated HT had significantly higher degree of aggregation with collagen, what indicates an increased adhesion of platelets to collagen of the injured vascular endothelium. Also, a significant increase in degree of thrombin aggregation was observed in all groups of patients, but patients with HT combined with OA and patients with isolated HT also had a significantly increased velocity of aggregation with thrombin in 30 seconds. These data indicate the stimulation of endothelin–1 synthesis with subsequent disturbance of procoagulants and anticoagulants ratio and can promote further endothelial dysfunction in vessels.

When determining the correlative relationships according to Spearman there was revealed that degree of platelet aggregation with ADP in patients with HT combined with OA and in patients with HT had reliable connections with the level of total cholesterol. At the same time, there was found a significant correlation between the degree of platelet aggregation with collagen and SBP daily index. Also, there was found correlative relationship between values of von Willebrand factor and level of total cholesterol.

In modern references there is discussed a question of the cardiovascular complications increased risk, which appears

when platelet dysfunction exists, so the study of platelet aggregation degree inducted by ADP, collagen, thrombin, and von Willebrand factor in patients with HT is quite relevant [16, 20, 21]. Authors Medvedev I.N.,Skoryatina I.A. (2013) indicates that one of the most common causes of death in the developed countries are cardiovascular diseases, which are often caused by thrombotic events in the vessels of vital organs [20].

HT is one of the most widespread among all cardiovascular diseases, and it is often combined with dyslipidemia. This combinationvery actively violates platelet function with the subsequent development of thrombosis, and it is confirmed in article of Medvedev I.N. in coauthorship with Gromnatsky N. I. and Skoryatina I. A. [21, 22].

BMI and waist size were increased in all groups of patients. Despite the lack of a reliable difference between groups, these indicators were high exactly in group with the combined pathology of HT and OA. According to the data which were received by Belovol A.N. (2007), Hromylev A.V. (2015), obesity has a significant negative impact not only on endothelial function causing induction of expression of TNF-alpha, IL-8 and cell adhesion molecules, but also affects platelet function by decreasing the production of adiponectin thereby contributing to increasing the risk of cardiovascular complications development [23, 24].

At the same time Shanchenko S.A., Lipatova T.E. pay attention to the fact that when BMI is above normal characteristic, there appears a decrease in the elasticity of the vascular wall, more expressed in patients with elevated blood pressure [25]. Depression of endothelium function in arteries of small muscular type is characteristic feature of patients with obesity [26]. An important indicator of growing thrombotic danger in patients with HT is activation of platelet adhesion and aggregation [26]. At the same time, these authors point out that the mechanism of platelet hemostasis disorders in hypertensive patients is not enough studied and that it is especially important to develop tactics of its correction [25].

In patients with OA the above stated indicators significantly didn't differ from indicators in persons of control group, most likely due to the fact that a week before starting of the study in patients were canceled NSAIDs, which negative effect was determined by a decrease in synthesis of prostaglandin (PG) E2 and prostacyclin, that have antithrombotic and vasodilatative effect according to observations of Eliseev MS, Barskova V.G. [14].

Also, the likely explanation is that studied patients were diagnosed with isolated osteoarthritis of the knee, not polyosteoarthritis, which, according to Alekseenko E.Y., Zwinger S.M. increasingly provides effects on platelet function [27].

At the same time despite normal levels of von Willebrand factor and degree of platelet aggregation inducted by ADP and collagen, in patients with OA was revealed a significant prolongation of platelet aggregation time with ADP, which indicates increased propensity for initiating of irreversible aggregation of circulating platelets. There is also noted the increase in degree of platelet aggregation induced by thrombin, which is consistent with the literature. So, Kurkina I.A. points at the fact that when there is an activation of thrombogenesis, thrombin forms a blood clot, even with low level of procoagulants [28]. According to Drobysheva V.A., Egorova E.A., Logacheva G.S., Filatov O.M. increase in thrombin levels is associated with increased membranous activation of platelets and intracellular synthesis of endogenic proagregants that leads to the stimulation of the endothelin-1 synthesis with the subsequent disturbance of procoagulant and anticoagulant ratio and promotes further endothelial dysfunction [29].

The revealed dependence of platelet aggregation from indicators of ambulatory blood pressure monitoring is confirmed with data obtained by Kislyak O. A., Postnikova S. L., Kopelev A. A., and also Delyagina V. M. and coauthors though they point only to an indirect role of the increased platelet aggregation in development of cardiovascular accidents. The data, obtained by authors, confirms the need of further studying in problem of platelet function change [26, 30].

The limitations of study were: age (40–65 years), stage and degree of HT and OA (stage, 2nd degree, combined with verified diagnosis of knee OA of the II stage with JDF 1–2 degree), patients shouldn't receive NSAID's and antihypertensive drugs during 10 days before studying, they shouldn't have established and verified diagnosis of ischemic heart disease; HT of the third stage and/or 3rd degree; chronic heart failure of the III–IV functional class; cardiac arrhythmia that causes a violation of hemodynamics and requires correction with the use of antiarrhythmic drugs; diabetes mellitus; hyper- and hypothyroidism; chronic renal insufficiency (glomerular filtration rate (GFR) <60 ml / min / 1,73 m2); obesity of the III–IV degree, tuberculosis, cancer, any chronic disease exacerbation, pregnancy, lactation, receiving the voluntary informed consent to participation in research.

Conclusions

Excessive body mass was revealed in all groups of the examined patients, which is one of the basic risk factors in the development of endothelial dysfunction and diseases of the cardiovascular system, which, if there is a presence of comorbidities (including OA), may lead to increased platelet aggregation and development of cardiovascular accidents. The analysis of blood pressure circadian rhythm showed that despite the lack of significant differences, circadian rhythm indexes – SBP and DBP were closer to normal in the group of patients with isolated HT in comparison with group of patients with HT combined with OA; in 26,7% of patients with OA was identified insufficient degree of blood pressure lowering (non-dippers). In patients with HT combined with OA and in patients with isolated HT degree of platelet aggregation induced by ADP and collagen were significantly higher in comparison with group of patients with OA and the control group, what confirms an increased initiation of irreversible aggregation of circulating platelets and an increased adhesion of platelets to the injured collagen of vascular endothelium in these patients. In patients with HT combined with OA and in patients with isolated HT was significantly increased von Willebrand factor, which testifies to the affection of endothelium with following dysfunction ($p<0.05$). The degree of platelet aggregation with thrombin was increased in all three study groups, indicating the probable stimulate of endothelin–1 synthesis with subsequent disturbance of procoagulant and anticoagulant ratio and contributes to endothelial dysfunction ($p<0.05$).

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