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Treatment of lower extremity peripheral arterial disease

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Contents

Editor's Welcome

Dear Colleagues,

For your attention, here is the new issue of the *International Heart and Vascular Disease Journal* published in Russian and English languages.

Five articles from different medical centres internationally present the results of their research and come to the following conclusions:

• The presence of peripheral arterial disease of the lower extremities increases the risk of death from all causes and cardiovascular system diseases, once again reminding us that atherosclerosis is a systemic disease and that approaches to prevention and treatment are related;

• Determination of polymorphic variants of some genes can be used to predict atrophic changes in the brain and cognitive dysfunction in patients with chronic heart failure of ischaemic origin;

• Therapeutic hypothermia has a cardioprotective effect and can be used to treat patients with myocardial infarction;

• Transthoracic echocardiography can determine right ventricular diastolic function in patients with aortic regurgitation;

• NT-proBNP plasma levels can be used for prognosis in patients with chronic heart failure and anaemic syndrome, and to select and evaluate a treatment's effectiveness; and,

• Also presented is a unique clinical case of an elderly man with atrial fibrillation who developed a spontaneous retroperitoneal psoas muscle hematoma during Rivaroxaban therapy.

I hope that the study results published in our journal will help you in treating your patients.. We would welcome any new manuscripts that can be shared with our readers.

Yours sincerely,
Rafael G. Oganov
President, Cardioprogress Foundation
Editor-in-Chief

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LEADING ARTICLE

Treatment of lower extremity peripheral arterial disease

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Abstract

Patients with lower extremity peripheral arterial disease (PAD) are at increased risk for all-cause mortality, cardiovascular mortality, and mortality from coronary artery disease (CAD). Smoking should be stopped and hypertension, dyslipidaemia, diabetes mellitus, and hypothyroidism treated. Statins reduce the incidence of intermittent claudication and improve exercise duration until the onset of intermittent claudication in patients with PAD and hypercholesterolaemia. Patients with PAD should be treated with high-dose statins which include atorvastatin 40 mg to 80 mg daily or rosuvastatin 20 to 40 mg daily. Antiplatelet drugs such as aspirin or clopidogrel, angiotensin-converting enzyme inhibitors, and statins should be given to patients with PAD unless contraindicated. Beta-blockers should be given if CAD, especially prior myocardial infarction (MI), is present unless contraindicated. Vorapaxar is an antiplatelet drug which reduces acute limb ischaemia and peripheral revascularization in patients with PAD but is contraindicated if there is a history of stroke, transient ischaemic attack, or bleeding in the head. Cilostazol improves exercise time until intermittent claudication. Exercise rehabilitation programmes should be used. Indications for lower extremity percutaneous transluminal angioplasty or bypass surgery are 1) incapacitating claudication in patients interfering with work or lifestyle; 2) limb salvage in patients with limb-threatening ischaemia as manifested by rest pain, non-healing ulcers, and/or infection or gangrene; and 3) vasculogenic impotence.

Keywords

Peripheral arterial disease; intermittent claudication; exercise rehabilitation; revascularization; aspirin; statins

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Introduction

Peripheral arterial disease (PAD) is chronic arterial occlusive disease of the lower extremities caused by atherosclerosis. PAD may cause intermittent claudication which is pain or weakness with walking that is relieved with rest. The Rutherford classification of PAD includes 7 stages [1]. PAD is classified as stage 0 if the person is asymptomatic, stage 1 if mild intermittent claudication is present, stage 2 if moderate intermittent claudication is present, stage 3 if severe intermittent claudication is present, stage 4 if ischaemic rest pain is present, stage 5 if the person has minor tissue loss, and stage 6 if the person has ulceration or gangrene.

If the arterial flow to the lower extremities cannot meet the needs of resting tissue metabolism, critical lower extremity ischaemia occurs with pain at rest or tissue loss. Critical ischaemia causes rest pain in the toes or foot with progression to ulceration or gangrene. Chronic arterial insufficiency ulcers commonly develop at the ankle, heel, or leg. Mummified, dry, black toes or devitalized soft tissue covered by a crust is gangrene caused by ischaemic infarction. Suppuration often develops with time, and dry gangrene changes to wet gangrene.

Risk factors

The prevalence of PAD increases with age. Modifiable risk factors that predispose to PAD include cigarette smoking [2-13], diabetes mellitus [2-12,14], hypertension [2-4,9-12,15,16], dyslipidaemia [2-5,7-12,14,17-19], obesity [20], the metabolic syndrome in women [21], and hypothyroidism [22]. These risk factors contribute to the development of PAD and to the increased risk for all-cause mortality, cardiovascular mortality, and cardiovascular events associated with PAD.

Coexistence of other atherosclerotic disorders

PAD coexists with other atherosclerotic disorders [4,12,23-28,29]. In a study of 1,886 men and women, 270 of 468 patients (58%) with PAD had coexistent CAD and 159 of 468 patients (34%) with PAD had prior ischaemic stroke [23]. In a study of 1,802 men and women, 161 of 236 patients (68%) with PAD had coexistent CAD and 100 of 236 patients (42%) with PAD had coexistent prior ischaemic stroke [24]. In 1,006 men and women, if PAD was present, 63% had coexistent CAD, and 43% had prior ischaemic stroke [4]. In 273 patients with CAD, the lower the ankle-brachial index (ABI), the higher the prevalence of 3-vessel or 4-vessel CAD [28]. Patients with PAD and CAD have more extensive and calcified coronary atherosclerosis, constrictive arterial remodelling, and greater disease progression [30]. Patients with PAD also have a higher prevalence of left ventricular systolic dysfunction than patients without PAD [31].

Cardiovascular mortality and morbidity

Patients with PAD are at increased risk for all-cause mortality, cardiovascular mortality, and cardiovascular events [7,32-39]. At 10-year follow-up of 565 men and women, PAD significantly increased the risk of all-cause mortality (relative risk = 3.1), of mortality from cardiovascular disease (relative risk = 5.9), and of mortality from CAD (relative risk = 6.6) [32]. At 4-year follow-up of 1,492 women, an ABI of 0.9 or less was associated with a relative risk of 3.1 for all-cause mortality after adjustment for age, smoking, and other risk factors [34]. At 7.5-year follow-up of patients in the Cardiovascular Health study in a propensity-matched study of community dwelling older adults, matched hazard ratios for PAD for all-cause mortality, incident heart failure, and symptomatic PAD were 1.57, 1.32, and 3.92, respectively [37]. In a well-balanced propensity-matched population of 2,689 patients with advanced chronic systolic heart failure, during 4.1 years of follow-up, PAD was significantly associated with increased mortality and hospitalization [38].

At 33-month follow-up of 414 patients with PAD and at 48-month follow-up of 89 patients without PAD followed in a vascular surgery clinic, the incidence of death, new stroke/transient ischaemic attack, new MI, new coronary revascularization, new carotid endarterectomy, or new PAD revascularization was significantly higher in patients with PAD (63%) than in patients without PAD (24%) [39]. PAD was a significant independent risk factor for all-cause mortality with a hazard ratio of 2.2.

Risk factor modification

Smoking cessation

Continuing smoking increases the risk of amputation in patients with intermittent claudication [40]. Patency in lower extremity bypass grafts is also worse in smokers than in non-smokers [41]. Smoking cessation reduces the progression of PAD to critical leg ischaemia and reduces the risk of MI and death from vascular causes [42]. Smoking cessation programmes should be strongly encouraged in persons with PAD (Table 1). Patients should be assisted with counselling and developing a plan for quitting that

may include pharmacotherapy and/or referral to a smoking cessation programme [43,44].

Approaches to smoking cessation include use of nicotine patches or nicotine polacrilex gum, which are available over the counter [45]. If this therapy is unsuccessful, nicotine nasal spray or treatment with the antidepressant bupropion should be considered [45,46]. A nicotine inhaler may also be used [47]. The dosage and duration of treatment of each of these pharmacotherapies are discussed in detail elsewhere [47]. Varenicline is also effective for smoking cessation [48]. Concomitant behavioural therapy may also be needed [49]. Repeated physician advice is very important in the treatment of smoking addiction.

Treatment of hypertension

Hypertension should be adequately controlled to decrease cardiovascular mortality and morbidity in patients with PAD [16,50] (Table 1). The blood pressure should be reduced to less than 140/90 mmHg [16]. In the Heart Outcomes Prevention Evaluation (HOPE) Study, 1,715 patents had symptomatic PAD, and 2,118 persons had asymptomatic PAD with an ABI less than 0.9 [50]. In the HOPE study, compared with placebo, ramipril 10 mg daily significantly reduced cardiovascular events by 25% in patients with symptomatic PAD [50]. In this study, ramipril reduced the absolute incidence of cardiovascular events by 5.9% in patients with asymptomatic PAD and by 2.3% in patients with a normal ABI [50].

Treatment of diabetes mellitus

Patients with diabetes mellitus and PAD and no CAD have a 1.5 times higher incidence of new coronary events than non-diabetics with PAD and prior MI [51]. The higher the haemoglobin A1c levels in patients with diabetes mellitus and PAD, the higher the prevalence of severe PAD [52]. Diabetes mellitus should be treated with the haemoglobin A1c level decreased to less than 7% to decrease the incidence of MI [53] (Table 1). The blood pressure should be reduced to less than 140/90 mmHg in diabetics with PAD [16] Diabetics with PAD should also be treated with high-dose statins which include atorvastatin 40 mg to 80 mg daily or rosuvastatin 20 to 40 mg daily [54].

Treatment of dyslipidaemia

Treatment of dyslipidaemia with statins has been documented to reduce the incidence of mortality, cardiovascular events, and stroke in patients with PAD [18,19,54-57]. At 5-year follow-up of 4,444 men and women with CAD and hypercholesterolaemia in the Scandinavian Simvastatin Survival Study, compared with placebo, simvastatin significantly decreased the incidence of intermittent claudication by 38% [55]. In a study of 264 men and 396 women with symptomatic PAD and a serum low-density lipoprotein (LDL) cholesterol of 125 mg/dL or higher, 318 of 660 patients (48%) were treated with a statin and 342 of 660 patients (52%) with no lipid-lowering drug [57]. At 39-month follow-up, treatment with statins caused a significant independent reduction in the incidence of new coronary events of 58%, of 52% in persons with prior MI, and of 59% in persons with no prior MI [57].

In the Heart Protection Study, 6,748 of the 20,536 patients (33%) had PAD [55]. At 5-year follow-up, treatment with simvastatin 40 mg daily caused a significant 19% relative reduction and a 6.3% absolute reduction in major cardiovascular events independent of age, gender, or serum lipids levels [55]. These data favour administration of statins to patients with PAD regardless of serum lipids levels.

Patients with PAD should be treated with high-dose statins to reduce cardiovascular mortality and morbidity and progression of PAD [54-57] and to improve exercise time until intermittent claudication [58-60] (Table 1). Statins also reduce perioperative MI and mortality [61,62] and 2-year mortality [62] in patients undergoing non-cardiac vascular surgery.

Other lipid-lowering drugs do not reduce cardiovascular events and mortality in patients with atherosclerotic vascular disease treated with statins [54]. Fenofibrate or fish oils may be used to treat patients with serum triglycerides greater than 500 mg/dL to prevent pancreatitis [54]. Niacin should especially not be administered because it does not reduce cardiovascular events and is associated with serious adverse events [63,64].

Increased plasma homocysteine

Increased plasma homocysteine level is a risk factor for PAD [65-68]. Lowering of increased plasma homocysteine levels can be achieved by a combination of folic acid, vitamin B6, and vitamin B12. However, double-blind, randomized, placebo-controlled data have not shown that reduction of increased plasma homocysteine levels will reduce coronary events and slow progression of PAD.

Hypothyroidism

Hypothyroidism is a risk factor for PAD [22]. However, there is no evidence showing that treatment with l-thyroxine will reduce the development of PAD or improve symptoms in patients with PAD.

Antiplatelet drugs

Antiplatelet drugs that have been demonstrated to decrease the incidence of vascular death, non-fatal MI, and non-fatal stroke in persons with PAD are aspirin, ticlodipine, and clopidogrel [69]. Aspirin plus dipyridamole has not been shown to be more efficacious than aspirin alone in the treatment of patients with PAD [69]. Oral platelet glycoprotein IIb/IIIa inhibitors have been shown to increase mortality in treating patients with CAD and have not been investigated in treating patients with PAD [70]. Adverse hematologic effects associated with ticlodipine limit the use of this drug in the management of PAD [71].

Thromboxane A2 induces platelet aggregation and vasoconstriction. Aspirin decreases the aggregation of platelets exposed to thrombogenic stimuli by inhibiting the cyclooxygenase enzyme reaction within the platelet and thereby blocking the conversion of arachidonic acid to thromboxane A2 [72]. Clopidogrel is a thienopyridine derivative that inhibits platelet aggregation by inhibiting the binding of adenosine 5'-diphosphate to its platelet receptor [73].

The Antithrombotic Trialists' Collaboration Group (ATCG) reported a meta-analysis of 26 randomized studies of 6,263 patients with intermittent claudication due to PAD [69]. At follow-up, the incidence of vascular death, non-fatal MI, and non-fatal stroke was 6.4% in patients randomized to antiplatelet drugs versus 7.9% in the control group, a significant reduction of 23% caused by antiplatelet therapy with significant reductions for all subgroups.

The ATCG reported a meta-analysis of 12 randomized studies of 2,497 patients with PAD undergoing peripheral arterial grafting [69]. At follow-up, the incidence of vascular death, non-fatal MI, and non-fatal stroke was 5.4% in patients randomized to antiplatelet drugs versus 6.5% in the control group, a significant reduction of 22% caused by antiplatelet therapy.

The ATCG also reported a meta-analysis of 4 randomized studies of 946 patients with PAD undergoing peripheral angioplasty [69]. At follow-up, the incidence of vascular death, non-fatal MI, and non-fatal stroke was 2.5% in patients randomized to antiplatelet drugs versus 3.6% in the control group, a significant reduction of 29% caused by antiplatelet therapy.

If one combines the 42 randomized studies of 9,706 patients with intermittent claudication, peripheral arterial grafting, or peripheral angioplasty, the incidence of vascular death, non-fatal MI, and non-fatal stroke at follow-up was significantly decreased 23% by antiplatelet drugs, with similar benefits among patients with intermittent claudication, those having peripheral arterial grafting, and those having peripheral angioplasty [69]. These data favour treatment with aspirin in men and women with PAD [69] (Table 1).

Aspirin

In high-risk patients, the incidences of vascular death, non-fatal MI, and non-fatal stroke were 19% with an aspirin dose of 500 to 1500 mg daily, 26% with an aspirin dose of 160 to 325 mg daily, 32% with an aspirin dose of 75 to 150 mg daily, and 13% with an aspirin dose of less than 75 mg daily [69]. Since aspirin doses greater than 150 mg daily do not reduce vascular death, non-fatal MI, and non-fatal stroke more than does an aspirin dose of 75 to 150 mg daily and cause more gastrointestinal bleeding than the lower doses, this author prefers an aspirin dose of 81 mg daily in treating patients with atherosclerotic vascular disease.

Clopidogrel

In the Clopidogrel versus Aspirin in Patients at Risk for Ischaemic Events (CAPRIE) trial, 5,795 patients with PAD were randomized to clopidogrel 75 mg daily and 5,797 patients with PAD were randomized to aspirin 325 mg daily [74]. At 1.9-year follow-up, the annual incidence of vascular death, non-fatal MI, and non-fatal stroke was 3.7% in patients randomized to clopidogrel versus 4.9% in persons randomized to aspirin, a 24% significant decrease with the use of clopidogrel [74].

On the basis of the available data, it is reasonable to treat patients with PAD with either aspirin or clopidogrel. Aspirin 75 to 325 mg daily or clopidogrel 76 mg daily are recommended by the 2011 updated *American College of Cardiology Foundation* (ACCF)/*American Heart Association* (AHA) guidelines to reduce the risk of MI, stroke, or vascular death in patients with PAD [43,75]. These guidelines recommend the use of aspirin or clopidogrel in patients with symptomatic atherosclerotic lower extremity PAD, including those with intermittent claudication or critical limb ischaemia, prior lower extremity revascularization (endovascular or surgical), or prior amputation for lower extremity ischaemia, with a class I indication [43,75]. These guidelines also recommend the use of aspirin or clopidogrel to reduce the risk of MI, or vascular death in asymptomatic patients with an ABI less than or equal to 0.90 with a class IIa indication [43,75].

Vorapaxar

Vorapaxar is a protease-activated receptor-1 antagonist. Of 26,449 patients with atherosclerotic vascular disease randomized to vorapaxar or placebo, 3,787

patients had PAD [76]. At 2.5-year follow-up, patients with PAD randomized to vorapaxar had a 6% insignificant reduction in MI, stroke or cardiovascular death, a significant 42% reduction in hospitalization for acute limb ischaemia from 3.9% to 2.3% (*P*=0.006), a significant 16% reduction in peripheral artery revascularization from 22.2% to 18.4% (*P*=0.017), and a significant 62% increase in bleeding from 4.5% to 7.2% (*P*=0.001) [76]. Vorapaxar has recently been approved by the *US Food and Drug Administration* to treat patients with PAD receiving aspirin or clopidogrel to reduce the need for peripheral artery revascularization. This drug should not be used in patients with a history of stroke or transient ischaemic attack or bleeding in the head.

Oral anticoagulants

In the Dutch Bypass Oral Anticoagulants or Aspirin Study, 2,690 patients were randomized after infrainguinal bypass surgery to aspirin 80 mg daily or to oral anticoagulation with phenprocoumon or acenocoumarol to maintain an INR of 3.0-4.5 [77]. At 21-month follow-up, there was no significant difference between the two treatments in the primary outcome of infrainguinal graft occlusion. There was no significant difference between the two treatments in the secondary outcomes of MI, stroke, amputation, or vascular death. However, persons treated with oral anticoagulant therapy had 1.96 times more major bleeding episodes than persons treated with oral aspirin [77]. The *ACCF/AHA* guidelines state that oral anticoagulant therapy with warfarin should not be given to reduce the risk of adverse cardiovascular ischaemic events in persons with atherosclerotic lower extremity PAD (class III indication with no benefit) [43,75].

Angiotensin-converting enzyme inhibitors

Data from the HOPE Study showed that ramipril 10 mg daily significantly decreased cardiovascular events in patients with symptomatic PAD and in patients with asymptomatic PAD [50]. Angiotensin-converting enzyme inhibitors as well as statins also have many pleiotropic effects to account for their vascular protective properties beyond their primary mode of action including inhibition of cellular proliferation, restoration of endothelial activity, inhibition of platelet reactivity, and an antioxidant potential [78]. The *ACC/AHA* guidelines recommend treating patients with PAD with angiotensin-converting enzyme inhibitors unless there are contraindications to the use of these drugs to reduce cardiovascular mortality and morbidity [43,75,79] (Table 1).

Table 1. **Medical treatment of peripheral arterial disease**

1	Smoking cessation programme
2	Treatment of hypertension with blood pressure reduced to less than 140/90 mmHg
3	Control diabetes mellitus with the haemoglobin A1c level reduced to less than 7%
4	Treat dyslipidaemia with high-dose statins
5	Antiplatelet drug therapy with aspirin or clopidogrel to reduce MI, stroke, or cardiovascular death with addition of vorapaxar considered to reduce peripheral artery revascularization
6	Treatment with an angiotensin-converting enzyme inhibitor
7	Treatment with beta-blockers in patients with CAD in the absence of contraindications to these drugs
8	Use of high-dose statins to reduce cardiovascular events and mortality and progression of PAD and to improve exercise time until intermittent claudication
9	Treatment with cilostazol in patients with intermittent claudication
10	Exercise rehabilitation programme
11	Foot care

Beta-blockers

Patients with PAD are at increased risk for developing new coronary events [7,32-39]. Many physicians have been reluctant to use beta-blockers in patients with PAD because of concerns that beta-blockers will aggravate intermittent claudication. However, a meta-analysis of 11 randomized controlled studies found that beta-blockers do not adversely effect walking capacity or the symptoms of intermittent claudication in patients with mild-to-moderate PAD [80].

An observational study was performed in 575 men and women with symptomatic PAD and prior MI [81]. Of the 575 patients, 85 patients (15%) had contraindications to the use of beta-blockers. Of the 490 patients without contraindications to the use of beta-blockers, 257 patients (52%) were treated with beta-blockers. Adverse effects causing cessation of beta-blockers occurred in 31 of the 257 patients (12%). At 32-month follow-up, use of beta-blockers caused a 53% significant independent decrease in the incidence of new coronary events in patients with PAD and prior MI [81]. In a vascular surgery clinic, 301 of 364 patients (83%) with PAD and CAD were treated with beta-blockers [82]. Beta-blockers should be used to treat CAD in patients with PAD in the absence of contraindications to these drugs (Table 1). The *ACC/AHA* guidelines state that beta-blockers are not contraindicated in treating patients with PAD [43,75,79].

Statins

On the basis of data from the Heart Protection Study, patients with PAD should be treated with statins regardless of age, gender, or initial serum lipids levels [56] (Table 1). Patients with PAD should be treated

with high-dose statins to reduce cardiovascular mortality and morbidity and progression of PAD [54-57] and to improve exercise time until intermittent claudication [58-60] (Table 1). Statins also reduce perioperative MI and mortality [61,62] and 2-year mortality [62] in patients undergoing non-cardiac vascular surgery.

In a study of 69 patients with intermittent claudication, a mean ABI of 0.63, and a serum LDL cholesterol of 125 mg/dL or higher, 3 of 34 patients (9%) treated with simvastatin and 6 of 35 patients (17%) treated with placebo died before the 1-year study was completed [58]. Compared with placebo, simvastatin significantly increased the treadmill exercise time until the onset of intermittent claudication by 24% at 6 months and by 42% at 1 year after therapy. In a study of 354 patients with intermittent claudication and hypercholesterolaemia, at 1-year follow-up, compared with placebo, atorvastatin 80 mg daily significantly improved pain-free treadmill walking distance by 40% and significantly improved community-based physical activity [59]. In a study of 86 patients with intermittent claudication and hypercholesterolaemia, at 6-month follow-up, compared with placebo, simvastatin 40 mg daily significantly improved pain-free walking distance and total walking distance on a treadmill, significantly improved the mean ABI at rest and after exercise, and significantly improved symptoms of claudication [60].

Statin use is also associated with superior leg functioning independent of cholesterol levels and other potential confounders [83]. The data suggest that non-cholesterol-lowering properties of statins may favourably influence functioning in persons with and without PAD [83].

Despite the data recommending use of statins, aspirin, and angiotensin-converting enzyme inhibitors or angiotensin receptor blockers for secondary prevention in patients with PAD, millions of adults in the United States with PAD are not receiving these drugs [84]. Use of these drugs in patients with PAD and no other cardiovascular disease was associated with a 65% significant reduction in all-cause mortality [84]. Statins also are associated with reduced amputation rates in patients with PAD [85,86].

Drugs to increase walking distance

Chelation therapy has been demonstrated to be ineffective in the therapy of PAD [87], has a class III indication for treating PAD, and may have harmful effects [75]. Numerous drugs have been shown to be ineffective in improving walking distance in patients with intermittent claudication [88,89]. Beraprost sodium, an orally active prostaglandin I2 analogue, was demonstrated to be no more effective than placebo in persons with intermittent claudication [90]. Oral vasodilator prostaglandins such as beraprost and iloprost have a class III indication for treating PAD [75]. Naftidrofuryl [91] and propionyl levocarnitine [92] have been reported to improve exercise walking distance in patients with intermittent claudication but have not been approved for use in the United States. Use of L-arginine, propionyl levocarnitine, and ginkgo biloba to improve walking distance is not established [75]. Use of vitamin E to treat intermittent claudication has a class III indication [75].

Two drugs, pentoxifylline and cilostazol, have been approved by the *United States Food and Drug Administration* for symptomatic treatment of intermittent claudication. However, many studies have found no consistent improvement with pentoxifylline in patients with intermittent claudication in comparison with placebo [93,94]. The clinical effectiveness of pentoxifyline to treat intermittent claudication is not established [75].

Cilostazol inhibits phosphodiesterase type 3, increasing intracellular concentration of cyclic adenosine monophosphate. Cilostazol suppresses platelet aggregation and also acts as a direct arterial vasodilator. Cilostazol has been documented in numerous trials to improve exercise capacity in patients with intermittent claudication [89,94-98], and in a dose of 100 mg twice daily, was shown to be superior to both placebo and pentoxifylline [97].

Cilostazol should be administered to patients with PAD to increase walking distance (Table 1) but should not be given to patients with PAD who also have heart failure. Other contraindications to the use of cilostazol include a creatinine clearance <25 mL/min, a known predisposition for bleeding, or coadministration of CYP3A4 or CYP2C19 inhibitors such as cimetidine, diltiazem, erythromycin, ketoconazole, lansoprazole, omeprazole, and HIV-1 protease inhibitors. The *ACCF/AHA* guidelines state cilostazol 100 mg orally 2 times daily is indicated to improve symptoms and increase walking distance in patients with intermittent claudication due to lower extremity PAD in the absence of heart failure with a class IA indication [75].

A randomized, placebo-controlled trial showed that in 212 patients with intermittent claudication due to PAD, 24-week treatment with ramipril caused a significant 75 second increase in mean pain-free walking time and a significant 255 second increase in maximum walking time [99]. Ramipril also signifi-

cantly improved the overall SF-36 median Physical Component Summary score by 8.2 [99]. Of 159 patients with intermittent claudication due to PAD, patients were randomized to 4 weeks of therapy with subcutaneous injections 3 times a week of granulocyte-macrophage colony-stimulating factor (GM-CSF) or placebo. At 3-month follow-up, treadmill walking performance was not improved by GM-CSF [100].

Exercise rehabilitation

Exercise rehabilitation programmes have been demonstrated to increase walking distance in persons with intermittent claudication through improvements in peripheral circulation, walking economy, and cardiopulmonary function [101,102]. The optimal exercise programme for improving claudication pain distance in patients with PAD uses intermittent walking to near-maximal pain during a programme of at least 6 months [103]. Strength training is less effective than treadmill walking [104]. The *ACC/AHA* guidelines recommend a supervised exercise programme for patients with intermittent claudication [75] (Table 1).

Supervised exercise training is recommended for a minimum of 30-45 minutes in sessions performed at least 3 times per week for a minimum of 12 weeks [75] and preferably for 6 months or longer [103]. Among persons with PAD, self-directed walking exercise performed at least 3 times weekly is associated with significantly less functional decline during the subsequent year [105]. A home-based walking exercise programme significantly improved walking endurance, physical activity, and speed in patients with PAD and should be used in patients unwilling to participate in a supervised exercise training programme [106].

Foot care

Patients with PAD must have proper foot care [75,107] (Table 1). They must wear properly fitted shoes. Careless nail clipping or injury from walking barefoot must be avoided. Feet should be washed daily and the skin kept moist with topical emollients to prevent cracks and fissures, which may have portals for bacterial infection. Fungal infection of the feet must be treated. Socks should be wool or other thick fabrics, and padding or shoe inserts may be used to prevent pressure sores. When a wound of the foot develops, specialized foot gear, including casts, boots, and ankle foot arthoses may be helpful in unweighting the affected area.

Lower extremity angioplasty and bypass surgery

Indications for lower extremity percutaneous transluminal angioplasty or bypass surgery are 1) incapacitating claudication in persons interfering with work or lifestyle; 2) limb salvage in persons with limb-threatening ischaemia as manifested by rest pain, non-healing ulcers, and/or infection or gangrene; and 3) vasculogenic impotence [108]. Percutaneous transluminal angioplasty can be performed if there is a skilled vascular interventionalist and the arterial disease is localized to a vessel segment less than 10 cm in length [108]. Compared to percutaneous transluminal angioplasty alone, stenting improves 3-year patency by 26%) [109]. After infrainguinal bypass surgery, oral anticoagulant therapy is preferable in persons with venous grafts, whereas aspirin is preferable in persons with non-venous grafts [77].

Percutaneous balloon angioplasty and/or stenting is indicated for short-segment stenoses, whereas multisegment disease and occlusions are most effectively treated with surgical revascularization [110]. Revascularization of PAD is discussed extensively elsewhere [75,107]. In patients presenting with severe limb ischaemia caused by infra-inguinal disease and who are suitable for either surgery or angioplasty, bypass surgery and balloon-angioplasty are associated with similar outcomes in terms of amputation-free survival [111]. Patients with intermittent claudication should be considered for revascularization to improve symptoms only in the absence of other disease that would limit exercise improvement such as angina pectoris, heart failure, chronic pulmonary disease, or orthopaedic limitations [75]. Endovascular intervention is not indicated as prophylactic therapy in an asymptomatic patient with lower extremity PAD (class III indication) [75]. Surgical intervention is not indicated to prevent progression to limb-threatening ischaemia in patients with intermittent claudication due to PAD (class III indication) [75].

However, 6-month outcomes from 111 patients with claudication due to aortoiliac PAD randomized to optimal medical therapy, optimal medical therapy plus supervised exercise, or optimal medical therapy plus stent revascularization showed that the greatest increase in treadmill walking performance occurred in the patients randomized to optimal medical therapy plus supervised exercise [112]. Cilostazol significantly reduced angiographic restenosis after endovascular therapy for femoropopliteal lesions with provisional nitinol stenting of femoropopliteal lesions in 200 patients [113].

Amputation

Non-randomized studies have shown that both immediate and long-term survival are higher in patients having revascularization rather than amputation for limb-threatening ischaemia [114,115]. However, amputation of lower extremities should be performed if tissue loss has progressed beyond the point of salvage, if surgery is too risky, if life expectancy is very low, or if functional limitations diminish the benefit of limb salvage [107].

Conclusion

In conclusion, patients with PAD are at increased risk for all-cause mortality, cardiovascular mortality, and mortality from CAD. Smoking should be stopped and hypertension, dyslipidaemia, diabetes mellitus, and hypothyroidism treated. Patients with PAD should be treated with atorvastatin 40 mg to 80 mg daily or rosuvastatin 20 to 40 mg daily. Antiplatelet drugs such as aspirin or clopidogrel and angiotensin-converting enzyme inhibitors should be given. Beta-blockers should be given if CAD, especially prior MI, is present unless contraindicated. Cilostazol improves exercise time until intermittent claudication. Exercise rehabilitation programmes should be used. Indications for lower extremity percutaneous transluminal angioplasty or bypass surgery are 1) incapacitating claudication in patients interfering with work or lifestyle; 2) limb salvage in patients with limb-threatening ischaemia as manifested by rest pain, non-healing ulcers, and/or infection or gangrene; and 3) vasculogenic impotence.

Conflict of interest: None declared

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REVIEW ARTICLE

Therapeutic hypothermia in the treatment of myocardial infarction with ST-segment elevation – state of the art for 2014

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Abstract
Therapeutic hypothermia is a modern procedure introduced into the cardiology guidelines in 2012. The main purpose of this state of the art for 2014 is to summarize relevant information about the use of therapeutic hypothermia in ST-elevation myocardial infarction (STEMI). Authors describe the role and benefits of the procedure, and review animal models and randomized clinical trials (COOL-MI, ICE-IT, RAPID MI-ICE, CHILL-MI) relating to hypothermia in STEMI. In conclusion we emphasize that results from randomised controlled trials indicate safe use and a cardioprotective effect of therapeutic hypothermia in patients with STEMI.

Keywords
Hypothermia, STEMI, CVD, infarction, cardioprotection, cooling

The fundamental principle of therapeutic hypothermia, involving a controlled reduction of body temperature to below 35°C, has not changed since its introduction [1]. However, its role in the treatment of emergencies has changed. The first attempts at using hypothermia in the treatment of cardiovascular disease (CVD) were made in cardiac centres during cardiac surgery procedures [2]. When used intraoperatively, it enables safe conduct of surgery that requires cessation of circulation for a short period of time, thereby reducing the risk of neurological complications and secondary heart failure.

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Therapeutic hypothermia was introduced to the modern cardiology relatively late. Only in 2012, it was included in the guidelines for treating STEMI, as a method recommended for patients after cardiac arrest to prevent secondary neurological damage (class of recommendation I, level of evidence B) [3]. Lowering the temperature of the central compartment inhibits adverse metabolic reactions associated with ischaemia and reperfusion. These positive effects include: 1) inhibition of adverse enzymatic reactions, 2) suppression of free radicals, 3) protection of the lipoprotein membranes, 4) reduction of oxygen demand in the areas of reduced perfusion, 5) reduction of intracellular acidosis, 6) inhibition of biosynthesis, 7) release and uptake of activating neurotransmitters [4].

The well-documented clinical efficacy of the therapeutic hypothermia in the prevention of the central nervous system injury gave rise to a hypothesis advertising its possible protective properties in myocardial reperfusion injury resulting from a MI. This hypothesis was first confirmed in the studies involving small animals, clearly indicating that mild cooling of the ischaemic muscle (by about 2-5°C) reduced the infarct size and improved cardiac output [5]. These results were verified in a large animal model (pig). Dae et al. conducted a study on a model of a MI of anterior wall (left anterior descending occlusion) in 22 individuals [6]. Hypothermia in the study group (34°C) was achieved by means of an intravascular catheter placed in the inferior vena cava. Histopathological analysis demonstrated a significant reduction in MI zone, reaching up to 80% (9% +/- 6% vs. 45 +/- 8%, *P* <0.0001). To evaluate the effect of hypothermia on hemodynamics of the circulatory system, the researchers also monitored the heart rate, stroke volume and cardiac output (duration of hypothermia, the heating phase, 30 min after achieving the normothermia). A significant physiological reduction of the heart rate during cooling, accompanied by a compensatory increase in the stroke volume (but constant cardiac output) were observed [6]. The results confirmed the clinical efficacy and safety of initiating the therapeutic hypothermia in large mammals with a large anterior MI (Figure 1).

The COOL MI study was the first study carried out in humans, whose aim was to assess the efficacy of the therapeutic hypothermia in reducing the infarct size [7]. It included patients with anterior and inferior MI and total duration of ischaemia less than 6 hours, excluding the patients with cardiogenic shock and those who suffered from the MI within

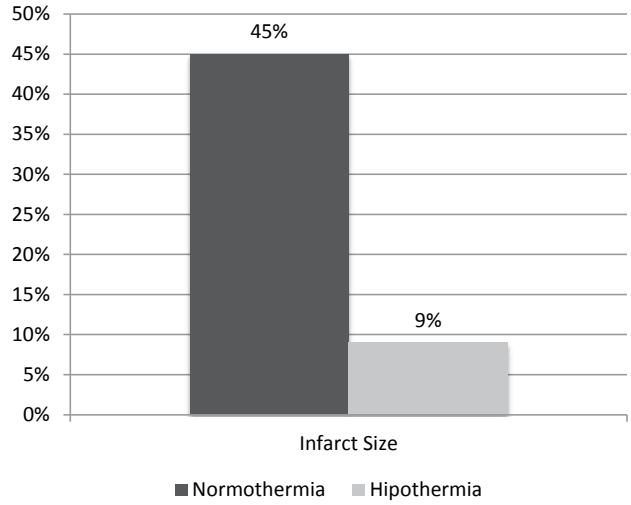

Figure 1. Effect of the therapeutic hypothermia on the size of left ventricular myocardial infarction (animal model)

the past month. Following randomisation, in half of the patients, apart from percutaneous coronary intervention (PCI), the endovascular therapeutic hypothermia was applied, using catheter of 10 French placed in the inferior vena cava (Repetitive, Radiant Medical). According to the protocol, the patients in the study arm were cooled during PCI to the target temperature of 32°C, with the intention of maintaining this temperature for a total of 3 hours. MI size was assessed by means of a single-photon emission computer tomography (SPECT) 30 days after PCI procedure. In neither of the groups an increased incidence of major cardiovascular complications (death, reinfarction, the need for repeat revascularisation, major bleeding) was observed. To the researchers' disappointment, the mean size of the MI assessed one month after the intervention did not differ between the groups (13.8% vs. 14.1%, ***P***=0.83) [7]. One year following the publication of the COOL MI study, the results of another clinical trial were reported that evaluated the clinical efficacy and safety of the therapeutic hypothermia in reducing the volume of myocardial necrosis in patients with STEMI – ICE-IT study[8]. Baseline clinical characteristics of the study group, including patients with anterior and inferior MI, were similar to the previous study. The second trial covered a total of 217 patients (108 in the hypothermia group and 109 in the control group). SPECT-based assessment of the MI size was performed on the 30th day after the intervention. However, there was still no significant improvement in the reduction of the infarction size in the patients treated with therapeutic hypothermia (10.2% vs. 13.2%, *P*=0.14) [8].

Detailed analysis of the data from these two studies provided valuable information that could help explain the differences in results between humans and animal models. In the COOL MI study, over 30% of patients did not reach the target temperature of 35°C at the time of reperfusion (balloon inflation, direct stent implantation). Only a post-hoc analysis, accounting exclusively for the patients who met this condition, confirmed a significant reduction in the size of myocardial injury (9.3% vs. 18.2%, *P*=0.05) [9]. In the ICE-IT study, the target temperature was also achieved in less than 62% of patients. Reduction of the infarct size was achieved in patients treated in the centres with high adherence to the study protocol (*P*=0.017). As shown in both studies, obtaining the hypothermia prior to a coronary reperfusion is a serious logistic problem, especially when the procedure is performed under time pressure, and is a key to a successful therapy.

Conclusions from the COOL MI and ICE-IT studies provided the basis for designing a third clinical trial called RAPID MI-ICE. The basic aim of the researchers was to cool all the patients included in the study to a temperature below 35°C before the reperfusion [10]. The study was carried out in a Swedish academic centre with extensive experience in therapeutic hypothermia treatments. It included 20 patients, half of whom were cooled using a high-performance endovascular system (RTx InnerCool, Philips). Necrosis size was assessed on the fourth day after PCI, using a nuclear magnetic resonance method (T2-weighted images). The mean temperature at the time of reperfusion was 34.7°C, and the threshold of below 35°C was achieved in all patients in the study. The time from the first contact with a medical professional to the reperfusion was longer in the group treated with hypothermia. However, the difference was only three minutes, which seems acceptable. The resonance showed a significant, 38% reduction in the size of myocardial necrosis in the cooled group. This observation was reflected in a 43% reduction of troponin concentration. The RAPID MI-ICE study provided a new impulse for further attempts at the implementation of hypothermia in the treatment of patients with STEMI and facilitated the design and introduction of so far the largest study in this field, called CHILL-MI [11]. Its results were announced on 30 October 2013, at Transcatheter Cardiovascular Therapeutics (TCT) 2013 conference in San Francisco, California (USA). The study design and methodology were based on the previous models. The patients with extensive anterior and inferior MI, lasting no longer than 6 hours, were enrolled. A temperature below 35°C at the reperfusion was achieved in 77 % of individuals (92 % < 35.4°C). The time of additional delay until PCI in the hypothermia group was +9 min. Infarct size assessed by magnetic resonance imaging on 4th day after PCI was lower in the group subjected to hypothermia, but the difference was not significant (relative reduction of the infarct size: –13%, *P*=0.15). The results were significant in the subgroup of patients at a very early stage of MI, lasting less than 4 hours, regardless of its location (relative reduction in the infarct size: -21%, *P*<0.05). Furthermore, a 30-day analysis confirmed significant reduction in death rate and heart failure in the study group (3.2% vs. 13.5%, *P*<0.05).

In conclusion, it should be emphasized that all clinical trials conducted so far clearly indicate the safety of therapeutic hypothermia in patients with acute STEMI. The benefits observed in selected subgroups of patients confirm the potential of this method to reduce the size of myocardial necrosis associated with reperfusion during PCI. Considering the lack of viable alternatives that could contribute to an improvement of reperfusion and cardioprotection of myocytes, hypothermia remains an important therapeutic option. Nevertheless, one of the factors in reducing the risk of death and serious complications is quick transportation of a patient with STEMI to the cath lab, ideally without stopping at a hospital emergency department [12]. Only by following this recommendation, together with modern methods of myocardial protection such as therapeutic hypothermia, can the chance of long-term prognosis and quality of life be optimised [3].

Conflict of interest: None declared

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Polymorphism of ABCA1, APOC3, and PON1 genes and indicators of the central nervous system in patients of European race with chronic heart failure of ischaemic origin

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Abstract

Aim

To examine the association of the polymorphic variants of the -455 T>C, -482 C>T; 3238 C>G in the APOC3 gene; R219K G>A in the ABCA1 gene; L55M A>T and Q192R A>G in the PON1 gene, and indicators of the central nervous system (CNS) in patients of European race with chronic heart failure (CHF) of ischaemic origin.

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Materials and methods

54 patients with CHF of ischaemic origin, who were no older than 65 years and had no other related diseases and conditions that could be a cause of pathology of the brain, had numerous tests and examinations. These included a physical examination; magnetic resonance imaging (MRI) of the brain; an assessment of cognitive functions by means of Wechsler's 5 and 7 subtests; proofreading Bourdon's test; mini mental state examination (MMSE); genetic polymorphism analysis of the -455 T>C, -482 C>T, 3238 C>G in the APOC3 gene; R219K G>A in the ABCA1 gene; and, L55M A>T and Q192R A>G in the PON1 gene.

Results

There were no significant differences in the results of the cognitive assessment and the state of the brain determined by MRI, depending on the R219K G>A polymorphism in the ABCE1 gene and 3238C>G polymorphism in the APOC3 gene. The AA genotype of the L55M A>T polymorphism in the PON1 gene, AA genotype of the Q192R A>G polymorphism in the PON1 gene, the presence of C allele of the -455 T>C polymorphism in the APOC3 gene, and T allele of the -482 C>T polymorphism in the APOC3 gene is associated with better cognitive functions in patients with CHF of ischaemic origin. Atrophic changes in the brain in patients with CHF, within the context of coronary artery disease (CAD), are associated with the CC genotype of the -482 C>T polymorphism in the APOC3 gene and G allele of the Q192R A>G polymorphism in the PON1 gene.

Conclusion

Determining the polymorphic variants of the -455 T>C in the APOC3 gene, -482 C>T in the APOC3 gene, Q192R A>G and L55M A>T in the PON1 gene can be effective for predicting the development of atrophic changes in the brain and cognitive dysfunction in patients with CHF of ischaemic origin.

Keywords

Chronic heart failure, coronary artery disease, cognitive functions, genetic polymorphism

Introduction

Chronic heart failure (CHF) is a complex syndrome accompanied by many systemic disorders, including changes in the CNS which are important [1-4].

Along with hypertension and atherosclerotic vascular disease, CHF is one of the extracerebral causes leading to the onset and deterioration of existing cognitive disorders, which can progress to some degree of dementia [1-5].

Prevention of diseases is often more important than their treatment. Identification of genetic factors associated with the high risk of cardiovascular disease and cognitive dysfunction among the population would make it possible to carry out preventive measures well before the onset of clinical symptoms. This preventive diagnosis might delay the onset of the cognitive disorders due to CHF, and perhaps in some cases even prevent their development. Each genetic locus characterizes a certain level of variation that is expressed by the presence of different variants of a gene (alleles) in different individuals. Changes in the sequence of deoxyribonucleic acid (DNA) (mutations) can result in the development of alternative variants of genes. If the mutation occurs at a frequency of 1.5-3% or more and does not lead to obvious phenotypic manifestations of the disease, it is considered a polymorphism. Genetic polymorphism in the human genome in 95% of cases is associated with single nucleotide substitutions – a single nucleotide polymorphism (SNP) [6,7]. Establishing links of certain polymorphisms of some genes, associated with lipid metabolism, with such parameters as the severity of CHF, the severity of cognitive dysfunction, and the presence of any morphological changes in the brain in patients with CHF of ischaemic origin might be useful, of course, for the development of a preventive approach at the population level.

Materials and methods

General inclusion criteria for the participants of the study were: the presence of CHF occurred on the background of proven CAD; not older than 65 years; the use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, and beta-blockers in a stable dose for four weeks before entering the study. The study excluded patients with acute or subacute CAD; diabetes; acute cerebrovascular accident, including in medical history; atherosclerotic plaques of the arteries of the head and neck leading to the development of hemodynamically significant stenoses – narrowing >50% of the arterial lumen, according to the duplex ultrasound of the vessels; signs of

dementia according to MMSE; alcohol abuse; intake during 90 days before inclusion in the study of neurometabolic, neurotrophic drugs, as well as any other substances that can directly or indirectly affect the cognitive functions of patients; myocarditis; thyroid disorders; manifest valvular lesions; laboratory signs of manifest disorders of the liver and kidneys; other somatic diseases which, in the opinion of a physician-scientist, could be an independent cause of cognitive impairment; contraindications for MRI.

The main clinical characteristics of patients are shown in Table 1.

Table 1. **The main clinical characteristics from the groups of patients studied (median and quartiles)**

Indicator	Patients with CHF (n=54)
Age, years	57.23 (54;62)
Male sex, n (%)	65 (58)
Higher education, n (%)	34 (63)
Height, cm	171 (160.5;174.5)
Body weight, kg	84.8 (74.5;95.5)
Myocardial infarction, n (%)	28 (52)
Hypertension, n (%)	49 (91)
Duration of CAD, months	60.1 (35.7;86.1)
Duration of CHF, months	46.2 (20.6;68.7)

All respondents were residents of Saratov (Russian city). They were of the European race, Slavs.

Data of past medical history and physical examination were recorded in a formalized medical history. If the presence of decompensated heart failure was noted in a patient he/she was included in the study 1 month after stabilization. All studies were performed in the morning after the procedure of signing the informed consent form. The study protocol was approved by the local ethics committee at the "Saratov State Medical University named after V. I. Razumovsky" of the Ministry of Healthcare of the Russian Federation.

To assess the morphological state of the CNS of patients, in addition to physical examination, MRI of the brain was performed on the Philips Achieva 1.5 T. The thickness of gray matter (GM) in the occipital, frontal, parietal, and temporal lobes of the brain was determined. To investigate the status of the white matter (WM) of the brain, an average width of the middle cerebellar peduncles was measured. In addition to the standard method of diffusion weighted imaging of the brain, diffusion coefficients (DC) of water molecules in the GM and WM of the occipital, frontal, parietal, and temporal lobes, and in the basal ganglia were calculated. Cognitive functions were assessed by verbal and nonverbal Wechsler's subtests (5 and 7) and proofreading Bourdon's test. MMSE was used in order to exclude dementia.

For genetic analysis venous blood sampling was carried out on an empty stomach. To study polymorphism of the genes involved in lipid metabolism, pyrosequencing, using AxyPrep Blood Genomic DNA Miniprep Kit for DNA isolation, was performed. Polymerase chain reaction was carried out in the MaxyGene Therm-1000 followed by obtaining a single-stranded DNA and sequencing, using a genetic analysis PyroMark Q24 system. Characteristics of the studied polymorphic variants are presented in Table 2.

Statistical analysis was performed by the program Statistica 6.0. Univariate analysis of variance, nonparametric correlations (Kendall's coefficient), and frequency analysis (cross-tabulation) with application of χ^2 and Fisher's criteria were used.

Based on the fact that some of the studied mutations were inherited in an autosomal dominant pattern and given that in some cases the frequency of homozygotes for the mutant allele was extremely small (Table 3), in the further comparative statistical analysis the division of patients into two groups was used, namely in accordance with the presence or absence of the mutant allele in a genotype.

Results

It is obvious that statistical analysis of the relationships between genetic polymorphisms in a relatively small group of patients is possible at a sufficiently high frequency of each of the studied polymorphism variants and moreover, compliance of selective frequency distribution, and prevalence of the studied variants in the population. Genotype frequencies of the studied polymorphisms of the ABCA1, APOC3

Table 2. **Characteristics of the polymorphisms studied**

Locus	Product	Polymorphism	rs	Types of genotype
ABCA1	ABCA1	R219K G>A	2230806	GG, GA, AA
APOC3	Apolipoprotein C3	-455 T>C	2854116	TT, CT, CC
APOC3	Apolipoprotein C3	-482 C>T	2854117	CC, CT, TT
APOC3	Apolipoprotein C3	3238C>G	5128	CC,CG, GG
PON1	Paraoxonase 1	L55M A>T	854560	AA, AT, TT
PON1	Paraoxonase 1	Q192R A>G	662	AA, AG, GG

and PON1 genes mostly correspond to this condition. Established distribution of the genotypes was in line with the expected, based on the Hardy-Weinberg equilibrium (Table 3).

When analyzing the results of the cognitive assessment in patients with CHF of ischaemic origin, there were established significant differences in cognitive indicators, depending on the polymorphism variants of the -455 T>C and -482 C>T in the APOC3 gene, and L55M A>T and Q192R A>G in the PON1 gene. The presence of the mutant C allele of the -455 T>C polymorphism in the APOC3 gene is associated with significantly better memory and attention defined by Wechsler's 7-subtest (28.6±9.3 points in patients with the TT genotype and 37.2±10.3 in patients with the CC and CT genotypes) and proofreading Bourdon's test, namely the speed of doing this test by patients with CC and CT genotypes was 115.98 ± 22.31 signs/min, and in patients with TT genotype – 99.77±20.12 signs/min; attention switching, also determined by the Bourdon's test, in patients with CT and TT genotypss was 46.75±4.25 conv. u, and in patients with CC genotype – 33.89±5.83 conv.u. The -482 C>T polymorphism in the APOC3 gene was associated with the speed of proofreading Bourdon's test, namely patients with CT and TT genotypes completed the test faster: 117.02±24.04 signs/min compared with patients with CC genotype – 104.17±18.60 signs/min. Thus, atherogenic mutations of the APOC3 gene (-455C and -482T) are associated with better memory and attention in patients, mutation carriers, compared with patients – homozygous for the normal allele.

A number of significant differences in the results of the cognitive assessment were established depending on a polymorphism of the PON1 gene. The average 7 minute attention span, determined by the proofreading Bourdon's test, in patients with the AA genotype of the L55M A>T polymorphism in the PON1 gene was 0.91±0.06 conv. u, and in patients with AT and TT genotypes – 0.83±0.11 conv. u. Significant differences in the average 7 minute attention span, determined by the proofreading Bourdon's test, were established depending on the Q192R A>G polymorphism in the PON1 gene. In patients with the AA genotype, it was 0.93±0.04 conv. u, and in patients with AG and GG genotypes – 0.85±0.10 conv. u.

Significant differences in the results of the cognitive assessment depending on the R219K G>A polymorphism in the ABCE1 gene have not been established.

Significant changes in the thickness of the GM and DC of water molecules in the brain were established depending on the -482 C>T polymorphism in the APOC3 gene and Q192R A>G polymorphismin the PON1 gene, whereas the polymorphism in the ABCA1 gene, just as in the analysis of its effects on cognitive functions, was not significant.

Table 3. **Distribution of genotype frequencies of some polymorphisms of genes ABCA1, APOC3 and PON1 in patients with CHF and its comparison with the population**

Gene	Polymorphism	Distribution of genotypes		x^2
ABCA 1	R219K G>A	GG	64.7%	22.3
		GA	20.2%	
		AA	15.1%	
		GA+AA	35.3%	
APOC3	-455 T>C	TT	22.5%	24.5
		CT	62.5%	
		CC	15%	
		CT+CC	77.5%	
APOC3	-482 C>T	CC	48.1%	24.4
		CT	44.5%	
		TT	7.4%	
		CT+TT	51.7%	
APOC3	3238 C>G	CC	1.8%	25.5
		GC	20.8%	
		GG	77.4%	
		GC+CC	98.2%	
PON1	L55M A>T	AA	50.0%	25.3
		AT	35.1%	
		TT	14.9%	
		AT+TT	50.0%	
PON1	Q192R A>G	AA	41.9%	25.6
		AG	40.6%	
		GG	17.5%	
		AG+GG	58.1%	

It should be noted that the -482 C>T polymorphism in the APOC3 gene had no significant effect on the width of the cortex or middle cerebellar peduncles, and established significant differences were related to the diffusion of water molecules in the GM and WM of the brain (Table 4).

Thus, the DC of water molecules in the GM of the frontal and parietal lobes and in the WM of the parietal and occipital lobes is significantly lower if a genotype has the mutant T allele of the -482 C>T polymorphism in the APOC3 gene. It is known that the DC increases, in particular in reducing the number of neurons in the brain which indirectly reflects the severity of the micromorphological changes in the brain [3,8-10]. Decrease in the diffusion of water molecules in the WM can be observed in violation of the myelination of the nerve fibers [3,8].

Regarding the Q192R A>G polymorphism in the PON1 gene, it was found that the average width of the GM of the parietal lobes was significantly lower in the presence of the G allele in a genotype (3.18±0.71 compared to 3.80±0.54, P<0.05).

Discussion

Apolipoprotein C3 is a transport protein which is predominantly a part of of the very low density lipoproteins (VLDL) and chylomicrons [6,7,11-14]. When there is an increased expression of the APOC3 gene, an excessive inhibition of lipoprotein lipase occurs which, in turn, is accompanied by increased levels of triglycerides, low density lipoprotein (LDL), and chylomicrons [11,15-17]. In the present study, the atherogenic APOC3 gene mutations (-455C and -482T) are associated with better memory and attention in patients, carriers of mutations, compared with patients – homozygous for the wild gene. Expressed hemodynamically significant atherosclerosis of the head and neck, as well as the presence of diabetes or acute cerebrovascular accident were the exclusion criteria in the study, and it is unknown what kind of relationship of the investigated polymorphic variants in the APOC3 gene with cognitive functions of patients with these diseases and conditions it could have been. As for the patients included in the present study, the revealed impairments of cognitive functions were caused mainly by the presence of CHF [4]. It can be assumed that in this case the atherogenic T-455C and C-482T polymorphisms in the APOC3 gene perform some protective role in respect of cognitive functions. This may be partly explained by the fact that cholesterol and other lipids are structural components of the brain, involved in the formation of cell membranes, myelin sheaths, and are necessary for normal functioning of the CNS [18-20].

The presence in a genotype of the minor allele of the L55M A>T or Q192R A>G polymorphisms in the PON1 gene is associated with the worst performance of the cognitive assessment and the signs of brain atrophy. These results are not surprising. The presence of these alleles in a genotype reduces the stability of the paraoxonase 1 which is one of the most important antioxidant enzymes in the body, which contributes to oxidation processes, including lipid peroxidation, and decrease in cellular resistance to oxidative stress [21-23]. Probably, these processes are important in the development of cognitive dysfunction.

Conclusion

Significant differences in the results of the cognitive assessment and the state of the brain determined by MRI, depending on the R219K G>A polymorphism in the ABCE1 gene and 3238C>G polymorphism in the APOC3 gene, have not been established.

Better indicators of cognitive function in patients with CHF of ischaemic origin were associated with the homozygous AA genotype of the L55M A>T polymorphism in the PON1gene, homozygous AA genotype of the Q192R A>G polymorphism in the PON1 gene, the presence of the C allele of the -455 T>C polymorphism in the APOC3 gene and T allele of the -482 C>T polymorphism in the APOC3 gene. Atrophic changes of the brain in patients with CHF on the background of CAD are associated with the homozygous CC genotype of the -482 C>T polymorphism in the APOC3

Table 4. **Diffusion coefficients (DC) of water molecules in different parts of the brain in patients with CHF of ischaemic origin, depending on the -482 C>T polymorphism in the APOC3 gene, (M±SD)***

Parameter	-482 C>T polymorphism in the APOC3 gene		Significant difference, *P*
	Patients with CC genotype (n=26)	Patients with CT and TT genotypes (n=28)	
DC of the GM of frontal lobes, m^2/c	0.43±0.04	0.38±0.05	0.046
DC of the GM of parietal lobes, m^2/c	0.44±0.03	0.39±0.05	0.04
DC of the WM of parietal lobes, m^2/c	0.44±0.05	0.37±0.08	0.03
DC of the WM of occipital lobes, m^2/c	0.43±0.02	0.37±0.07	0.048

Note: * – there are only statistically significant differences (*P*<0.05)

gene and the presence of the G allele of the Q192R A>G polymorphism in the PON1 gene.

To predict the development of atrophic changes in the brain and cognitive dysfunction in patients with CHF of ischaemic origin, determination of the polymorphic variants of the -455 T>C and -482 C>T in the APOC3 gene, Q192R A>G and L55M A>T in the PON1 gene are recommended.

Conflict of interest: None declared

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Dynamics of N-terminal fragment of the brain natriuretic peptide as a marker and prognostic factors in patients with chronic heart failure and anaemia

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Abstract

Aim

To determine plasma levels of the N-terminal of the prohormone brain natriuretic peptide (NT-proBNP) in patients with chronic heart failure (CHF) and anaemia during different treatments with the use of basic drugs and iron supplements.

Materials and methods

An open, randomized study included 208 patients aged 45-75 years (mean age 60.6±1.4) with New York Heart Association (NYHA) class I-IV CHF of ischaemic origin (mean class 3±0.85). Among 174 patients, there were 78 men (44.8%) and 95 women (55.2%). Depending on the therapy, all patients were divided into 4 groups: Group I received basic drugs only; Group II received basic drugs and methoxy polyethylene glycol-epoetin beta; Group III (which included patients with iron deficiency) received basic drugs and iron supplements; Group IV received combination therapy comprising basic drugs, methoxy polyethylene glycol-epoetin beta, and iron supplements. Before and after treatment, the levels haemoglobin, iron, ferritin, transferrin, erythropoietin, NT-proBNP, and systolic and diastolic function of the left ventricle were determined.

Results

In all groups of patients with CHF and anaemia, an increase in NT-proBNP plasma levels was diagnosed. During the therapy with basic drugs, a decrease in NT-proBNP plasma levels was not significant. In the three other groups with different combinations of therapy, a decrease in NT-proBNP plasma levels was statistically significant.

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Conclusion

These results reflect the prognostic value of determining NT-proBNP plasma levels in patients with CHF of ischaemic nature and anaemic syndrome in order to select an effective treatment and evaluation of treatment.

Keywords:

Chronic heart failure, anaemia, N-terminal of the prohormone brain natriuretic peptide

Introduction

In recent years, the relationship between chronic heart failure (CHF) and anaemia has been actively discussed. Main neurohumoral mediators in heart failure are divided into vasodilating (nitric oxide, natriuretic peptide (NP), [1] prostaglandins, adrenomedullin) and vasoconstricting (angiotensin, aldosterone, adrenaline, vasopressin, endothelin 1). Hormones that are natural antagonists of the renin-angiotensin system, sympathoadrenal system, aldosterone, and vasopressin refer to NP [1].

In 1988, the NP, isolated from guinea pig brain, was called brain natriuretic peptide (BNP) [2,3].

In CHF, BNP is produced mainly in the ventricles of the heart, although normally BNP gene expression is determined predominantly in the atrial tissue. Initially, BNP is synthesized as a prohormone (pro BNP 108), which is subsequently cleaved into biologically active C-terminal, BNP 32, and inactive N - terminal fragment (NT-pro BNP 76); and it is stored in the granules of cardiomyocytes [4]. Normally, BNP and NT-proBNP in equal picomolar concentrations are present in blood plasma. With the onset and progression of left ventricular (LV) dysfunction, NT-proBNP levels exceed BNP levels by 2-10 times. Comparison of the data of echocardiography with BNP levels showed the possibility of the diagnosis of systolic and diastolic dysfunction of the LV according to NP levels [5].

Together with the diagnostic and prognostic role of BNP, it can be also used in the plasma to monitor therapy in patients with severe CHF. Results of the study [6] showed that control of the BNP levels is an important criterion for evaluating the effectiveness of therapy.

The dynamics of BNP levels in patients with NYHA class II-IV CHF with ventricular tachycardia during amiodarone therapy was evaluated [7]. However, the results of the studies evaluating the effect of ß-blockers are contradictory [8-11]. In patients with isolated diastolic dysfunction, plasma BNP levels were significantly increased proportionally to the severity of diastolic dysfunction [4].

It is noted that according to BNP levels, a differential diagnosis of complex forms of CHF can be conducted; severity of LV dysfunction can be assessed; treatment tactics can be chosen; its performance can be monitored; and prognosis can be assessed. Leading pathophysiological form of CHF in patients with hypertension is LV diastolic dysfunction with preserved contractility of the heart. NT-proBNP is produced by the myocardium of the ventricles in response to stretching their walls and an increase in LV end-diastolic pressure [12]. Thus, the determination of BNP and its final fragment, NT-proBNP, enables to evaluate the effectiveness of a given therapy.

In some studies [13], an increase in NT-proBNP >128 pg/mL during 20 weeks in women with congenital heart disease was shown. It should be noted that the increase in BNP levels is accompanied by LV diastolic dysfunction during formation and progression of its hypertrophy [14-16]. The question of the relationship of changes of NT-proBNP plasma levels in patients with CHF and anaemic syndrome during treatment still remains little known and highly controversial.

The purpose of this study is to determine NT-proBNP plasma levels in patients with CHF and anaemia during different treatments using basic drugs and iron supplements.

Materials and methods

An open, randomized study included 208 patients aged 45-75 years (mean age 60.6±1.4 years) with NYHA class I-IV CHF of ischaemic origin (mean class 3±0.85). 158 patients had a history of myocardial infarction (MI) which happened from 1 to 10 years ago. According to the criteria for inclusion, 174 patients (78 (44.8%) men and 95 (55.2%) women) had clinical signs of CHF and anaemia. The mean duration of the disease was 16.5±1.2 years. Anaemia was diagnosed in women with haemoglobin levels (Hb) <11g/dL and in men with Hb levels <12g/dL.

Exclusion criteria were severe or malignant hypertension, acute disorders of cerebral circulation of <12 months, acute MI of 6 months, acute coronary syndrome, chronic obstructive pulmonary disease, and mental disorders.

All patients, depending on the therapy, were divided into 4 groups: Group I received only basic drugs

for CHF: angiotensin-converting enzyme (ACE) inhibitors, ß-blockers, diuretics, glycosides, nitrates; Group II received therapy of basic drugs and methoxy polyethylene glycol-epoetin beta; Group III (included patients with iron deficiency) received basic drugs and iron supplements; Group IV received combination therapy comprising basic drugs, methoxy polyethylene glycol-epoetin beta and iron supplements. Each group, depending on NYHA classification of CHF, was divided into A and B subgroups.

The subgroup IA included 27 patients with NYHA class I-II CHF of ischaemic origin and anaemia, and the subgroup IB included 22 patients with NYHA class III-IV CHF and anaemia. Of the 49 patients, 34 patients developed CHF as a result of NYHA class III-IV stable angina, and 15 patients had it as a result of postinfarction myocardiosclerosis. 8 patients were diagnosed with concomitant type 2 diabetes and 1 patient with hypertension.

Group II included 38 patients with CHF and anaemia treated with combination therapy of methoxy polyethylene glycol-epoetin beta at a dose of 0.60 mg/kg (50 units) once a month and basic drugs. If Hb levels increased by less than 10 g/L per month, the dose was increased by about 25% per month until an individual target Hb level was reached. If the rate of increase in Hb levels was more than 2 g/dL per month or Hb concentration rose, approaching 12 g/dL, the dose was reduced by about 25%. If Hb levels continued to rise, the treatment was stopped until Hb levels started to decline. Methoxy polyethylene glycol-epoetin beta was appointed to patients without iron deficiency. Iron deficiency was considered when ferritin levels were <100 µg//L and 299 µg/L if transferrin saturation was <20%. The mean age of patients was 59±1.5 years, including 18 men and 20 women. Group II was also, depending on the NYHA classification of CHF, divided into subgroups A and B. The subgroup IIA included 18 patients with NYHA class II CHF of ischaemic origin and anaemia, and the subgroup II B included 20 patients with NYHA class III CHF and anaemia. Of the 39 patients, 19 patients developed CHF as a result of stable angina, 19 patients developed CHF as a result of postinfarction myocardiosclerosis. 14 patients were diagnosed with concomitant type 2 diabetes, and 26 patients were diagnosed with hypertension.

Group III included 43 patients with CHF and anaemia treated with combination therapy of intravenous (IV) iron and basic drugs. Iron (III)-hydroxide sucrose complex was prescribed as Venofer at a dose of 200 mg 2 times per week during 5 weeks. Intravenous iron supplements were administered to patients with CHF and anaemia with iron deficiency. The mean age was 62.5±1.4 years, including 16 men and 27 women. Group III, depending on the NYHA classification of CHF, was divided into subgroups A and B. The subgroup IIIA included 20 patients with NYHA class I-II CHF of ischaemic origin and anaemia, and the subgroup IIIB included 23 patients with NYHA class III-IV CHF and anaemia. Of the 43 patients, 15 patients developed CHF as a result of the stable angina, and 28 patients developed CHF as a result of postinfarction myocardiosclerosis. 13 patients were diagnosed with concomitant type 2 diabetes, and 31 patients were diagnosed with hypertension.

Group IV included 44 patients with CHF and anaemia treated with combination therapy of methoxy polyethylene glycol-epoetin beta, IV iron, and basic drugs. Methoxy polyethylene glycol-epoetin beta was administered in a dose of 50 IU once a month, and iron (III)-hydroxide sucrose complex (Venofer) in a dose of 200 mg 2 times per week for 5 weeks. IV iron was administered to patients with CHF and anaemia with iron deficiency. The mean age of patients was 59.9±1.2 years, including 19 men and 25 women. Group IV was also, depending on the NYHA classification of CHF, divided into subgroups A and B. The subgroup IVA included 24 patients with NYHA class I-II CHF of ischaemic origin and anaemia, and the subgroup IVB included 20 patients with NYHA class III-IV CHF and anaemia. Of the 44 patients, 17 patients developed CHF as a result of NYHA class III-IV stable angina and 27 patients developed CHF as a result of postinfarction myocardiosclerosis. 19 patients were diagnosed with concomitant type 2 diabetes and 30 patients were diagnosed with hypertension.

In each group, the patients were divided according to sex, age, duration of disease, and treatment strategy. The distribution of the patients with CHF and anaemia in groups and their clinical characteristics are shown in Table 1.

The control group included 34 patients with NYHA class I-IV CHF of ischaemic origin without anaemia. The mean age of patients was 58.4±1.6 years; mean duration of disease 14.2±2.1 years; there were 21 women and 13 men. The control group was also like the main groups divided into subgroups A and B: the subgroup A included 16 patients with NYHA class I-II CHF of ischaemic origin without anaemia; the subgroup B included 18 patients with NYHA class III-IV CHF of ischaemic origin without anaemia. Table 2 shows the demographic and clinical characteristics of the patients in the control group.

Table 1. **Clinical characteristics of patients from the main groups and laboratory parameters from the subgroups**

Indicators	I group n=49		II group n=38		III group n=43		IV group n=44	
	n	%	n	%	n	%	n	%
NYHA class I CHF and anaemia	11	22.5%	–	–	1	2.3%	2	4.5%
NYHA class II CHF and anaemia	16	32.6%	18	47.3%	19	44.2%	22	50%
NYHA class III CHF and anaemia	17	34.7%	20	54.1%	16	37.2%	17	38.6%
NYHA class IV CHF and anaemia	5	10.2%	–	–	7	16.2%	3	6.8%
MI	15	30.6%	19	51.4%	28	65.1%	27	61.3%
Hypertension	11	2%	26	68.4%	31	72.1%	30	68.2%
Type 2 diabetes	8	16.3%	14	37.8%	13	30.2%	19	43.2%
Previous treatment:								
ACE inhibitors	40	81.6%	30	78.9%	37	86%	30	86.4%
Angiotensin II receptor blockers	9	18.4%	8	21.1%	14	32.6%	14	31.8%
Nitrates	39	79.6%	25	67.5%	28	65.1%	32	72.7%
Diuretics	27	55%	21	56.7%	40	93%	42	95.5%
Digoxin	4	8.1%	5	13.5%	8	18.6%	7	15.9%
ß-blockers	41	83.7%	29	78.3%	39	90.7%	32	72.7%
Amiodarone	29	76.3%	21	55.2%	19	44.1%	17	38.6%
Ivabradine	10	20.4%	8	21.6%	11	25.6%	8	18.2%
Laboratory indicators	**Subgroup IA**	**Subgroup IB**	**Subgroup IIA**	**Subgroup IIB**	**Subgroup IIIA**	**Subgroup IIIB**	**Subgroup IVA**	**Subgroup IVB**
Hb, g/L	103.8±1.3	104.0±30	100.2±3.2	87.9±4.3	101.2±1.9	103±2.1	97.8±2.2	94.6±2.5
Hematocrit, %	47.2±6.8	48.0±7.5	38.1±1.5	38.8±1.3	39.1±1.5	38.5±1.2	41.8±1.4	53.3±9.7 1
Iron, µmol/mL	14.7±1.3	15.8±1.3	17.2±1	17.1±2.1	14.4±1.4	15.5±0.8	18.1±4.1	2.8±1.3
Plasma ferritin, µg/L	45.2±10.2	50.5±11	160.3±23.5	127.6±24.8	77.8±15.8	90.6±15.8	42.3±7.7	63.3±12.4
Transferrin saturation,%	<20%	<20%	>20%	>20%	<20%	<20%	<20%	<20%
Erythropoietin, IU/mL	18.6±6.1	24.1±6.4	7.3±1.8	12.8±5.7	7.2±1.8	50.1±19.1	2.8±0.4	3.7±0.8
NT-proBNP, pg/mL	1500±415.2	1173±144.9	1779.5±206.9	1817.5±170.2	2245.4±175.1	2421±154	2478.4±201.7	2306.1±260.5

At the initial stage in hospital, patients underwent some tests and examination, namely their medical history and complaints were studied; heart rate and blood pressure on both arms were measured; general clinical blood and urine tests, electrolyte composition of the blood, levels of lipids, glucose, creatinine, uric acid and hepatic enzymes were also checked.

All patients had levels of Hb, iron, ferritin, transferrin, erythropoietin, NT-proBNP, and parameters of systolic and diastolic LV function before and after treatment determined. All patients underwent a follow-up examination after 1 month. Echocardiography and Doppler echocardiography were performed again after 20 weeks. LV ejection fraction in patients with NYHA class I CHF was ⩽50%, with class II ⩽45%, with class III ⩽35%, and with class IV ⩽25%.

Statistical analysis

Software packages of Excel and Statistica were used for statistical processing of the results. Data were analyzed using paired Student's t-test. Differences were considered significant at $P<0.05$.

Results

According to the results, NT-proBNP plasma levels decreased in the subgroup IA from 1500±415.2 pg/mL to 962.6±164.7 pg/mL (P=1.2) and in the subgroup IB from 1173±144.9 pg/mL to 874.3±129.1 (P=1.5). In patients with CHF and anaemia, the dynamics of NT-proBNP during the treatment with basic drugs was not significant. And the confirmation of these insignificant results was observed among patients with mild, moderate, and severe CHF.

Table 2. **Clinical characteristics of patients from the control group and laboratory indicators from its subgroups A and B**

Indicators	Control group, n=34	
NYHA class I CHF and anaemia	n	%
	1	2.9%
NYHA class II CHF and anaemia	15	44.1%
NYHA class III CHF and anaemia	17	50%
NYHA class IV CHF and anaemia	1	2.9%
MI	13	38.2%
Hypertension	17	50%
Type 2 diabetes	11	32.4%
Previous treatment:		
ACE inhibitors	30	88.2%
Angiotensin II receptor blockers	4	11.8%
Nitrates	13	38.2%
Diuretics	33	97.1%
Digoxin	13	38.2%
ß-blockers	27	79.4%
Amiodarone	14	41.1%
Ivabradine	9	26.5%
Laboratory indicators	**Subgroups of the control group**	
	A	**B**
Hb, g/L	125.1±1.1	126.8±1.2
Hematocrit,%	54.8±1.8	53.5±1.2
Iron, µmol/mL	16.3±0.7	16.3±1.2
Plasma ferritin, µg/L	143.8±26.8	149.9±27.5
Transferrin saturation,%	>20%	>20%
Erythropoietin, IU/mL	13.3±4.7	14.4±3.9
NT-proBNP, pg/mL	1545.6±204.5	1688.5±187

NT-proBNP plasma levels in the subgroup IIA decreased from 1779.5±206.9 pg/mL to 837.3±198.6 pg/mL (P<0.01). NT-proBNP plasma levels in group II decreased from 1817.5±170.2 pg/mL to 999.6±160.9 pg/mL (P<0.01). Attention was drawn to the fact that patients with CHF and anaemia during the treatment with a combination of basic drugs and methoxy polyethylene glycol-epoetin beta had positive dynamics of NT-proBNP which was statistically significant. These changes were observed among patients with mild, moderate, and severe CHF.

NT-proBNP plasma levels in the subgroup IIIA decreased from 2245.4±175.1 pg/mL to 1128.7±118 pg/mL (P<0.001); in the subgroup IIIB decreased from 2421±154 pg/mL to 1782±184.4 pg/mL (P<0.05). In patients with CHF and anaemia during the treatment with a combination of basic drugs and IV iron, positive dynamics of NT-proBNP was significant. Reliability of the results in patients with mild CHF was observed more often than in patients with moderate and severe CHF.

Dynamics of NT-proBNP plasma levels in the subgroup IVA was negative. Their levels decreased from 2478.4±201.7 pg/mL to 1128.7±118 pg/mL (P<0.001). In the subgroup IVB, NT-proBNP plasma levels decreased from 2306.1±260.5 pg/mL to 1314.8±159.51 pg/mL (P<0.01). Compared with baseline values, patients with CHF and anaemia during the treatment with a combination of methoxy polyethylene glycol-epoetin beta, IV iron, and basic drugs, had significant positive dynamics of NT-proBNP. High reliability of the results was observed in patients with mild, moderate, and severe CHF.

Comparison of the results showed that NT-proBNP plasma levels were diagnosed high in all groups and subgroups of patients with CHF and anaemia. NT-proBNP plasma levels decreased in patients with CHF and anaemia during all 4 compared treatment tactics. However, a decrease in NT-proBNP plasma levels during the treatment with basic drugs in the subgroups IA and IB was not significant. In contrast to the results of Group I, three other groups and their subgroups had a significant decrease in NT-proBNP plasma levels. Attention was drawn to the degree of reduction in NT-proBNP plasma levels in these three groups. The compared results, indicating differences in a decrease of NT-proBNP plasma levels according to applied treatment strategy, are presented in Table 3.

Table 3. **Comparable figures of decrease of NT-proBNP plasma levels from patients with CHF and anaemic syndrome**

Groups and subgroups	NT-proBNP levels before treatment, pg/mL	NT-proBNP levels after treatment, pg/mL	P	Δ,%
Control A	1545.6±204	–		
Control B	1688.5±187	–		
IA	1500±415	962.6±164.7	1.2	–35.83
IB	1173±144.9	874.3±129.1	1.5	–25.46
IIA	1779.5±206.9	837.3±198.6	<0.01	–29.01
IIB	from 1817.5±170.2	999.6±160.9	<0.01	–45
IIIA	2245.4±175.1	1128.7±118	<0.001	–49.73
IIIB	2421±154	1782±184,4	<0.05	–26.4
IVA	from 2478.4±201.7	1128.7±118	<0.001	–54.45
IVB	2306.1±260.5	1314.8±159.51	< 0.01	–42.98

Discussion

According to the results, patients with CHF and anaemic syndrome, during the therapy with basic drugs, had an insignificant decrease in NT-proBNP plasma levels. This implies that the main therapy for patients in this category should primarily be the treatment of anaemia. In patients with CHF and anaemic syndrome during therapy, the most significant decrease in NT-proBNP plasma levels was observed in the subgroup IVA. Among severely affected patients of this subgroup, a reduction in NT-proBNP plasma levels was -42.98% (P<0.01). In patients with NYHA class I-II CHF and anaemia, a triple combination of IV iron with methoxy polyethylene glycol-epoetin beta reduces NT-proBNP plasma levels to the greatest degree by -54.45 (P<0.001). When comparing the results of different treatments in patients with NYHA class I-II CHF and anaemia, a marked reduction in NT-proBNP plasma levels by -29.01% (P<0.01) was found in patients who had erythropoietin therapy, methoxy polyethylene glycol-epoetin beta, and a greater reduction in NT-proBNP plasma levels by -45% (P<0.01) in severely affected patients of this category.

Group III patients with CHF and anaemia treated with IV iron had the most reduced NT-proBNP plasma levels, by -49.7% (P<0.001), in moderately affected patients; on the other hand, the least reduced NT-proBNP plasma levels, by -26.4% (P<0.05), were in severely affected patients.

The literature also suggests that in presence of anaemia in patients with CHF, its treatment with methoxy polyethylene glycol-epoetin beta or IV iron reduces NT-proBNP plasma levels. The greatest reduction of NT-proBNP plasma levels was observed during combination therapy of methoxy polyethylene glycol-epoetin beta and IV iron [13,17].

Conclusion

The results of the study reflect the prognostic value of determining NT-proBNP plasma levels in patients with CHF of ischemic origin and anaemic syndrome in order to select correct treatment and evaluate the effectiveness of treatment.

Conflict of interest: None declared

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Violation of ventricular interactions in patients with severe aortic regurgitation

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Abstract

Aim

The aim was to study the effect of severe chronic aortic regurgitation (AR) on right ventricular (RV) diastolic function by using transthoracic echocardiography.

Materials and methods

This study examined 57 patients with AR. All patients who had lesions of other heart valves, coronary arteries, left ventricular ejection fraction (LVEF) <55%, and an increase in pulmonary artery pressure >25 mmHg were excluded from the analysis of the results. The remaining 25 (44%) patients were enrolled in a study group. All patients were male with a mean age 35±5 years. Patients had New York Heart Association (NYHA) class II-III chronic heart failure. The control group consisted of 10 healthy volunteers (mean age 34±6 years). All patients underwent echocardiography. RV diastolic function was evaluated during sinus rhythm using PW-Doppler echocardiography. The

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parameters of transtricuspid flow were calculated, namely early filling velocity (E) of the RV; right atrial systolic velocity (A); their ratio (E/A); acceleration, deceleration, and duration times of E; duration time of A, velocity–time integrals of E and A (VTI E and VTI A); RV isovolumic relaxation time (IVRT). Statistical data processing was performed using STATISTICA 6.0 software. The value of P<0.05 was considered statistically significant.

Results

There was no statistically significant difference identified between patients and controls with regard to age, height, body weight and heart rate. Systolic and diastolic blood pressure (BP), left ventricular mass index (LVMI), left ventricular end-diastolic (LVED) dimension, left ventricular end-diastolic volume (LVEDV), left ventricular end-systolic (LVES) dimension, left ventricular end-systolic volume (LVESV), and left atrial size were significantly greater in patients with AR than in controls. There was no significant difference in patients with AR and controls regarding echocardiographic parameters characterising the right chambers of the heart: RV fractional area change, RV anterior wall thickness and the area of the right atrium. Significant difference between controls and patients with AR was observed in the right ventricular end-diastolic (RVED) dimension. Transtricuspid flow parameters in patients with AR, namely E/A of RV, RV IVRT, and VTI, were significantly different from those in controls. A high correlation was observed between the degree of AR and the occurrence of RV diastolic dysfunction (r=0.71).

Conclusion

LV volume overload violates interventricular interaction and negatively affects RV diastolic function. It is necessary to analyse in detail transtricuspid flow in patients with severe chronic AR to assess the condition of their RV.

Keywords

Right ventricle, aortic regurgitation, interventricular interaction, structure of the myocardium of the heart, right ventricular diastolic function

Introduction

The role of the RV to ensure adequate performance of the heart has been a subject of scientific and clinical interest >50 years. The results of experimental studies in 1943 and 1963 showed that destruction of the RV free wall or its complete replacement by a synthetic patch do not significantly affect the pumping function of the heart and systemic hemodynamic parameters [1,2]. In the literature until the mid 1980s of the last century, there were not many discussions about the functional significance of the RV because it was seen as a passive conduit or vessel via which blood travels from the venous system through the pulmonary circulation in the arterial bed of the systemic circulation.

In recent years, a view of the RV as a simple "conductor" of blood from a large to a small circle has been completely revised. In clinical practice, it has become extremely important to identify the prognostic value of the RV functional status compared to the LV, both at conservative and surgical treatments of various diseases of the heart, as evidenced by the high incidence of RV dysfunction (up to 37%) in the structure of hospital mortality from acute heart failure [3-5].

It is known that the ventricles are in close interaction. This implies three mechanisms: the unified volume of blood pumped, the unified pericardium, and, finally, the shared wall – septum, which carries out the mechanical interaction between the ventricles [6,7].

Studying muscle fibre orientation of the ventricles of the heart began almost 400 years ago when William Harvey (1628) discovered the circulation of blood. Studies by the Spanish scientist Torrent-Guasp F., et al. changed an understanding of the anatomical structure of the ventricular myocardium [8]. In these studies, it was shown that the ventricular myocardium is rolled into a spiral and during dissection of the heart in a certain sequence; it unfolds into a single muscle strip, the edges of which are the trunk of the pulmonary artery and the aorta (Figure 1).

In recent years, many scientists from leading cardiology clinics have successfully proved the "theory of a spiral single layer structure of the myocardium". In the *Russian Research Centre of Surgery named after Academician B.V. Petrovsky,* the study has been conducted which also proved the legitimacy of Torrent-Guasp's claims.

We studied a direction of the muscle fibres of the LV and RV myocardium by the Torrent-Guasp method (Figure 2).

When dissecting the myocardium through the passage of the left anterior descending artery, the RV free

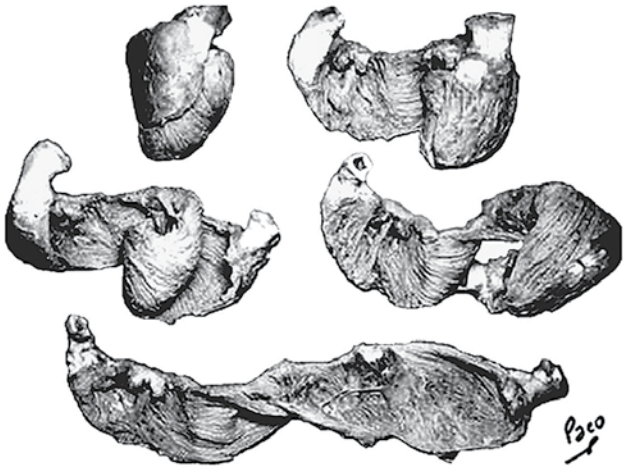

Figure 1. Ventricular myocardium rolled into a spiral (from La Mecanica Ventricular. Rev Lat Cardiol. 2001;22(2):50)

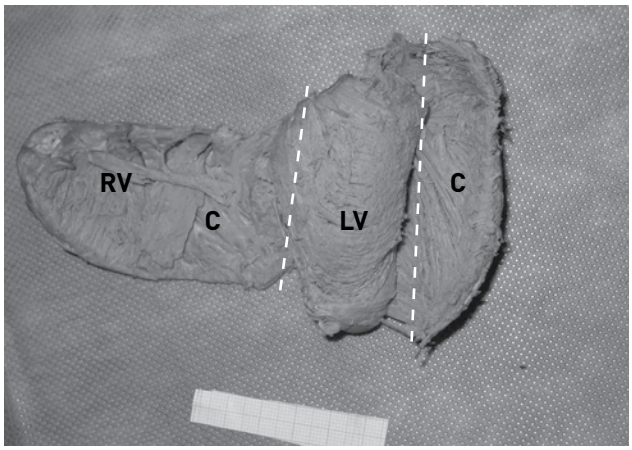

Figure 2. Dissection image of a lamb's ventricles

wall gets separated, and the bulk of the myocardium, including the interventricular septum, belongs to the LV. The great muscular layer in Figure 2, indicated by the letter "C", departs from the RV, covers the LV and becomes woven again into the RV myocardium. As a result, the heart unfolds on the RV and LV, taking a form of a muscle strip.

The idea of dividing the myocardium of the heart on LV and RV parts is very conditional. At least in functional terms, they should be considered as a whole [4].

The muscular frame of the walls of both ventricles is formed by longitudinal, transverse, and circular fibres of the superficial and deep muscle groups, which cover the RV and LV cavities with 4 layers, similar to the layers of fabric in a Turkish turban [7,9]. This structure explains the occurrence of simultaneous contraction of the entire myocardium and the close cooperation of all anatomical structures of the heart.

Close anatomical relations of muscle fibres cause changes in the RV during the remodelling of the LV of the heart [10-12].

Despite the extensive experience of surgical treatment of acquired valve disease [4-5], the problem of comprehensive use of simple and non-invasive techniques in determining the functional state of the RV in patients with abnormal heart valves is not currently described. In this context, the problem of an echocardiographic assessment of the RV at present becomes very important.

Diastolic myocardial dysfunction often plays a key role in the clinical manifestations of cardiovascular disease. It can be an early sign of pathology, and precedes clinical manifestations of systolic dysfunction. RV diastolic function attracts increasing attention of researchers and clinicians [13-17].

Taking into account a new understanding of the anatomical structure of the myocardium, a study was conducted, the purpose of which was to study the effect of chronic severe AR on the RV diastolic function, using transthoracic echocardiography.

Materials and methods

To assess the RV diastolic function, 57 patients with severe chronic AR were examined. The data of patients with combined defects of other heart valves, coronary artery lesions, LVEF <55%, and with an increase in pulmonary artery pressure >25 mmHg were excluded from the analysis of the results. The remaining 25 (44%) patients were enrolled in the study. All patients were male. The mean age of the patients was 35±5 years. 10 patients showed signs of LV hypertrophy. The main complaint of patients was dyspnoea, corresponding to NYHA class II-III.

All patients included in the study had severe AR according to echocardiography and angiographic criteria.

The control group consisted of 10 healthy volunteers with the mean age of 34±6 years.

All patients underwent comprehensive two-dimensional echocardiography using an ultrasound scanner (GE Vivid 7) equipped with a 2.5–4.7 MHz multifrequency probe allowing simultaneous recording of one standard lead electrocardiogram. All echocardiographic measurements were performed according to the recommendations of the American Society of Echocardiography [18].

Assessment of RV diastolic function was performed in sinus rhythm in the mode of pulsed Doppler echocardiography.

The following parameters of transtricuspid flow were calculated: maximum early filling velocity of

the RV (VmaxE), right atrial peak systolic velocity (VmaxA), their relationship (VE/VA), E wave acceleration time (AccT E), E wave deceleration time (DecT E), E wave duration time (DT E), A wave duration time (DT A), integral of the linear peak velocity of E and A (VTI E and VTI A, respectively), RV isovolumic relaxation time (IVRT), which was defined as a period between closing of the pulmonary valve and opening of the tricuspid valve. Diastolic indices were measured in 3 consecutive complexes; their values were averaged in order to minimize the effect of the act of breathing on the RV diastolic filling.

Statistical data processing was performed using STATISTICA 6.0 software. When analyzing, the mean (M) ± standard deviation (SD) were calculated. The significance of differences was assessed by the Student's t-test. The value of P<0.05 was considered statistically significant.

Results and discussion

There was no statistically significant difference between patients and controls with regard to age, height, body weight, and heart rate. Systolic and diastolic BP, LVMI, LVED dimension, LVEDV, LVES dimension, LVESV, and left atrial size were significantly greater in patients with AR than in controls. There was no significant difference between patients with AR and controls regarding echocardiographic parameters characterizing the right chambers of the heart: RV fractional area change, RV anterior wall thickness and the area of the right atrium. RV systolic pressure was estimated according to maximal tricuspid regurgitation velocity, and was <30 mmHg in all patients included in the study. Significant difference between patients with AR and controls was observed in the RVED dimension (Table 1).

Patients with AR had lower peak E-wave velocity than peak A-wave velocity, and the E/A ratio was lower as compared with controls (Figure 3).

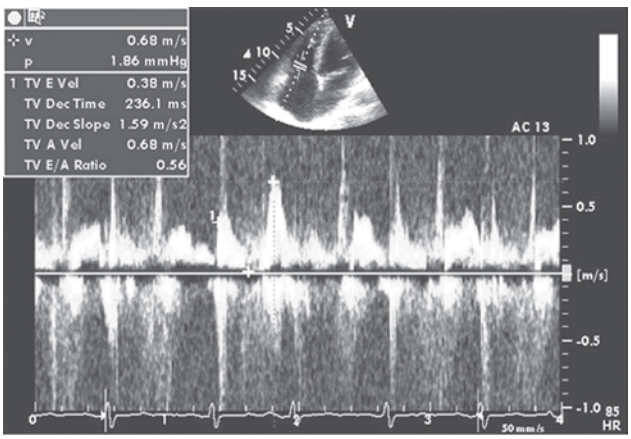

Figure 3. Diastolic transtricuspid blood flow

Table 1. **Comparison of clinical and echocardiographic parameters in patients with AR and controls (M±SD)**

Parameters	Controls (n=10)	Patients with AR (n=25)	P
Age, years	34±6	35±5	0.610
Height, m	1.72±0.22	170±0.08	0.866
Weight, kg	74.2±8.7	73.7±7.7	0.773
Heart rate, beats/min	69±6	74±5	0.955
Systolic BP, mmHg	131±6	152±9	<0.01
Diastolic BP, mmHg	75±4	54±4	<0.01
LVMI, g/m^2	98±13	188±43	<0.001
LVED dimension, cm	5.1±0.3	6.8±0.5	<0.001
LVEDV, mL	105±1.1	183±35	<0.001
LVES dimension, cm	3.1±0.2	3.9±0.5	<0.001
LVESV, ml	45±3	85±14	<0.001
LV, cm	3.5±0.1	4.5±0.1	<0.001
RVED dimension, cm	1.9±0.2	2.9±0.1	<0.001
RV anterior wall thickness, cm	0.4±0.02	0.5±0.01	0.43
RV fractional area change, %	49±6	48±7	0.74
Area of the right atrium, cm^2	12±0.5	14±0.4	0.55

The transtricuspid flow parameters, such as ratio of RV filling velocities (E/A), RV IVRT, and VTI, in patients with AR were statistically significantly different from those in controls, and were lower (Table 2).

Table 2. **Comparison of the echocardiographic parameters of transtricuspid flow in patients with AR and controls (M±SD)**

Parameters	Controls (n=10)	Patients with AR (n=25)	P
VE/VA	1.33±0.07	0.98±0.09	<0.01
RV IVRT, msec	70.75±2.70	76.86±3.7	<0.01
VTI, cm	21.20±0.72	20.2±1.01	0.65

The RV creates a sucking effect during early diastole, which ensures free flow of blood into the cavity. During late diastole, right atrial contraction contributes to additional RV filling. Early manifestation of RV myocardial dysfunction is a disorder of its diastolic compliance.

A high correlation (r=0.71) between the degree of AR and violation of RV diastolic function was noted (Figure 4).

These results demonstrate the relationship between the LV volume overload, violation of interventricular communication and emergence of RV diastolic dysfunction in patients with AR.

This study allowed us to estimate the influence of LV volume overload and violation of interventricular communication on RV diastolic function. These data indicate impairment and degradation in relaxation of the RV which is filled with redistributed transtricuspid blood flow during early and last diastoles. The key

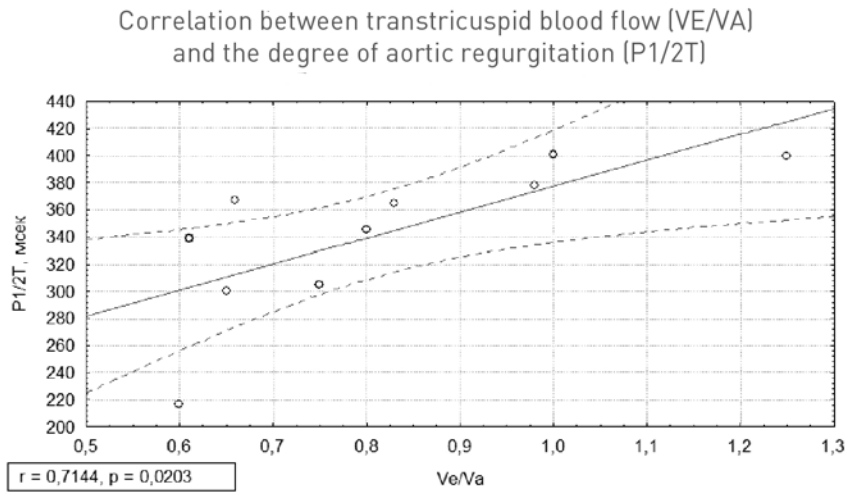

Figure 4. Dependence of the parameters of RV diastolic function and degree of AR

mechanism of this action is a violation of interventricular communication as a result of the LV dilatation and diastolic changes of the RV side of the interventricular septum. Thus, in patients with severe AR and chronic LV volume overload, a violation of RV diastolic function occurs.

Conclusion

Transthoracic echocardiography allows evaluation of intracardiac blood flow and diastolic function of the RV and LV [19].

Comprehensive echocardiographic study in patients with severe chronic AR enables diagnosis of a violation of the interventricular communication and the occurrence of RV diastolic dysfunction.

The analysis of echocardiographic indices indicates an abnormality in transtricuspid blood flow, deterioration in myocardial relaxation, and occurrence of RV diastolic dysfunction in patients with severe chronic AR.

RV diastolic dysfunction plays an important role in progression of chronic heart failure [17,20]. Determination of the RV functional state is an important criterion for assessing the severity of the clinical course and prognosis of surgical treatment in these patients.

Conflict of interest: None declared

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CLINICAL CASE

Spontaneous psoas muscle hematoma during Rivaroxaban therapy

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Abstract

We report on the case of an 81 year old male who developed a spontaneous retroperitoneal bleed of the psoas muscle while on Rivaroxaban therapy for the prevention of arterial emboli due to atrial fibrillation (AF). Rivaroxaban is a factor Xa inhibitor which is indicated for use in patients with a history of AF, pulmonary emboli and deep vein thrombosis. Rivaroxaban is associated with increased risk of bleeding. Few reports exist in the literature describing spontaneous bleeding associated with the use of Rivaroxaban. But, none reported spontaneous retroperitoneal psoas muscle hematoma, as in the case we are presenting.

Keywords

Rivaroxaban, hemorrhage/etiology, drug-related side effects and adverse reactions, retroperitoneal space, adult

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Introduction

Rivaroxaban is a factor Xa inhibitor that has been shown to be non-inferior to warfarin in stroke prevention in AF and in treatment of venous thromboembolism [1,2]. The most common reported side effect of Rivaroxaban use is bleeding. In the Dresden NOAC Registry, gastrointestinal Rivaroxaban related bleeding is the most common type of bleeding with an estimated incidence of 31 per 1,000 patients/year (95 % CI 22–43) for stroke prevention in AF [3]. There is a lack of specific antidotes for bleeding reversal in Rivaroxaban-induced bleeding. Spontaneous retroperitoneal bleeding has not previously been discussed; we present the first case here.

Case Report

An 81 year old male, with a history of AF and daily use of Rivaroxaban, was being evaluated and treated for pneumonia and recurrent episodes of forceful coughing 3 days before he presented to the emergency department with right sided cramping pain in his thigh with an antalgic gait. The pain was severe enough to prevent him from standing or walking, and was presumed to be musculoskeletal in nature. The patient was admitted to the hospital. On admission, his vital signs included – temperature: 98.2 °F, pulse: 65 beats/min, blood pressure (BP): 143/73 mmHg, pulse oximetry: 92% on room air. His physical exam was significant for an antalgic gait and right medial thigh pain upon internal rotation of the right hip. He had intact range of motion in both the right knee and hip. His abdominal exam was normal. His labs were significant for white blood cells (WBC): 10.8 x 10^9/L, haemoglobin (Hgb): 120 g/L, haematocrit (Hct): 36.8%, platelets (Plt): 207 x 10^9/L, prothrombin time (PT): 24.6 seconds and international normalized ratio (INR): 2.3. The right knee, hip and femur X-ray revealed chronic osteoarthritic changes in the knee and hip with no evidence of fractures. The next day (day 2) post admission, his Hgb and Hct levels decreased, with Hgb trending from 120 g/L on admission, to 92 g/L the next day, and to 69 g/L on day 3. On day 3, the patient developed a syncopal episode and found to have a significant orthostatic BP drop. Because of the sudden drop in his Hgb level, he was subsequently taken for a computerised tomography (CT) scan of his abdomen/pelvis which revealed a large diffuse psoas muscle hematoma (Figure 1, Figure 3 supplemental) with blood escaping the muscle and surrounding the renal (Gerota's) fascia (Figure 2, Figure 4 supplemental).

He subsequently received 2 units of blood as well as fluids and on day 4 was watched to assess for continued bleeding as well as the possibility for compartment syndrome. His right thigh pain improved and his anaemia subsequently improved to 93 g/L after transfusion and remained stable for the rest of his admission. His orthostatic hypotension was corrected with fluids and the blood transfusion. The patient was discharged home with the instructions to hold Rivaroxaban and to follow up with his cardiologist for reassessment of his anticoagulation regimen.

Discussion

Newer oral anticoagulant agents are currently being utilized to address the shortcomings of traditional anticoagulation with warfarin and heparin. Rivaroxaban directly inhibits Factor Xa and interrupts both the intrinsic and extrinsic pathway of the coagulation cascade [4]. Rivaroxaban is currently indicated for use in patients for AF, prophylaxis of

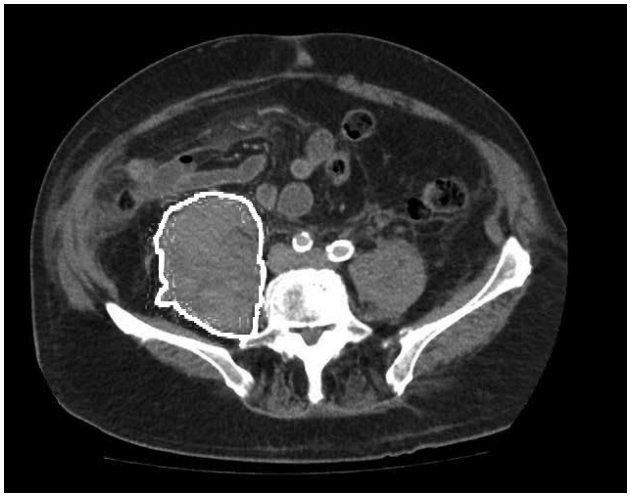

Figure 1. CT scan without contrast showing enlargement of the psoas muscle due to infiltration of blood into the tissues of the psoas

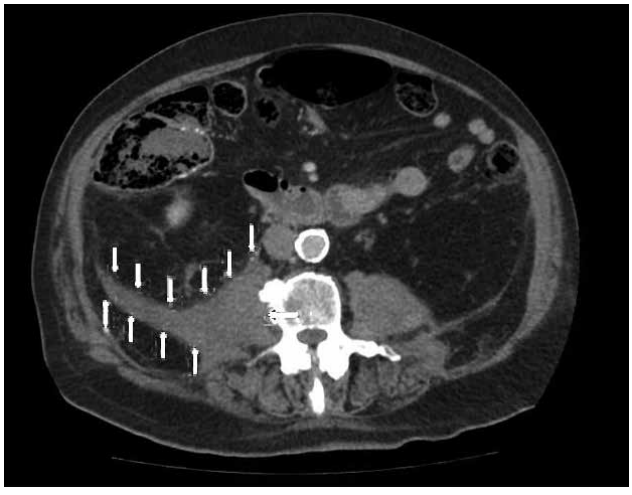

Figure 2. A CT scan without contrast showing bleeding into the psoas muscle with subsequent blood loss surrounding the renal fascia

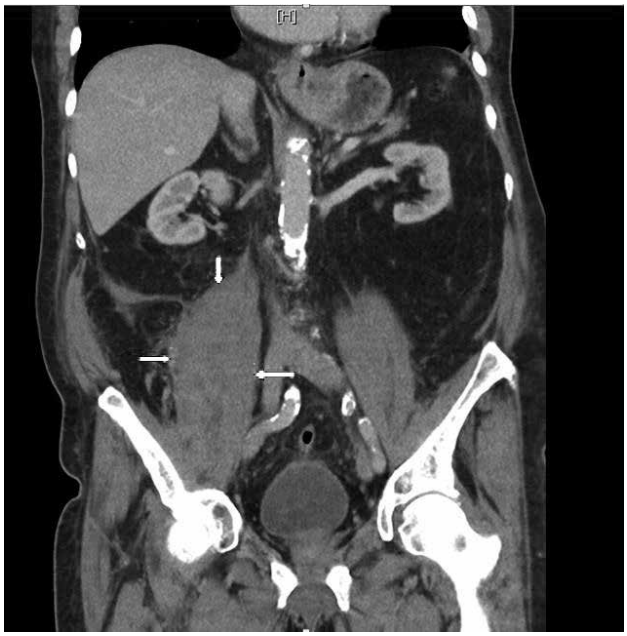

Figure 3. CT scan without contrast; coronal view; showing enlargement of the psoas muscle due to infiltration of blood into the tissues of the psoas.

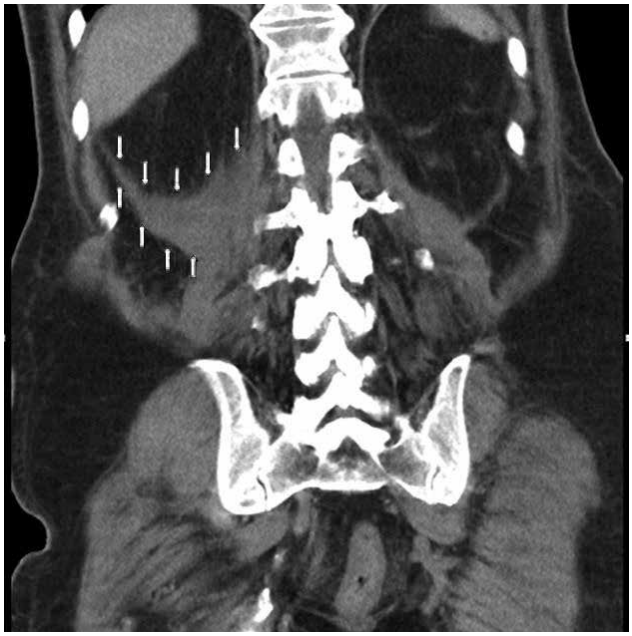

Figure 4. CT scan without contrast; coronal view; showing bleeding into the psoas muscle and the surrounding renal fascia

deep venous thrombosis, and prophylaxis of deep vein thrombosis after hip and knee replacement surgery [5-9]. The use of Rivaroxaban is increasing as it does not require INR monitoring, leading to more events of bleeding complications. There are no specific antidotes for the anticoagulant effect of Rivaroxaban, thus the management of the bleeding complications include support and observation. The non-Vitamin K antagonist oral anticoagulants (NOACs) have a short half-life with large inter-individual variability and the possibility of available reversion is poorly known, especially the efficacy/tolerance profiles of non-specific pro-coagulant drugs. 4-factor prothrombin complex concentrates (PCCs), activated PCC, and factor VIII inhibitor bypassing activity (FEIBA) are proposed modalities of treatment in life threatening bleeding [10].

Spontaneous bleeding associated with the use of Rivaroxaban has been reported in the literature. Jaeger *et al.* describes a case of a 61 year old female who developed a spontaneous spinal subdural hematoma while using Rivaroxaban and subsequently developed a transient paralysis which resolved without surgical intervention [11]. Kocayigit *et al.* reported a 75 year old female with repeated coughing episodes who developed a spontaneous rectus sheath hematoma [12]. In our case, the patient developed spontaneous retroperitoneal psoas muscle hematoma and was managed conservatively with fluids and a blood transfusion. No similar reported cases of a spontaneous retroperitoneal hematoma of the psoas muscle due to Rivaroxaban therapy have been previously reported in the literature.

Conclusion

Rivaroxaban use is associated with several adverse events, most prevalent is an increased bleeding risk. Healthcare providers need to be aware of the risk of spontaneous bleeding associated with Rivaroxaban use. Further studies need to be conducted to fully quantify the incidence and risk factors for spontaneous retroperitoneal bleeding while on Rivaroxaban therapy.

Conflict of interest: None declared

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1.14. The Editors recommend that submitted manuscripts conform with the 'Uniform Requirements for Manuscripts Submitted to Biomedical Journals', developed by the *International Committee of Medical Journal Editors* (ICMJE), and available on the **International Heart and Vascular Disease Journal** website www.cardioprogress.ru, in the 'For Authors' section.

1.15. Adhering to the standards outlined in this document will lead to faster reviewing, editing, and publishing of manuscripts accepted for publication. Manuscripts submitted outside the standards on design and formatting for this journal may not be accepted by the Editors.

2. General recommendations for submission of original scientific works

2.1. The Editors recommend that results of randomized controlled trials conform to the 'Consolidated Standards of Reporting Trials' (CONSORT) guidelines. Information on these standards are available on the CONSORT website: www.consort-statement.org

2.2. A manuscript should be typed using the Times New Roman font (12 points, double spacing; with 2 cm at the top, bottom, left and right margins). The length of a manuscript, including references, schedules, drawings and tables, should not exceed 12 standard typewritten pages (1 page is 1800 letters or symbols, including spaces). A case study should not exceed 6 standard pages. Reviews and lectures should not exceed 25 standard pages.

2.3. Manuscripts should be organized as follows: 1) title page; 2) structured summary and keywords; 3) list of abbreviations; 4) text; 5) acknowledgements (if applicable); 6) references; 7) names and legends of pictures, tables, graphics, and photocopies in the order they appear in the manuscript; 8) drawings, tables, graphics, and photocopies should be submitted on separate pages in the order they appear in the manuscript. Numeration of pages should begin from the title page.

2.4. If the manuscript contains pictures, tables, graphics, or photocopies that have been published previously, reference to the author(s) and publication is necessary. It is the Author's responsibility for determining whether permission is required for the duplication of material, and for obtaining relevant permission.

2.5. Manuscripts based on reviews of original research works should contain the following sections: Introduction (reflecting the urgency of a problem and research goals); Material and methods; Results; Discussion of the obtained results and Conclusion. The text should be clear, brief and without repetition.

3. Publication of uncontrolled trials results

3.1. An uncontrolled trial is a research without a control group.

3.2. Manuscripts based on uncontrolled trials results will be accepted for publication in the 'Practical Experience' column only if the uncontrolled design of the study is described in the Material and methods and Discussion sections. It is important not to exaggerate the significance of results in the Conclusion' section.

4. Ethical aspects

4.1. Trials should be conducted in accordance with principles of "good clinical practice". Participants of a trial should be informed about the purpose and main aims of the trial. They must sign to confirm their written informed consent to participate in the trial. The «Material and methods» section must contain details of the process of obtaining participants informed consent, and notification that an Ethics Committee has approved conducting and reporting the trial. If a trial includes radiological

methods it is desirable to describe these methods and the exposure doses in the «Material and methods» section.

4.2. Patients have the right to privacy and confidentiality of their personal data. Therefore, information containing pictures, names, and initials of patients or numbers of medical documents should not be presented in the materials. If such information is needed for scientific purposes, it is necessary to get written informed consent from the research participant (or their parent, their trustee, or a close relative, as applicable) prior to publication in print or electronically. Copies of written consent may be requested by the Editors.

4.3. Animal trials must conform to the 'International Guiding Principles for Biomedical Research Involving Animals', adopted by the *Council for International Organizations of Medical Sciences* (CIOMS) in 1985.

5. Authorship

5.1. Each author should significantly contribute to the work submitted for publication.

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6.1. It is desirable for authors to disclose (in a covering letter or on the title page) any relationships with industrial and financial organizations, which might be seen as a conflict of interest with regard to the content of the submitted manuscript. It is also desirable to list all sources of financing in a footnote on the title page, as well as workplaces of all authors (including corporate affiliations or employment).

7. Manuscript content

7.1. Title page

7.1.1. It should include the name of the article (in capital letters); initials and last names of the authors; the full name of the institution which supported the manuscript, together with the city and country, and full mailing address with postal code of that institution.

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7.2.1. Summary (limited to 300 words) should be attached to the manuscript. It should include the full title of the article, last names and initials of the authors, the name of the institution that supported the manuscript, and its full postal address. The heading of the summary should contain the international name(s) of any drug(s) mentioned.

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7.3. List of abbreviations and their definitions

7.3.1. To conserve space in the journal, up to 10 abbreviations of general terms (for example, ECG, ICV, ACS) or names (GUSTO, SOLVD, TIMI) can be used in a manuscript. List of abbreviations and their definitions should be provided on a separate page after the structured summary (for example, ACS – aortocoronary shunting). Only words generally accepted in scientific literature should be used.

7.4. Text

7.4.1. Original studies should be structured as follows: Introduction, Material and methods, Results, Discussion and Conclusion.

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Periodicals

Go AS, Hylek EM, Phillips KA, et al. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the Anticoagulation and Risk factors in Atrial Fibrillation (ATRIA) Study. JAMA. 2001;285(18):2370-5.

Sources in Russian with transliteration:

Baevskiy RM, Ivanov GG, Chireykin LV, et al. Analiz variabel'nosti serdechnogo ritma pri ispol'zovanii razlichnyh jelektrokardiograficheskih sistem (metodicheskie rekomendacii) [Analysis of heart rate variability using different ECG systems (guidelines)]. Vestnik aritmologii. 2002;24:65-86. Russian.

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Chapters in a book

Swanton RH, Banerjee S. Cardiac Failure. In: Swanton RH, Banerjee S., editors. Swanton's Cardiology: A concise guide to clinical practice. 6th ed. Oxford: Blackwell Publishing; 2008. p. 255-309.

Sources in Russian with transliteration:

Belenkov YuN. Kardiomiopatii [Cardiomyopathies]. In.: Chazov EI, Belenkov YuN., editors. Racional'naja farmakoterapija serdechno-sosudistyh zabolevanij: Rukovodstvo dlja praktikujushhih vrachej [Rationale for drug therapy of cardiovascular diseases: A guide for medical practitioners]. Moscow: Litterra; 2006. p. 431-452. Russian.

Reference to a book chapter should be arranged in the following order: authors of the corresponding chapter; name of the chapter; «In:»; editors (title authors) of the book; name of the book; number of issue, publisher; city of publishing; year of publishing; pages of the corresponding chapter. Punctuation should be considered. There are no quotation marks.

Books

Sources in Russian with transliteration:

Shlyakhto EV, Konradi AO, Tsyrlin VA. Vegetativnaja nervnaja sistema i arterial'naja gipertenzija [The autonomic nervous system and hypertension]. St. Petersburg (Russia): Meditsinskoe izdatel'stvo; 2008. Russian.

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Websites should be provided in the list of references, but not in the text. References to websites should be made only when original text is not available. References should be provided in the following way:

WHO. Severe Acute Respiratory Syndrome (SARS) [Internet]. [place unknown: publisher unknown]; [updated 2010 June 1; cited 2010 June 10]. Available from: http://www.who.int/csr/sars/.

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