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Effects produced by automated plasmapheresis on morphofunctional data on cardiovascular system performance in ischemic heart disease patients

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Abstract

We have performed the study of the effects made by the automated plasmapheresis application on ischemic heart disease clinical manifestations, echocardiographic indices and heart rate variability in patients with exertional angina III-IV functional class. It has been found that the applied plasmapheresis method is capable to reduce the severity of the disease clinical manifestations and improve the echocardiographic characteristics of the heart, in particular, reduce the level of end-diastolic volume, and increase ejection fraction. The clinical effect is already apparent at the early stages of the treatment and remains unchanged even after 6 months thereof. Also revealed has been the normalization of heart rate variability, indicating a decreased activity of the sympathetic nervous system. It is concluded that the plasmapheresis method can be successfully used in practice by a wide range of hospitals, where patients with ischemic heart disease are monitored, including the ambulatory conditions.

Keywords

Exertional angina, Plasmapheresis, Echocardiography, Heart rate variability, Holter monitoring

Imprint

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Introduction

It is well known that so far CVD and first of all ischemic heart disease (IHD) remain the main causes of mortality of population in the Russian Federation [2]. In addition to the existing medication and a wide application of invasive methods for IHD treatment, for last decades some methods of alternative treatments have being introduced into clinical practice for this sort of patients that includes the efferent therapy techniques [1, 3-5]. In this connection, we should mention that the problem of an adequate extracorporeal assistance retains its topicality in the context of the complex treatment of ischemic heart disease because there are a number of factors as listed below: a high occurrence rate of this pathology, the disease severity, some predictable complications, an increasing cohort of younger patients and resistance to medication due to available metabolic disorders [2, 4, 12].

One of the most pathogenetically substantiated and, therefore, promising approaches to the treatment of the patients with ischemic heart disease (IHD), in particular exertional angina, is the use of plasmapheresis (PP). However, at the same time, there are only some fragmented single reports on capabilities of this approach, and there are no data on factors responsible for effects and determining efficacy of the plasmapheresis method application; no works are available which relate to justification of the use of different modes of PP application in CHF therapy.

Aims

The aim is to study some effects produced by the automated plasmapheresis (PP) technique on clinical signs in ischemic heart disease patients and on on instrumental laboratory data on the cardiovascular system performance

Materials and methods

The study was carried out on the basis of the Russian Institution for Medical Problems of the North Region of the North Division of the Russian Academy of Med-

ical Sciences and the Clinical Transfusiology Chair at the Federal State Autonomous Educational Institution of Higher Education I.M. Sechenov – First Moscow State Medical University of the Ministry of Health of the Russian Federation (Sechenov University).

For the purpose of investigation of the PP efficacy, an examination and treatment of 130 IHD patients (exertional angina pectoris functional class III-IV) have been performed. The recorded disease history of the patients has been ranged from 2 till 22 years. The main test group covered 65 males and 33 females, aged from 40 to 75, with an average age 56,8±15,1 years.

32 patients (in the reference group) have completed the standard medication treatment without PP applications (medication including nitrates, beta-blockers, antiplatelets, angiotensin converting enzyme inhibitors and some other medical drugs).

The main test group has covered patients (n=98) who have undergone plasmapheresis (PP) in addition to the standard treatment.

Plasmapheresis was carried out using the Haemonetics device. Before performing the plasmopheresis treatment, a patient's state was assessed, laboratory tests were performed (complete blood count, biochemical studies, coagulogram), a vascular access was selected, a volume of extracted plasma was identified and an amount and the character of plasma-substituting solutions, which were expected to use, were evaluated. When selecting the treatment procedure options, we took into account the volume of plasma removed per treatment session and per course, and the characteristics of substituting solutions (crystalloid, colloid). The total volume of plasma, which was removed in a treatment session, ranged from 0.3 to 1.5 l, and the course included 3-4 treatment sessions. During a single treatment procedure, 25-50% and more of the circulating plasma volume was removed, depending on the patient's actual state, his/her clinical symptoms, comorbidity, the patient's age, the presence of cardiac arrhythmias and the level of electrolytes. The removed plasma was replaced with crystalloid (0.9% sodium chloride solution, Ringer's solution) and colloid (rheopolyglukin) or protein (5% albumin) solutions.

During the comprehensive examination of all above mentioned patients, the following has been carefully analyzed: their medical history records, their complaints and disease manifestations; performed were the relevant instrumental laboratory tests and examinations. The clinical efficacy of the treatment has been evaluated according to the following parameters:
- the number of anginal chest pain episodes per day (NACPED);
- the duration of a pain episode (DPE);
- a total of nitroglycerin tablets taken by the patient in a day (NTT).

Carried out was an instrumental examination, including roentgenoscopy of the lungs and the mediastinum using X-ray machine Siemens Axiom R 200; for each individual recorded were an ECG using GE MAK 5000 device and an echocardiogram with GE Vivid 4. When assessing morphofunctional cardiac parameters, measured were an end-systolic left ventricular volume (ESV), an end-diastolic left ventricular volume (EDV), stroke volume (SV), ejection fraction (EF), left atrial volume (LA), hemodynamic parameters Ve and Va, Ve/Va ratio and VIR.

The 24 hour-Holter montoring has been completed in all patients followed by Heart Rate Variability (HRV) analysis, including both the time-related and power spectral analysis, since the Holter monitoring is the most informative, wide-spread, technique to assess the tonus of the autonomic nervous system. In doing so, the time and frequency domain analysis has been applied. For the purpose of this study, we have used the complete set of the following parameters: the R-R interval data (standard deviation, SDNN, μs.), the standard deviation of all mean 5-minute normal sinus intervals over 24 hours, SDANN, μs., and square root of the mean of the sum of the squares of differences between adjacent normal R-R intervals, r-MSSD. In this case, the SDNN index reflects the general tonus of the autonomous system activity; the parasympathetic tonus is described by the r-MSSD index, and the SDANN parameter is a fingerprint of the sympathetic system activity.

For the purpose of the heart rate variability analysis, we have utilized the complete sets of the parameters as listed below: the spectral power of High Frequency waves (HF), the respective Low Frequency (LF) and Very Low Frequency (VLF) components (the frequency ranges 0,15-0,35 Hz, 0,05-0,15 Hz and 0,004-0,05 Hz, respectively); we have also estimated an LF/HF ratio, too. It is considered that HF is an indication of the tonus modulated by the parasympathetic activity of ANS, while the LF component, the LF/HF ratio and the VLF component are distinguishing features of the sympathetic nervous system activity.

The data have been collected and their profiles have been compared upon the completion of 1, 7, 30 and 180 days of the treatment.

The obtained statistics parameters have been processed with use of the Statistica 8.0 software package. The applied methods of the descriptive statistics analytics have employed estimation of the set's mean value (M) and the standard deviation. The Chi-square test (known as $\chi 2$test) with the Yates continuity correction has been applied by us in order to establish statistically significant relationships between categorical qualitative binary variables between the compared paired groups. The nonparametric Mann–Whitney U test has been conducted in order to compare the differences that come from the quantitative indicators in different groups.

The critical level to indicate that the null hypothesis is true has been assumed to be 0,05.

Results and discussion

The completed designed studies have shown that plasmapheresis, included into the therapy scope, administered to the patients with exertional angina functional class III-IV, has made a noticeable effect on the majority of the recorded clinical and instrumental laboratory data. So, the changes in the clinical manifestations in these patients have been detected already within the first 7 days from the beginning of the plasmapheresis use, and the changed parameters have been maintained within the 1- to 6-month period: a number of the parameters have demonstrated significant changes as compared with the respective parameter values recorded in the reference group. Specifically, we have reported an improved condition pattern in the above category of the patients: the number of angina-attack-associated chest pain episodes has been decreased by 24-43%; recorded has been a reduction in the chest pain episode duration by 34-48 %, and the use of the nitroglycerine tablets has been reduced up to 32-41 % (see Table 1 herein).

Improved echocardiographic characteristics in the patients with exertional angina functional class III-IV, who have completed plasmapheresis procedures, have been reported within the 1- to 6-month period: there have been significant changes in the parameters detected, as compared with those in the reference group, as follows: the EDV value has been found to be higher by 2-6 %, the ESV parameter has been detected by 6-14% higher, and the ejection fraction value has been increased by 6-7% (see Table 2 herein). In general, the patients in the main test group have demonstrated favorable changes in the parameters, that has indicated the normalization both of the diastolic and systolic function of the heart.

Table 1
Dynamics of clinical data in patients with stable exertional angina functional class III-IV: the standard treatment vs. standard treatment approach including PP (M±m)

Data	Reference group (n=32)			Main test group (n=98)		
	7 days	1 month	6 months	7 days	1 month	6 months
NACPED	2,72±0,34	3,61±0,51	3,78±0,62	1,49±0,30*	2,06±0,40*	2,88±0,49
DPE, min.	5,72±0,74	4,78±0,68	5,83±0,96	2,32±0,59*	3,18±0,79*	3,06±0,79*
NTT a day	1,67±0,34	1,79±0,40	2,82±0,45	0,49±0,20*	1,06±0,40*	1,92±0,49*

Note: * - variances are plausible (at p<0,05) referred to the respective level in the reference group

Table 2
Dynamics of echocardiographic data in patients with stable exertional angina functional class III-IV: the standard treatment vs. standard treatment approach including PP (M±m)

Data	Reference group (n=32)			Main test group (n=98)		
	7 days	1 month	6 months	7 days	1 month	6 months
ESV (ml)	61,2±1,6	59,4±3,6	60,4±1,1	55,3±2,8*	51,3±4,8*	56,7±2,8
EDV (ml)	142,2±8,3	138,5±7,2	140,3±2,7	138,5±5,6	130,5±3,6	138,2±5,6
SV (ml)	81,0±8,7	79,1±1,7	81,8±1,2	83,2±1,8	79,2±1,8	80,2±10,1
EF (%)	57,0±4,7	57,1±3,7	51,8±1,1	60,1±2,8	60,7±2,8	55,6±2,8
LA (ml)	41,5±3,1	40,5±5,1	40,9±2,1	40,2±4,8	39,5±1,3	40,8±2,5
Ve (m/s)	0,513±0,16	0,532±0,24	0,521±0,019	0,525±0,015	0,553±0,011	0,522±0,019
Va (m/s)	0,502±0,27	0,493±0,18	0,508±0,014	0,478±0,029	0,467±0,029	0,492±0,039
Ve/Va	0,981±0,16	1,091±0,08	1,052±0,018	1,086±0,067*	1,213±0,087*	1,061±0,027
VIR (ms)	94,6±4,1	93,4±3,6	94,3±3,6	93,4±1,8	90,3±2,8	92,2±2,4

Note: * - variances are plausible (at p<0,05) referred to the respective level in the reference group.

Table 3
Dynamics of heart rate variability values in patients with stable exertional angina functional class III-IV: the standard treatment vs. standard treatment approach including PP (M±m)

Data	Reference group (n=32)			Main test group (n=98)		
	7 days	1 month	6 months	7 days	1 month	6 months
STE episodes	3,16±0,62	2,90±0,51	3,10±0,57	1,48±0,49	1,39±0,40	1,47±0,49*
STD	142,2±8,3	138,5±7,2	140,3±2,7	138,5±5,6	130,5±3,6	138,2±5,6
episodes	1,97±0,40	1,95±0,34	1,88±0,40	1,48±0,30*	1,33±0,30*	1,42±0,40
VE	435,2±87,7	415,1±80,9	423,3±86,0	76,5±21,8*	67,5±18,8*	72,2±20,8*
SVE	58,2±17,0	57,4±16,4	56,2±17,0	54,1±25,7	53,1±24,7	55,4±24,7
SDNN (ms)	107,3±12,4	112,0±13,6	108,4±14,1	114,2±19,8	118,2±20,8	113,3±21,8
SDANN (ms)	98,8±12,4	101,2±13,6	99,3±13,6	110,2±34,6	109,6±36,6	109,3±36,6
RMSSD (ms)	61,5±13,0	63,1±13,0	62,7±13,6	82,4±30,7*	89,5±32,7*	85,1±31,7*
VLF	1833±482	1857±534	1838±552	1963±659	2055±719	1725±619
LF (ms2)	994,5±203,1	989,3±207,0	986,7±210,4	1354±342	1356±331	1299±320
HF (ms2)	785±143	854±165	805±152	999±236*	1006±241	1004±242*
L/H	1,261±0,351	1,109±0,311	1,221±0,407	1,399±0,287*	1,337±0,307	1,292±0,346

Note: * - variances are plausible (at p<0,05) referred to the respective level in the reference group.

Upon expiration of 6 months of the studies, the dynamics of the changes has been found to be slightly less pronounced, but however in this period of time the majority of the analyzed parameters in the patients of the main test group has shown positive dynamics of the changes: we have observed a decrease in the ESV and EDV values and an increase in the Ve and Ve/Va parameters.

Our HRV analysis of the Holter monitoring data in patients with exertional angina functional class III-IV has shown that the applied approaches to the treatment in the patients both of the reference group and main test group have produced some effects on the HRV data: that has induced an increase in the HRV HF component (RMSSD, HF), a decrease in the LF/HF index, a reduction in the number of ST depression and elevation episodes and the VE and SVE events a day (see Table 3 herein). At the same time, we should note when comparing the efficacy of both treatment versions, more favorable outcomes have been found in the main test group, where the combined therapy including PP has been used. In case with the PP-integrated treatment, we have detected differences in the data characterizing the efficacy of the treatment in all periods of our studies: the parameters of the Holter monitoring, which reflect the heart rate variability, the state of the electrical stability of the heart and the occurrence of the supraventricular extrasystole episodes have demonstrated better dynamics in those patients with stable exertional angina functional class III-IV, who have completed the PP-integrated therapy course.

So, all major Holter monitoring data, which reflect the heart rate variability, the state of the electrical stability of the heart and the occurrence rate of ventricular and supraventricular extrasystole episodes have been characterized by more favorable dynamics in those patients, suffering from exertional angina functional class III-IV, who have completed the treatment with PP included. The positive differences have been detected in this sort of patients already after day 7 from the beginning of the therapy, and the improved data have remained unchanged even 6 months later from the date of the treatment beginning.

Conclusion

Despite the fact that at present most experts believe that surgery techniques used to treat IHD are considered to be rather effectively in elimination of occlusions in the blood vessels, however the application of this approach cannot prevent further progression of an atherosclerotic process, since homeostasis disorders, which form the basis for atherogenesis, remain unaffected. Threatening recurrence of angina pectoris after surgery or surgical radiography, the probable MI recurrence, the necessity of completion of repeated more dangerous surgery, despair of a patient in case of his/her affected distal vascular bed can impose the condition to search for fresh methods of prevention of coronary atherosclerosis and vascular damages of other localization [3, 4, 6, 11].

Our completed studies have demonstrated that the use of PP within the framework of the complex therapy of the patients suffering from exertional angina functional class III-IV makes a favorable effect on clinical signs of the disease and the relevant data on the morphofunctional state of the cardiovascular system in this category of the patients.

It is known that the main mechanisms of atherogenesis are hypercoagulation in the coronary arteries, deficit of fibrinolysis factors, activation of thrombocytes, damage of the coronary vessel intima, dysfunction of endothelial cells and the NO production. The activation of the full spectrum thereof takes place in the acute phase of atherogenesis [10, 12]. Taking into account all the above, we can arrive at a conclusion that PP, designed to eliminate the widest range of pathogenic agents and substances, shows most pronounced clinical effect in patients with unstable or progressing angina pectoris. This phenomenon has been supported by the results not only of our study, but also by the evidence data presented by other researchers [1].

As to pathogenesis of developing pathological damages in blood vessels, a role of chronic inflammation, inducible and maintainable by a variety of infection agents, cannot be excluded [3, 8, 12]. According to most advanced concepts, a local (in an atherosclerotic plaque) and a systemic inflammation play their fundamental role in developing atherosclerosis and complications of the latter [7-10]. The presence of hemodynamically significant stenosis cases of the vascular bed in patients is reported both for a low cholesterol level and a low atherogenicity index. Our assessment of the echocardiographic parameters in the examined patients has demonstrated that there is a tendency to the normalization of the above parameters with a more pronounced effect in the main test group. Improved echocardiographic characteristics in the chronic heart failure patients functional class III-IV upon completion of their PP-integrated therapy have been reported within the 1- to 6-month period: there have been significant changes in the parameters detected, as compared with those in the reference group, which are as follows: the EDV and the ESV values have been decreased; the ejection fraction value has been increased, and the Ve index has been reported to be higher. The clinical effect of plasmapheresis has been revealed at the early stages of the treatment and remained unchanged even 6 months later. The comparison study of the data collected in the above two groups bears witness to the fact that an integration of plasmapheresis into the combined therapy of the patients leads to more pronounced favorable shifts in the echochardiography examination data.

Our HRV analysis has shown that there are changes in some spectral power analysis data. In particular, in the patients of this category we have recorded an increase in shares of the Very Low and High Frequency waves that has indicated an elevated activity of the parasympathetic nervous system. The variance of the HRV parameters recorded on day 7 from the beginning of the treatment has remained unchanged later: upon expiration of 1 month to 6 months from the beginning of the standard approach therapy in chronic IHD patients, respectively. In general, the comparative study of the Holter monitoring results obtained in the group of the patients who have been treated according to the standard approach to therapy versus those who have received the plasmapheresis-added therapy have shown that the latter has many points in its favor: the patients of the main test groups have been characterized by the reduced occurrence rate of ST depression and elevation episodes and VE and SVE events. Significant differences have been detected in the data profiles pertaining to the spectral analysis data on the HF, LF components and the LF/HF ratio.

So, we may conclude that the offered introduced method as described above has demonstrated its safety for the specified category of the patients; the method shows its clinical and laboratory-related efficacy, so that it makes possible to integrate the PP option in the framework of other therapy schedules. We should note that the applicability of the method is cost-effective: it can be easily introduced in practice by a wide range of hospitals and treatment institutions, which focus on treatment of IHD, including ambulance entities.

Statement on ethical issues

Research involving people and/or animals is in full compliance with current national and international ethical standards.

Conflict of interest

None declared.

Author contributions

The authors read the ICMJE criteria for authorship and approved the final manuscript.

References

1. Voinov VA. Plasmapheresis in antiphospholipid syndrome. Efferent and physico-chemical medicine.2012;1:47–50. [in Russian]

2. Oganov RG, Maslennikova GY. Demographic trends in the Russian Federation: the contribution of diseases

of the circulatory system. Cardiovascular therapy and prevention. 2012; 1: 5-10. [in Russian]
3. Petukhov EV, Konovalov GA, Barinov V. Rheopheresis value in the treatment of patients with atherosclerosis. XIV Conference of the Moscow City Society hemopheresis "Transfusion and detoxification therapy in case of emergency." M., 2006, pp 33-34. [in Russian]
4. Postnikov AA, Model SV, Bozhyev AA, et al. Coagulation and rheological mechanisms of therapeutic efficacy of plasmapheresis in patients with coronary heart disease. Mat. First All-Russian scientific. conf. "Clinical Hemostasis and hemorheology in cardiovascular surgery." Moscow, 2003. p. 75 [in Russian]
5. Andrulli S, Bigi MC, Granata A, et al. Therapeutic plasma exchange: a review of the literature. G. Ital. Nefrol. 2012;29(54):40-8.
6. Baskurt OK. In vivo correlates of altered blood rheology. Biorheology. 2008;45(6):629-38.
7. Chin SP, Jeyaindran S, Azhari R, et al. Acute coronary syndrome (ACS) registry-leading the charge for National Cardiovascular Disease (NCVD) Database. Med. J. Malaysia. 2008;63:29-36.
8. Filipovic N, Ravnic D, Kojic M. et al. Interactions of blood cell constituents: experimental investigation and computational modeling by discrete particle dynamics algorithm. Microvasc. Res. 2008;75(2):279-84.
9. Leschke M. Rheology and coronary heart disease. Dtsch. Med. Wochenschr. 2008;133(8):270-3.
10. Libby P, Ridker PM, Maseri A. Inflammation and atherosclerosis. Circulation. 2002;105:1135–43.
11. Mancini E, Santoro A. Plasmapheresis in intensive care. G. Ital. Nefrol. 2012;29(54):91-102.
12. Ridker PM. Inflammatory biomarkers and risks of myocardial infarction, stroke, diabetes, and total mortality: implications for longevity. Nutr. Rev. 2007;65(12):253–9.