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СОДЕРЖАНИЕ

CONTENTS

СОДЕРЖАНИЕ

CONTENTS

CARDIAC RESYNCHRONIZATION THERAPY WITH OR WITHOUT AN IMPLANTABLE CARDIOVERTER DEFIBRILLATOR IN DIFFERENT GROUPS OF HEART FAILURE PATIENTS

Perisic Zoran[1,4], Kostic Tomislav[1], Ilic Stevan[2,5], Koracevic Goran[1,4], Djindjic Boris[1,4], Milic Dragan[2,4], Mitov Vladimir[3], Salinger Martinovic Sonja[1,4], Stanojevic Dragana[1], Golubovic Mladjan[2]

Aim. Patients with heart failure have poor prognosis and mortality rate is between 15–60% per year. Implantable cardioverter-defibrillators and cardiac resynchronization therapy have been shown to improve survival, decrease hospital readmissions and mortality, and improve functional status and quality of life in patients with heart failure and left ventricular systolic dysfunction. Aim of the study was to examine the effects of different CRT devices in carefully selected heart failure patients during 1 year.

Material and methods. We included 98 heart failure patients. First group (n=60) received CRT-P, while in second group (n=38) were patients with CRT-D pacemaker (with an additional cardioverter-defibrillator option).

Results. Data gathered in our the study showed that both CRT-P and CRT-D in adequately selected heart failure patients improve different clinical parameters: symptoms, echocardiographic parameters, decrease QRS duration, increase 6 min walk test distance, decrease mortality rate.

Conclusion. Patients with both CRT-P and CRT-D showed improvement in heart failure symptoms and CRT had significant influence on disease prognosis during 1 year of follow up. Nevertheless we do not have the perfect criteria for selection of patients and their follow up after the device implantation. In patients with the rhythm disturbances CRT-D option is the right choice only if the patient has the indications for resynchronization therapy as well. This choice however depends on clinical judgment of the operator more than on strict protocols and guidelines which are necessary but we need more clinical trials to support current hypothesis.

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Key words: chronic heart failure, pacemaker, prognosis.

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CRT — cardiac resynchronization therapy, CRT-P — cardiac resynchronization therapy pacemaker, CRT-D — cardiac resynchronization therapy pacemaker with an ICD, COMPANION — Comparison of Medical Therapy, Pacing, and Defibrillation in Chronic Heart Failure study, CARE-HF — Cardiac Resynchronization–Heart Failure study, EDD — end-diastolic diameter, EDV — end-diastolic volume of left ventricle, ESV — end-systolic volume of left ventricle, ICD — Implantable cardioverter defibrillator, IVCD — inter-ventricular conduction delay, LV — left ventricle, LVEF — left ventricle ejection fraction, MIRACLE — Multicenter InSync randomized Clinical evaluation study, MUSTIC-SR — MUltisite STimulation In Cardiomyopathies in Sinus Rhythm study, NYHA — New York Heart Association, PEP LV — pre-ejection interval of left ventricle, PEP RV — pre ejection interval of right ventricle, RV — right ventricle, Six (6) MWD — six minute walking distance, SPWMD — septal-posterior wall motion delay, VT — ventricular tachycardia, VF — ventricular fibrillation.

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СЕРДЕЧНАЯ РЕСИНХРОНИЗИРУЮЩАЯ ТЕРАПИЯ С ИЛИ БЕЗ ИМПЛАНТИРУЕМОГО КАРДИОВЕРТЕР-ДЕФИБРИЛЛЯТОРА В РАЗЛИЧНЫХ ГРУППАХ ПАЦИЕНТОВ С СЕРДЕЧНОЙ НЕДОСТАТОЧНОСТЬЮ

Perisic Zoran[1,4], Kostic Tomislav[1], Ilic Stevan[2,5], Koracevic Goran[1,4], Djindjic Boris[1,4], Milic Dragan[2,4], Mitov Vladimir[3], Salinger Martinovic Sonja[1,4], Stanojevic Dragana[1], Golubovic Mladjan[2]

Цель. Пациенты с сердечной недостаточностью (СН) имеют плохой прогноз, а уровень смертности между 15–60% в год. Имплантируемые кардиовертеры-дефибрилляторы и сердечная ресинхронизирующая терапия показали улучшение выживаемости, снижение повторных госпитализаций и смертности, а также улучшение функционального статуса и качества жизни больных с СН и систолической дисфункции левого желудочка. Цель исследования состояла в изучении влияния различных СРТ-устройств на тщательно отобранных пациентов, страдающих СН в течение 1 года.

Материал и методы. Мы включили в исследование 98 пациентов с СН. Первая группа (n=60) получила РСТ-Р, в то время, вторую группу (n=38) составляли пациенты с CRT-D кардиостимуляторами (вариант с дополнительным кардиовертер-дефибриллятором).

Результаты. Данные, полученные в нашем исследовании показали, что и РСТ-Р и РСТ-D у надлежащим образом выбранного пациента с СН способны улучшить различные клинические параметры — симптомы, эхокардиографические параметры, уменьшение длительности комплекса QRS, увеличение теста 6 мин ходьбы, снижение смертности.

Вывод. Пациенты с РСТ-Р и РСТ-D показали улучшение симптомов СН, и СРТ имела значительное влияние на прогноз заболевания в течение 1 года наблюдения. Тем не менее, мы не имеем идеальные критерии для отбора пациентов и их последующего ведения после имплантации устройства. У пациентов с нарушениями ритма РСТ-D вариант является правильным выбором, только если пациент имеет показания для ресинхронизирующей терапии. Однако этот выбор зависит от клинического решения лечащего врача больше, чем от строгих протоколов и рекомендаций, которые являются необходимыми, но мы нуждаемся в дополнительных клинических испытаниях для поддержки существующей гипотезы.

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Ключевые слова: хроническая сердечная недостаточность, наличие кардиостимулятора, прогноз.

Introduction

Prognosis is poor in heart failure patients and mortality rate is 15–60% in different population groups. It mainly depends on cardiac status which important indicators are left ventricular ejection fraction (LVEF), end-systolic and end-diastolic volumes of left ventricle (EDS, EDV), and left ventricular wall stress. The major cause of heart failure in developed countries is myocardial infarction [1]. It has been shown that mortality rate in patients after myocardial infarction and LVEF<25% was about 50% after one year,

while in those with LVEF around 55% it was <10%. Therefore, prognosis depends on preserved myocardial tissue after myocardial infarction [2]. It should be emphasized that mentioned correlation is not linear but exponential. If LVEF is lower than so called "critical value" of 30% mortality rapidly increases.

Ventricular arrhythmias and ventricular extrasystoles are common in patients with chronic heart failure and they are independent factors of worse prognosis. Patients with mild forms of chronic heart failure die of sudden cardiac death while those with advanced forms die of worsening heart failure.

Implantable cardioverter-defibrillators and cardiac resynchronization therapy have been shown to improve survival, decrease hospital readmissions and mortality, and improve functional status and quality of life in patients with heart failure and left ventricular systolic dysfunction. Implantable cardioverter-defibrillators are 99% effective in stopping life-threatening arrhythmias and are the most successful therapy to treat ventricular fibrillation, the major cause of sudden cardiac arrest. The use of these devices to prevent sudden cardiac arrest is supported by published guidelines. However, challenging patient cases exist that do not meet guideline requirements but due to recently published data, may benefit from cardiac resynchronization therapy pacemaker or cardiac resynchronization defibrillator therapy [3].

Current evidence-based guidelines recommend an implantable cardioverter-defibrillator for the primary prevention of sudden cardiac death in selected patients with impaired left ventricular function, and cardiac resynchronization therapy for improvement of symptoms and survival in selected patients with impaired left ventricular function and abnormal ventricular conduction. Many patients may be eligible for both treatments, but it does not necessarily follow that such patients would obtain additional benefit from the combined treatment over one treatment alone. A simple pragmatic approach would be to use resynchronisation therapy, in order to reduce symptoms and extend life in patients with New York Heart Association (NYHA) class 3 or 4 heart failure, with the addition of an implantable cardioverter-defibrillator left to clinical judgment on an individual basis when additional indications exist. When such an addition is contemplated the hypothesized incremental benefits in survival would need to be balanced by the possible increase in morbidity owing to, for example, inappropriate shocks [4].

Matherial and methods

Patient selection. We included in our study 98 patients with heart failure treated in Clinic for Cardiovascular diseases Nis during 2009 — January 2012. The first examined group consisted of 60 patients with CRT pace-maker – CRT-P (NYHA class 3/4, LVEF≤35%, QRS≥120ms, with dilated left ventricle (LV>55mm), on optimal drug therapy of heart failure and with fulfilled echocardiographic criteria for CRT therapy response (pre-ejection period of left ventricle >140msec, difference between left and right pre-ejection period >40msec, septal-posterior wall motion delay — SPWMD >135msec)) [5]. In the second examined group (n=38) we included patients with heart failure and CRT pace-maker with additional cardioverter-defibrillator option- CRT-D (NYHA class 3/4, LVEF≤35%, QRS ≥120ms, with dilated left ventricle (LV>55mm), on optimal drug therapy of heart failure and with fulfilled echocardiographic criteria for CRT therapy response and with heart rhythm disturbances as ventricular arrhythmias detected on 24-hour Holter ECG, patients who survived ventricular fibrillation (VF) or hemodynamically unstable ventricular tachycardia (VT), patients with non-ischemic dilated cardiomyopathy and significant left ventricular dysfunction with sustained VT and life expectancy longer than 1 year) [5].

All patients were on optimal drug therapy that included beta blocker, ACE inhibitor, aldosterone antagonist, diuretic, digitalis and antiarrhytmic agent as needed.

Parameters of interest and follow-up. In all patients before CRT implantation we performed 12 channels ECG, echocardiography, we measured 6 minute walking distance (6MWD), and determined subjective health status and drug compliance. After 1 year (at average) of CRT implantation we determined: NYHA functional class, QRS complex duration, echocardiographic parameters (LVEF; end-diastolic and end-systolic diameter of left ventricle — EDD, EDS; end-diastolic and end-systolic volumes of left ventricle — EDV, ESV; pre-ejection intervals of left and right ventricle — PEPLV, PEPRV; SPWMD), 6MWD and mortality rate. We also compared the number of hospitalizations due to worsening heart failure between observed groups.

In ***statistical analysis*** continuous variables are provided as means ±SD, and categorical variables are shown as percentages. Comparisons between groups for continuous variables were performed using Student *t* test or Wilcoxon's rank-sum test, as appropriate. Comparisons for categorical variables were performed using the chi-squared test. Multivariable logistic regression was used for the composite end point of death or re-hospitalization.

Results

Parameters at CRT-P and CRT-D implantation were not different in observed groups of patients (Table 1). The average age in patients with resynchronization therapy alone — CRT-P was 61,77±9,81 years while in those with CRT-D the average age was 58,11±13,24 with no significant difference (F=0,972, p=0,384). In the observed groups of patients there were more male patients: 44 (73,3%) with CRT-P and 34 (89,5%) with CRT-D pacemaker implanted. We did not find statistical difference in gender structure between groups (p>0,05). We found no significant difference in heart failure aetiology between observed groups of patients (Table 2). Dilated

Table 1

Parameters at CRT-P and CRT-D pacemaker implantation

	CRT-P (n= 60)	CRT-D (n= 38)
Pacing threshold A (volt, 0.5msec±SD)	1,16±0,76	0,9±0,45
Pacing threshold RV (volt, 0.5msec±SD)	0,75±0,85	0, 8±0,3
Pacing threshold LV (volt, 0.5msec±SD)	1,75±0,9	1,75±1,1
Sensing A (mv±SD) Sensing RV (mv±SD) Sensing LV (mv±SD)	2±0,76 9±4,7 11±3,8	1,8±0,65 12±3,6 12±4,4
Duration of the procedure (min)	70±12,8	87±14,3
Duration of the radiation (min) per procedure	9,6±5,3	10,8±0,3
Received dose of radiation (μGy/m^2) per procedure	1786±141,3	1911±95
Complications haematoma pneumothorax infection extracardiac stimulation	5 0 0 3	3 0 0 1

cardiomyopathy was a cause of heart failure in the majority of our patients.

After 1 year of follow-up only 26 (43,3%) patients with CRT-P pacemaker and 15 (39,4%) patients with CRT-D pacemaker were not hospitalized due to worsening of heart failure. Only 4 patients (6,7%) with CRT-P and 3 patients with (7,9%) pacemaker had 3 or more hospitalizations during 1 year after implantation (Table 3). There was not direct correlation between group of patients (type of CRT implanted) and number of hospitalizations (p>0,05). In the group of patients with CRT-P pacemaker before device implantation 40 patients (66,7%) were in NYHA 3 class, and 20 patients (33,3%) were in NYHA 4 class. One year after pacemaker implantation 30 patients (50%) were in NYHA 2 class. In the group of patients with CRT-D pacemaker before device implantation 26 patients (68,4%) were in NYHA 3 class and 12 patients (31,6%) were in NYHA 4 class. One year after device implantation there was no patients in NYHA 4 class. In the CRT-D pacemaker group 18 patients (47,4%) were in NYHA 2 class after follow up. After pacemaker implantation in both groups of patients

Table 2

Aetiology of heart failure in different groups of patients

	CRT-P		CRT-D	
	N	%	N	%
non-ischemic	42	70	25	65,8
ischemic	18	30	13	34,2
Total	60	100,0	38	100,0

Table 3

Number of hospitalizations in patients with different heart failure therapy

		CRT-P		CRT-D	
		N	%	N	%
No. hospitaliz.	0	26	43,3	15	39,4
	1	22	36,7	14	36,8
	2	8	13,3	6	15,7
	3	4	6,7	2	5,2
	4	0	0,0	1	2,6
	5	0	0,0	0	0,0
Total		60	100,0	38	100,0

n.s. p>0,05

Table 4

Comparative analysis of investigated parameters in heart failure patients with different types of therapy

	CRT-P		CRT-D	
	Before $\bar{x}$ (sd)	After $\bar{x}$ (sd)	Before $\bar{x}$ (sd)	After $\bar{x}$ (sd)
QRS (ms)	149,23 (10,30)	125,33 (10,66)	153,16 (5,58)	124,95 (5,91)
LVEF (%)	24,63 (5,08)	36,27 (8,37)	27,16 (6,59)	34,00 (5,89)
6MWD (m)	220,83 (38,53)	296,00 (67,63)	209,89 (28,18)	273,11 (32,62)
EDV (ml)	283,87 (55,81)	167,43 (44,38)	266,37 (24,40)	164,11 (23,97)
EDS (ml)	185,50 (50,63)	112,80 (22,33)	173,68 (21,19)	108,05 (21,43)
PEP LV	180,77 (17,58)	146,17 (8,57)	175,89 (6,93)	138,95 (5,13)
PEP RV	115,10 (20,41)	94,73 (17,31)	113,68 (13,76)	92,58 (12,79)
SPWMD	193,90 (44,27)	140,67 (22,44)	187,11 (11,43)	135,00 (10,57)

Abbreviations: LVEF — left ventricle ejection fraction, 6MWD — six minute walking distance, EDV — end-diastolic volume of left ventricle, ESV — end-systolic volume of left ventricle, PEP LV — pre-ejection interval of left ventricle, PEP RV — pre ejection interval of right ventricle, SPWMD — septal-posterior wall motion delay.

Table 5

Comparative analysis of parameters (end-diastolic and end-systolic diameters of left ventricle in heart failure patients with different types of therapy

	CRT-P		CRT-D	
	Before $\bar{x}$ (sd)	After $\bar{x}$ (sd)	Before $\bar{x}$ (sd)	After $\bar{x}$ (sd)
EDD	71,60 (6,00)	64,67 (4,95)	73,58 (4,78)	66,05 (3,88)
ESD	61,77 (5,91)	57,17 (4,31)	62,95 (2,69)	58,53 (1,77)

Abbreviations: EDD — end-diastolic diameter of left ventricle, ESD — end-systolic diameter of left ventricle.

significant improvement in NYHA functional class was observed.

Analysis of the parameters presented in Table 4 showed that all echocardiographic parameters and indicators of life quality improved. LVEF and 6MWD were significantly increased, while other parameters of interest were significantly lower after CRT-P and CRT-D pacemaker implantation, p<0,001. Between observed groups we found no significant difference between observed parameters.

Significant decrease of end-diastolic and end-systolic diameters of left ventricle (EDD, ESD) was observed in both groups of patients, p<0,001 (Table 5). We found no significant difference between those parameters before and after the CRT pacemaker implantation in both groups. Not only functional but structural improvement of left ventricle was determined.

In the group of patients with CRT-P pacemaker 4 patients (6,7%) died during the period of 1 year of follow-up. In patients with CRT-D pacemaker implanted 2 patients (5,3%) died during the same period, however no statistical difference in mortality rate was observed in 2 examined groups. Patients with CRT-P had longer survival period (389,4 days) than those in CRT-D group (349,5 days), but with no statistical difference (Figure 1).

Discussion

In the early period of use of resynchronization therapy some authors claimed that this therapy was accepted without necessary randomized clinical trials which could show its benefit. However, nowadays we have more than 4000 patients included in trials of CRT.

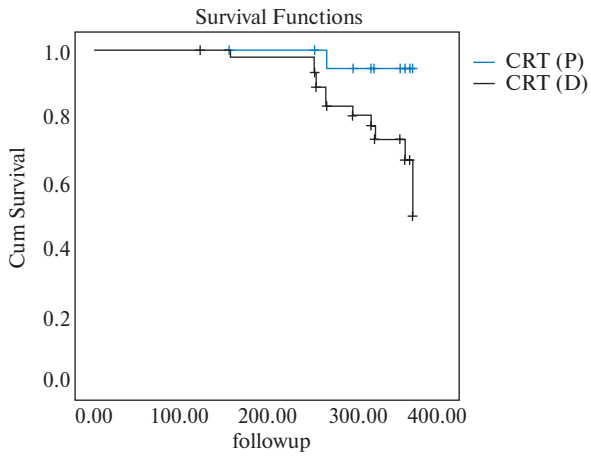

Figure 1. Kaplan Meier survival curve in patients with different therapy modalities.

Inclusion criteria for clinical CRT studies are relatively strict such as having NYHA class 3/4, long duration of QRS complex, sinus rhythm and bi-ventricular pacing configuration.

Since CRT-D devices became widely available, patients with ICD labelled devices are included in trials and era of examinations of safety and efficiency of CRT-D and effects of CRT on development of potentially malignant ventricular arrhythmias started.

The design of the MIRACLE-ICD study was nearly identical to that of the MIRACLE trial. MIRACLE-ICD was a prospective, multicenter, randomized, double blind clinical trial intended to assess the safety and clinical efficacy of another combined ICD and cardiac resynchronization system in patients with dilated cardiomyopathy (LVEF<35%, LV EDD>55 mm), NYHA class 3 or 4, inter-ventricular conduction delay (IVCD) (QRS>130 ms), and an indication for an ICD. Primary and secondary efficacy measures were essentially the same as those evaluated in the MIRACLE trial but also included measures of ICD function (including the efficacy of antitachycardia therapy with biventricular pacing). In a cohort of 369 patients randomly assigned to ICD on and CRT off (n=182), or ICD on and CRT activated (n=187), those with the CRT activated showed significant improvements in quality of life, NYHA class, exercise capacity and composite clinical response compared with control subjects. The magnitude of improvement was comparable to that seen in the MIRACLE trial, suggesting that heart failure patients with an ICD indication benefit as much from CRT as those patients without an indication for an ICD [6]. Of interest, the efficacy of biventricular anti-tachycardia pacing was significantly greater than that seen in the univentricular (RV) configuration. This observation suggests another potential benefit of a combined ICD plus resynchronization device in such patients. In our study benefit and efficiency of CRT-D was clearly demonstrated ant it was comparable with that achieved in the CRT-P group.

The COMPANION trial was a multicenter, prospective, randomized, controlled trial that assessed optimal pharmacological therapy alone or with CRT using a pacemaker or a combination pacemaker-defibrillator in patients with dilated cardiomyopathy, IVCD, NYHA 3 or 4

functional class, and no indication for a device. The trial design called for random assignment of 2200 patients into one of three treatment groups: I (440 patients) receiving optimal medical care only, group II (880 patients) receiving optimal medical care and biventricular pacing alone, and group III (880 patients) receiving optimal medical care and CRT-ICD device. The trial was terminated prematurely after assignment of 1520 patients at the recommendation of an independent data and safety monitoring board. Over 12–16 months, the primary composite end-point of all-cause death or any hospitalization was decreased by approximately 20% with use of either device therapy compared with pharmacologic therapy alone. Further, a pacing only resynchronization device reduced the risk of death from any cause by 24% (p=0,06) and a resynchronization device with ICD reduced the risk by 36% (p=0,003) [7]. In our study mortality rate was lower in CRT-D group (not significantly, though).

Five randomized controlled trials met the inclusion criteria, recruiting a total of 3434 participants. Four studies compared CRT-P with Optimal Pharmacologic Therapy (OPT), two studies compared CRT-D with OPT and one study compared CRT-P with CRT-D. In all trials, patients with an indication for an ICD were excluded. Studies were of good to moderate quality. Two trials reported that allocation to treatment group had been concealed (CARE-HF and MIRACLE), blinding occurred in three trials (CONTAK-CD, MUSTIC-SR and MIRACLE) and intention-to-treat was used in four analyses (CARE-HF, COMPANION, MIRACLE and MUSTIC-SR) [8–11]. In our study only patients who fulfilled criteria for an ICD also got the CRT-D pacemaker according to the guidelines of European Society of Cardiology [12].

Conclusion

Meta-analyses showed that both CRT-P and CRT-D devices significantly reduced the mortality and level of heart failure hospitalisations. They also improved health-related quality of life in people with New York Heart Association (NYHA) class 3 and 4 heart failure and evidence of dyssynchrony (QRS interval >120 ms) who were also receiving optimal drug treatment. A single direct comparison (COMPANION) indicated that the effects of the CRT-P and CRT-D were similar, with the exception of an additional reduction in sudden cardiac death, associated with CRT-D [7]. On average, implanting a CRT device in 13 people would result in the saving of one additional life over a 3-year period, compared with optimal drug treatment [13].

After use of resynchronization therapy as CRT-P or CRT-D option we noticed significant improvement in echocardiographic parameters (increase in LVEF, decrease in end-diastolic and end-systolic diameters of left ventricle, pre-ejection intervals of left and right ventricles) decrease in NYHA functional class. There was no significant difference in those parameters between two observed groups of patients including the number of re-hospitalizations and mortality rate.

Cardiac resynchronization therapy rapidly advanced as a result of data gained through clinical trials. Clinical studies resulted in general acceptance of CRT for patients with standard criteria. The benefit of CRT alongside with the optimal drug therapy is clearly demonstrated in patients with heart failure and asynchrony. CRT showed paramount improvements in clinical symptoms and disease progression. Nevertheless we do not have the perfect criteria for selection of patients and their follow up after the device implantation. In patients with the rhythm disturbances CRT-D option is the right choice only if the patient has the indications for resynchronization therapy as well. This choice nowadays depends on clinical judgment of the operator more than on strict protocols and guidelines.

It is certain that in the future we will have wider indication area for this type of therapy and more sophisticated selection criteria for patients in order to gain better and adequate therapeutic response.

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INCREASE IN QTC DISPERSION PREDICTS ARRHYTHMIC EVENTS IN PATIENTS WITH CARDIAC RESYNCHRONIZATION THERAPY

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Aim. Benefits of CRT on mortality and morbidity in patients with severe CHF are clear but the effect of CRT on sudden cardiac death is more controversial. It has been suggested that CRT may catalyze arrhythmogenicity by reversing the normal depolarization pattern. The purpose of this study was to examine the effect of CRT on dispersion of repolarization as assessed by ECG. We also sought to determine the value of dispersion of repolarization ECG parameters in predicting the occurrence of major arrhythmic events (MAE) in follow-up.

Material and methods. A total of 48 patients with end-stage heart failure and QRS duration >120 ms underwent CRT. QT dispersion (QTd), T peak t end interval (Tpe) and T peak t end dispersion (Tpe dispersion) were measured before and immediately after CRT implantation. All patients were followed at least 12 months for ventricular tachycardia or fibrillation that were treated with antitachicardia pace or cardioversion.

Results. Over 16±7.1 months, 14 patients had a MAE. Compared to baseline, after CRT, QTc dispersion (84.66±37.7 vs 100.36±47.4, p=0.04) and Tpe interval (104.1±20.4 vs 122.03±33, p=0.02) increased significantly. Increase in QTD (ΔQTD) (31.66±39.5 vs 5.57±5.59, p=0.03), and QTc dispersion (ΔQTc dispersion) (40.19±46.6 vs 4.39±14.35, p=0.04) from baseline was signifcantly higher in MAE group. In multiple regression analyses, ΔQTc dispersion predicted MAE (p=0.045, CI: 1.000–1.033).

Conclusion. Immediately after CRT implantation QTc dispersion and Tpe interval increases and increase in QTc dispersion predicts MAE in one year follow up.

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Key words: CRT, repolarization dispersion, major arrhythmic events, QT dispersion.

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УВЕЛИЧЕНИЕ ДИСПЕРСИИ QTC ПРОГНОЗИРУЕТ АРИТМИЧЕСКИЕ СОБЫТИЯ У БОЛЬНЫХ С СЕРДЕЧНОЙ РЕСИНХРОНИЗИРУЮЩЕЙ ТЕРАПИЕЙ

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Цель. Преимущества сердечной ресинхронизирующей терапии (CRT) в снижении смертности и заболеваемости больных с тяжелой ХСН ясны, но действие CRT при внезапной сердечной смерти является более спорным. Было высказано предположение, что CRT может катализировать аритмогенность, реверсируя нормальную деполяризационную структуру. Целью данного исследования было изучить влияние CRT на дисперсию реполяризации, при оценке ЭКГ. Мы также стремились определить значение дисперсии реполяризации параметров ЭКГ в прогнозировании возникновения крупных аритмических событий (MAE) в последующем.

Материал и методы. Всего 48 пациентов с терминальной стадией сердечной недостаточности и длительностью комплекса QRS >120 мс прошли CRT. Дисперсия QT (QTd), T пик t end интервал (Tpe) и T пик t end дисперсии (Tpe дисперсии) были измерены до и сразу после CRT имплантации. Все пациенты находились под наблюдением, по крайней мере, 12 месяцев, желудочковая тахикардия или аритмия лечились кардиостимуляцией или кардиоверсией.

Результаты. Более 16±7.1 месяцев у 14 пациентов были MAE. По сравнению с исходными данными, после CRT, QTc дисперсия (84.66±на 37,7 против 100.36±47.4, p=0,04) и Tpe интервал (104.1±20.4 против 122.03±33, p=0.02) значительно увеличились. Увеличение QTD (t QTd) (31.66±39.5 против 5.57±5.59, p=0,03), и QTc дисперсии (t QTc дисперсии) (40.19±против 46.64.39±14.35, p=0,04) от исходного уровня были значительно выше в группе с MAE. При множественном регрессионном анализе ΔQTc дисперсия предсказывала развитие MAE (p=0,045 (CI): 1.000–1.033).

Заключение. Сразу после CRT имплантации QTc дисперсии и Tpe интервал увеличиваются, и увеличение QTc дисперсии прогнозирует MAE при наблюдении в течение одного года.

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Ключевые слова: CRT, дисперсия реполяризации, крупные аритмические события, дисперсии QT.

Introduction

Cardiac resynchronization therapy (CRT) has become an established adjunctive treatment to optimal pharmacologic therapy in patients with advanced chronic heart failure (CHF), diminished left ventricular (LV) function and cardiac dyssynchrony [1]. Several studies have demonstrated that CRT improves ventricular haemodynamics, quality-of-life, exercise capacity, and reduces mortality and hospitalization rates in patients with advanced CHF [2–4]. Despite clear benefits of CRT on mortality and morbidity in patients with severe CHF, the effect of CRT on sudden cardiac death is more controversial. In the Comparison of Medical Therapy, Pacing and Defibrillation in Heart Failure (COMPANION) trial, the addition of an implantable cardioverter-defibrillator (ICD) to CRT was necessary to reduce global mortality and sudden cardiac death [5,6]. There have been several case reports over the past 5 years describing significant ventricular proarrhythmia, which manifests primarily as ventricular tachycardia (VT) storm. It has been suggested that CRT may catalyze arrhythmogenicity by reversing the normal depolarization pattern from endocardium to epicardium, which enhances transmural dispersion of repolarization and propagation of early after-repolarizations. These changes may facilitate the development of ventricular tachyarrhythmias [7]. In this light the purpose of this study was to examine the effect of

CRT on dispersion of repolarization as assessed by ECG in a population of HF patients who received CRTICDs. We also sought to determine the value of dispersion of repolarization electrocardiogram (ECG) parameters in predicting the occurrence of ventricular arrhythmias in follow-up.

Material and methods

Patients. The study population consisted of 48 consecutive patients who had undergone successful CRD-D placement at our clinic between February 2008 and August 2010. The study protocol was approved by the local ethics commitee. All patients gave written informed consent, and the study was approved by the local ethics committee.

The inclusion criteria for our study were as follows: 1- New York Heart Association (NYHA) functional class III or IV HF symptoms despite optimal medical therapy. 2- Left ventricular ejection fraction <35% as assessed by echocardiography, angiography, or radionuclide scanning. 3- QRS duration >130 ms or QRS <130 ms and left intraventricular dyssynchrony as assessed by transthoracic echocardiography with Doppler tissue imaging analysis (difference of at least 60 ms between the timing of the peak systolic velocities of the septum versus the lateral wall. Exclusions criteria were: 1- contraindications to cardiac pacing; 2- myocardial infarction or acute coronary syndrome within the previous 3 months; 3-presence of comorbidities likely to threaten survival for 12 months.

Implantation technique. The CRT device with a biventricular pacemaker (C174AWK, Medtronic, Minneapolis, MN, USA) was implanted according to the established methods reported previously. Transvenous left ventricular pacing was performed in all cases. Under the guidance of coronary sinus angiograms, left ventricular lead was introduced into the lateral or posterolateral cardiac vein. The right ventricular lead was implanted in the apex. The final position was determined visually with the right and left anterior oblique views.

ECG parameters. ECG was recorded before and within 24 hours postimplantation. Twelve-lead body surface electrocardiograms were recorded at a speed of 50 mm/s. Two different experts, who were blinded to follow-up of the patients, manually analyzed all ECGs. For each ECG, the following parameters were measured: heart rate, QRS duration, QT interval, QT dispersion, Tpeak–Tend (Tp–e), and Tp–e dispersion. For each parameter, the difference between postimplantation and baseline values (ΔQRS), (ΔQTc), (ΔQT dispersion), (ΔTp–e), and (ΔTp–e dispersion) was calculated. Each measurement represented the average of the 12 leads. QTc was calculated using the Bazett Formula. QT interval was measured from the beginning of the QRS complex to the end of T wave, defined as the tangent to the downslope of the T wave and the isoelectric line.22 QT dispersion was defined as the difference between the maximum and the minimum QT interval of the 12 ECG leads. Tp–e was measured in all derivations and was obtained from the difference between QT interval and QT peak interval (measured from the beginning of the QRS to the peak of the T wave). In the case of negative or biphasic T waves, QT peak was measured to the nadir of the T wave. Tp–e dispersion was obtained by the difference between the maximum and the minimum Tp–e interval in the precordial leads. Pearson correlation coefficient (r) between the two observers for QRS, QT, Tp–e was 0.93, 0.79 and 0.85 respectively. This coefficient evaluating intraobserver variability for QRS, QT and Tp–e was 0.95, 0.81 and 0.88, respectively.

Arrhythmic events-follow up. Patients were evaluated 1 month after implantation and every 3 months thereafter for 1 year. Occurrences of ICD shocks or antitachycardia pacing were confirmed in all cases by device interrogation. Major arrhythmic events (MAE) were defined as sustained ventricular tachycardia or ventricular fibrillation, which were treated by the device with either shock or ATP. Two-blinded expert electrophysiologists confirmed the appropriateness of the device therapies.

Clinical parameters were used to state responders and non responders. Patients were assumed as responders if the following criteria met: (1) no cardiovascular death, (2) no hospitalization for decompensated HF and (3) >1-point decrease in NYHA functional class.

Statistical Analysis. Continuous variables are expressed as mean ± SD. Categorical variables, expressed as numbers or percentages, were analyzed using the Chi-square test or Fisher's exact test. Comparisons between normally distributed continuous variables were made using the Student *t* test. The Mann-Whitney *U* test was used for analysis of non-normally distributed data. The Cox proportional-hazards model was used to evaluate the risk of MAE in relation to ΔQTc, amiodarone usage and LVEDD. Variables showing significant group differences were entered into multivariate regression models. To evaluate interobserver and intraobserver variability, the Pearson correlation coefficient (r) was calculated for each ECG parameter. Statistical analyses were performed using Analyses were performed using the statistical package SPSS 16.0 software for Windows. A two-tailed p value of <0.05 was considered statistically significant.

Results

The characteristics of study population are given in Table 1. Mean age was 56.9±11.8 years, 44 (93.6%) of patients were male. Ischemic cardiomyopathy was present in 36 (59.6%) patients. Mean ejection fraction of study population was 23.7±7.2% and mean QRS duration was 161.54±35.9 ms. Mean follow-up period was 16.0±7.1 months. Thirty-one (66%) patients were CRT-responders.

Comparison of electrocardiographic, echocardiographic measurements and NYHA Class of study population before and after CRT are given in Table 2. NYHA class significantly reduced after CRT implantation (3.24±0.53 vs 2.39±0.51, p=0.001). EF increased without statistical significance (23.7±7.0% vs 27.4±7.0%, p=0.07). Tpe interval (104.1±20.4 vs 122.03±33,0, p=0.02) and QTc dispersion (84.66±37.7 vs 100.36±59.8, p=0.04) increased significantly after CRT implantation. Other electrocardiographic parameters did not change significantly after CRT implantation.

Table 1

Baseline characteristic of study population

Age (years)	56.9±11.8
Sex (Male)	44 (93.6%)
Diabetes mellitus	11 (23.4%)
Hypertension	24 (51.8%)
Atrial fibrillation	3 (6%)
Amiodarone usage	24 (51.1%)
Ischemic cardiomyopathy (%)	36 (59.6%)
LAD (cm)	4.8±0.6
LVEDD (cm)	7.2±0.7
LVESD (cm)	6.2±0.7
EF (%)	23.4±6.2
QRS duration (ms)	161±35.6
QT dispersion	80±36.7
QTc dispersion	86.9±39.9
NYHA class	3.24±0.5
Mean follow-up (months)	16±7.1
CRT responders	31 (66%)
Arrhythmic event	14 (29%)

Abbreviations: LAD — left atrium diameter, LVEDD — left ventricular end-diastolic diameter, LVESD — left ventricular end-systolic diameter; EF — ejection fraction, NYHA — New York Heart Association.

Table 2

Electrocardiographic, echocardiographic measurements and NYHA Class; before and after CRT

	Before CRT	After CRT	p value
NYHA Class	3.24±0.53	2.39±0.51	0.001
LA (cm)	4.93±0.65	5.0±1.0	NS
LVEDD (cm)	7.30±0.78	6.20±0.69	NS
LVESD (cm)	6.20±0.70	6,0±0.98	NS
EF (%)	23.7±7.20	27.40±7.10	0.07
QRS duration (ms)	161.54±35.90	151.44±40.4	NS
QTd	77.89±34.70	86.32±50.80	NS
Tpe duration (ms)	104.10±20.40	122.03±33	0.02
Tpe dispersion	45.56±12.02	54.44±34.43	NS
QTc dispersion	84.66±37.70	100.36±47.40	0.04

Abbreviations: LAD — left atrium diameter, LVEDD — left ventricular end-diastolic diameter, LVESD — left ventricular end-systolic diameter; EF — ejection fraction, NYHA — New York Heart Association, QTc — corrected QT.

Study population divided into two groups according to presence of arrhythmic events (Table 3). 14 (29%) patients received appropriate ATP or shock for arrhythmic events. Frequency of ischemic cardiomyopathy, DM, hypertension and arrhythmic event before CRT implantation were similar between groups. Age (52.5±14.4 vs 58.7±10.2, p=NS) and EF before CRT (20.40±3.4 vs 24.8±6.7, p=NS) were also similar between groups. Amiodarone use was more frequent (71.6% vs 42.4%, p=0.06) and LVEDD before CRT (7.56±0.66 cm vs 7.0±0.7 cm, p=0.06) were higher in arrhythmic event group without statistical significance. As shown in Table 2 electrocardiographic measurements of repolarisation dispersion were also similar between groups. As given in Table 3, an additional analysis of groups intended to determine the change of repolarisation dispersion in groups; revealed a significant increase in QTd (31.66±39.5 vs 5.57±5.59, p=0.03) and QTc dispersion (40.19±46.6 vs 4.39±14.35, p=0.04) in arrhythmic event group.

Multivariate Cox proportional hazard analysis was performed, including ΔQTc dispersion, amiodarone usage and LVEDD (Table 4). ΔQTc dispersion was the only independent predictor of arrhythmic event (p=0.045, CI 1.000–1.033).

Discussion

This study has shown that CRT is associated with an increase in Tpe duration and QTc dispersion in advanced heart failure patients. Another important finding is the increase in QTc dispersion predicts major arrhythmic events in CRT patients (Table 5).

Previous investigators have reported the role of repolarisation dispersion on the basis of ventricular malignant arrhythmias in heart failure patients [8–10]. Heterogenity of ventricular repolarisation facilitates transmural early after depolarization propagation and also can cause intramural conduction blocks that predispose to re-entrant tachyarrhythmias [11]. Measurement of QTd, JTd, and Tp-e interval from surface ECG provides an index of repolarisation dispersion [12, 13]. Our findings of increase in QTc dispersion and Tp-e interval after CRT are consistent with previous experimental and clinical studies [14, 15]. Fish et al. [14] observed that reversing the direction of LV wall activation leads to an increase in QTc duration in arterially perfused canine LV wedge preparations. This has been linked to increased transmural dispersion of repolarisation resulting from earlier repolarisation of the epicardium and delayed activation and repolarisation of the midmyocardial M cells. In a clinical study Santangelo et al. [16] studied 50 CRT patients with end-stage heart failure and showed that left ventricular epicardial only pacing increase QTd, JTd and Tp-e interval whereas biventricular pacing reduced these parameters.

Following mentioned above studies; clinical studies focused on predicting arrhythmic events by using same ECG parameters in CRT patients. Chalil et al. [17] examined retrospectively the prognostic value of these parameters in predicting sudden cardiac death in CRT patients. Like our study they reported that increase in QT dispersion was the independent predictor of sudden cardiac death. In their study primary end point was sudden cardiac death but sudden cardiac death is not always due to ventricular arrhythmias. In our study all patients received CRT-D devices so we could catch all sustained ventricular arrhythmias during follow-up period. Lellouche N et al. [18] investigated the same ECG parameters in CRT patients. They reported that Tp-e interval increased after CRT implantation in patients with LBBB or narrow QRS at baseline. Another important finding was the post implantation Tp-e interval was the independent predictor of ICD therapy. Although our study has similarities with Lellouche's study there are main differences especially in study group; our study group consisted of patients with QRS duration >120 ms whereas Lellousche's groups consisted of

Table 3

Electrocardiographic measurements and clinical characteristics of patients with and without arrhythmia

	Patients with arrhythmia (n=14)	Patients without arrhythmia (n=34)	P value
Ischemic cardiomyopathy	% 35.7	% 42.4	NS
Diabetes mellitus	% 7.1	% 30.3	NS
Hypertension	% 42.9	% 54.5	NS
Amiodarone usage	% 71.6	% 42.4	NS (0.06)
Age (years)	52.5±14.4	58.7±10.2	NS
LVEDD (Before CRT) (cm)	7.56±0.66	7±0.7	NS (0.06)
EF (Before CRT) (%)	20.40±3.4	24.8±6.7	NS
LVEDD (After CRT) (cm)	7.10±0.8	7.10±0.9	NS
EF (After CRT) (%)	27.90±6.4	25.6±8.1	NS
QRS duration before CRT (ms)	172.31±32.18	155.56±36.51	NS
QRS duration after CRT (ms)	156.41±25.64	149.32±22.13	NS
QTd (Before CRT)	70±20.28	84.44±40.12	NS
Tpe (Before CRT)	114±27.49	102.15±18.86	NS
Tpe dispersion (Before CRT)	48.33±26.22	51.54±26.03	NS
QTc dispersion (Before CRT)	76.08±28.57	91.78±43.61	NS
QTd (After CRT)	93.85±46.46	78.52±39.19	NS
Tpe (After CRT)	124.36±33.52	120.4±33.52	NS
Tpe dispersion (After CRT)	59.17±44.81	50±27.87	NS
QTc dispersion (After CRT)	109.12±54.02	91.3±45.57	NS

Table 4

Change of repolarization dispersion parameters in patients with and without arrhythmia

	Patients with arrhythmia (n=14)	Patients without arrhythmia (n=34)	P value
Δ QTd	31.66±39.5	5.57±5.59	0.03
ΔTpe	14.82±34.95	19.35±33.96	NS
ΔTpe dispersion	10±6.44	0.35±4.67	NS
ΔQTc dispersion	40.19±46.6	4.39±14.35	0.04

three different patient groups; with narrow QRS complex, LBBB and upgraded right ventricular paced patients. So our study can represent general CRT patient population.

Ermis et al. reported that arrhythmia frequency and number of appropriate ICD treatments were reduced after upgrade to CRT-ICD for HF treatment [19]. The CARE–HF study [20] has demonstrated that CRT reduced sudden cardiac death in heart failure patients in 2 years follow-up.

Randomized controlled studies on the safety and efficacy of cardiac resynchronization suggest that this therapy may have a neutral or antiarrhythmic effect. However, a potentially proarrhythmic effect has been described, and while relatively infrequent, clinicians should be aware of this phenomena. The ultimate impact on arrhythmic vulnerability is likely dependent on propagation patterns and the underlying cardiac substrate. As demonstrated by this study and several studies mentioned here, reversal of transmural activation and repolarisation may set the stage for re-entry and proarrhythmia.

Our results demonstrated important findings: firstly; repolarisation dispersion in means of QTc dispersion and mean Tpe duration increased following CRT implantation; secondly, increase in QTc dispersion predicts major antiarrhythmic events in CRT patients.

Table 5

Predictors of arrhytmic event

	p value	Confidence Interval
QTc dispersion	0.045	1.000–1.033
LVEDD	0.99	
Amiodarone usage	0.15	

Conclusion

Our study has shown that CRT causes a significant increase in QTc dispersion and Tpe interval in advanced heart failure patients also increase in QTc dispersion predicts one-year MAE in this population.

Study limitations

This study has several limitations. First, it is small and observational single centre study. Second, the electrocardiographic measurements were performed manually on paper-printed ECG may limit the accuracy and reproducibility of the measurements. Third, the surface ECG has limitations reflecting the cardiac electric activity compared to body surface mapping or vector cardiography.

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THE FREQUENCY OF HEART RHYTHM DISORDERS IN PREHOSPITAL PHASE OF ACUTE CORONARY SYNDROME

Jasna Milutinović-Puača, Slađana Anđelić

Prehospital management of patients with acute coronary syndrome (ACS) is the essential element which influences the survival of patients and the outcome of the disease. Most lethal outcomes occur within the first hour after the onset of acute myocardial infarction (AMI), and the usual cause is some of heart rhythm and conduction disorder.

Aim. To assess the frequency of each form of ACS, and the incidence of the development of rhythm and conduction disorders during the first 12 hrs in relation to the localization of ACS and disease outcome.

Material and methods. We analyzed prospectively 107 patients transported under continual ECG monitoring to the Coronary Unit after ACS diagnosed prehospitally by the team of the Belgrade Emergency Medical Services. AMI localization was detected and the development of rhythm (supraventricular and ventricular), and conduction disorders were followed by prehospital ECG monitoring. Patients' outcome was under follow-up until discharge from hospital.

Results. Acute ST-elevation myocardial infarction (STEMI), both anterior and diaphragmatic, is most frequent in men aged 50–59 years. There were no statistically significant differences in the occurrence of heart rhythm and conduction disorders both in the STEMI and non-STEMI (NSTEMI) groups. The most frequent rhythm disorders during the first 4 hrs after STEMI onset were sinus bradycardia, sinus tachycardia and ventricular tachycardia, while atrial fibrillation and single ventricular extrasystole were most frequent after 5–12 hrs. In STEMI, AV blocks occurred exclusively during the first 4 hrs, while bundle branch blocks occurred statistically more significantly during the first 4 hrs. Sinus bradycardia and atrioventricular blocks were statistically significantly associated with diaphragmatic STEMI. In this localization there were no bundle branch blocks. The most frequent rhythm disorder associated with anterior STEMI was sinus tachycardia that occurred exclusively during the first 4 hrs. The occurrence of ventricular tachycardia and ventricular fibrillation in any of STEMI locations was statistically more significant in the first 4 hrs after complaints onset. In the studied group of patients with ACS mortality rate was 12,1%, while in the group of STEMI patients it was 11%, with a significant frequency of infarction with anterior localization and bundle branch block in men.

Conclusion. Future studies should be directed toward identifying methods, as precise as possible, for early screening of heart rhythm and conduction disorders in ACS so as to enable a timely, preventive and therapeutic management.

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Key words: acute coronary syndrome, disorder, rhythm, conduction, prehospital. Emergency Medical Services, Belgrade, Serbia.

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ЧАСТОТА СЕРДЕЧНОГО РИТМА НА ДОГОСПИТАЛЬНОМ ЭТАПЕ ОСТРОГО КОРОНАРНОГО СИНДРОМА

Jasna Milutinović-Puača, Slađana Anđelić

Догоспитальный этап лечения пациентов с острым коронарным синдромом (ОКС), является существенным элементом, который влияет на выживаемость больных, и исход болезни. Большинство летальных исходов происходит в течение первого часа после начала острого инфаркта миокарда (ОИМ), и обычная причина — расстройства сердечного ритма и проводимости.

Цель. Оценить частоту каждого вида ОКС, развитие расстройств нарушения ритма и проводимости в течение первых 12 часов, по отношению к локализации ОКС и исхода заболевания.

Материал и методы. Мы проспективно проанализировали 107 пациентов, помещенных под непрерывный мониторинг ЭКГ в коронарном отделении после диагностирования у них ОКС бригадой врачей скорой медицинской помощи в больнице Белграда. На догоспитальном этапе мониторинга ЭКГ было обнаружено наличие ОИМ и развитие ритма (наджелудочкового и желудочкового), нарушение проводимости. Пациенты были под наблюдением до выписки из больницы.

Результаты. Острый подъем сегмента ST при инфаркте миокарда (ИМ с ST), как при переднем, так при диафрагмальном, наиболее часто встречается у мужчин в возрасте 50–59 лет. Отсутствуют статистически значимые различия в распространенности нарушений ритма сердца и расстройств проводимости, как при ИМ с ST, так и при ИМ без поднятия сегмента ST (ИМ без ST). Наиболее частыми нарушениями ритма в течение первых 4 часов после ИМ с ST были синусовая брадикардия, синусовая тахикардия, желудочковая тахикардия, в то время как мерцательная аритмия и одиночная желудочковая экстрасистолия были наиболее частыми после 5–12 часов. При ИМ с ST атриовентрикулярная блокада, как и блокада ножки пучка Гиса происходила исключительно в течение первых 4 часов. Синусовая брадикардия и атриовентрикулярная блокада были статистически значимо связаны с диафрагмальным ИМ с ST. При этой локализации не было блокады ножки пучка Гиса. Наиболее частым нарушением ритма, связанным с передним ИМ с ST, была синусовая тахикардия, которая проявлялась исключительно в течение первых 4 часов. Возникновение желудочковой тахикардии и фибрилляции желудочков при любой локализации ИМ с ST было статистически более значимым в первые 4 ч после начала жалоб. В обследованной группе больных с ОКС смертность составила 12,1%, в то время как в группе пациентов с ИМ с ST она была 11%, со значительной частотой поражения миокарда передней локализации и блокады ножки пучка Гиса у мужчин.

Вывод. Будущие исследования должны быть направлены на выявление методов, для, как можно точнее, раннего скрининга сердечного ритма и нарушений ритма и проводимости при ОКС, с тем, чтобы обеспечить своевременное, профилактическое и терапевтическое лечение.

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Ключевые слова: острый коронарный синдром, расстройство ритма, проводимость, догоспитальный этап.

Introduction

Different presentations of acute coronary syndrome (ACS) share identical pathophysiological substrate. The diagnosis of ACS, i.e. acute myocardial infarction (AMI) as the most severe form of this syndrome, is passed with high probability if evolutionary changes are present in two out of the following three criteria: clinical features, ECG or biochemical markers of myocardial necrosis [1]. The main symptom that initiates the diagnosis is chest pain; however, the classification of patients is based on ECG

findings. Accordingly, there are two categories of patients: patients with typical acute chest pain and persistent (>20 min) ST-segment elevation (STE-ACS) that most develop ST-segment myocardial infarction (STEMI), and patients with acute chest pain but without ST-segment elevation (NSTE-ACS). At first presentation these patients develop ST-segment depression or T-wave inversion, low-voltage T-waves or they are without ECG changes at first presentation. In Serbia STEMI is more frequent and has a moderately higher rate of mortality than NSTE-ACS (7%:5%), but after 6 months the rates of both conditions are very similar (12%:13%).

ACS is a wide spectrum of clinical manifestations caused by a sudden reduction in supply of a portion of myocardial O2 caused by the disruption of unstable atherosclerotic plaque with consequent thrombosis, vasoconstriction and distal microembolization. Prevention of acute coronary event, early identification of ACS, rapid and effective prehospital treatment enable preservation of functional myocardium, which correlates to the decrease of morbidity and mortality from AMI [2]. A number of studies have shown the significance of rapid ACS symptoms recognition, early activation of healthcare system, and if necessary, early cardiopulmonary resuscitation, rapid prehospital diagnostics, triage, adequate treatment and transport (with monitoring of patient's vital parameters) [3]. As the result of these studies guidelines for the treatment of patients with chest pain as well as the guidelines for the management of patients with ACS have been formed. In 2010 the American Heart Association (AHA), the International Liaison Committee on Resuscitation (ILCOR) and the European Council Resuscitation (ERC) published guidelines that paid special attention to the prehospital treatment of patients with ACS [4]. The presence of a protocol for the management of such patients helps doctors in decision making when meeting the patient for the first time, and in suspecting and/or passing the diagnosis of ACS.

ACS can become complicated in each phase of the disease, and particularly during the first several hours after symptoms onset of ventricular rhythm disorders, primarily ischemic, ventricular fibrillation (VF). Therefore, the physician's first task is to help the patient survive, i.e. eliminate heart rhythm disorder which is the most frequent cause of lethal outcome.

The aim of the study was to determine the frequency of different forms of ACS and the incidence of the development of heart rhythm and conduction disorders during the first 12 hrs of AMI related to MI localization, as well as the disease outcome.

Material and methods

A prospective study involved 107 patients treated at the Coronary Unit of the Clinical Centre of Serbia after prehospitally passed diagnosis of ACS and under continual ECG monitoring by the Belgrade EMS. The prehospital diagnosis was made based on two out of three known criteria: typical anginal pain in duration of at least 30 minutes, typical ECG features of ST-segment elevation in two consecutive leads (in AMI with ST-segment elevation) as well as ST-segment depression in several leads (in unstable angina — UNA and AMI without ST-segment elevation). It was not possible to the increase of cardio-specific enzymes due to the lack of a rapid test.

The patients were examined at the site of event (residence, working place, public place), and after passed diagnosis and initiated treatment, were transported to the Centre Coronary Unit of the Clinical Center of Serbia under continual ECG monitoring by the team, composed of a physician, medical technician and driver of the Belgrade Emergency Medical Services. On admission all patients were continually monitored, and ECG was performed at least once daily.

Prehospital ECG was used to determine AMI localization, and to analyze the development of the following heart rhythm disorders: 1/ supraventricular: sinus tachycardia (ST), sinus bradycardia (SB), supraventricular extrasystole (SVES), atrial flatter (AFL), atrial fibrillation (AF), and 2/ ventricular: ventricular extrasystole (VES) — single, in pairs and polymorphic, R/T phenomenon, ventricular tachycardia (VT) and ventricular fibrillation (VF), and conduction disorders (AV blocks, bundle branch blocks). Patients' outcome until discharge from hospital was under follow-up.

The collected data were statistically analyzed using SPSS 10.0 for Windows. In the analysis of the data the following statistical methods were used: arithmetic mean and standard deviation, while in the assessment of statistical significance regarding differences in the frequency of distribution Chi-square test and Student's t-test were used. By using the method of two-way analysis of variance (ANOVA) for proportions we tested the significance of frequency difference of various categories of rhythm disorders in relation to MI localization and time. A statistically significant difference was represented by $p<0.05$. In the presentation of the obtained results Word for Windows-6.0 was used. The observed characteristics are presented by histogram frequency, circular graph for frequencies and column diagram for frequencies.

Results

Over a 6-months period 217 patients were transported by the Belgrade EMS team to the Coronary Unit of the Clinical Centre of Serbia, all diagnosed with ACS of whom 124 (57,14%) were hospitalized. The studied group of 107 ACS patients, 60.7% male and 39,3% female, all of whom had a complete illness history. The distribution of ACS is shown on Figure 1.

ACS was most frequent in men aged 50–59 years (33,9%), and less in women aged 30–49 years (20%). Women develop the disease only after 50 years of age. According to the localization of STEMI, diaphragmal was

more frequent (53,66%) than anterior (42,69%) or combined localization (3.65%). Among diaphragmal STEMI, 16 (36.4%) also had right ventricular infarction. Anterior STEMI was more frequent in men (65,7%) than in women (34%) ($p<0,05$), as well as infarction of diaphragmal localization (men 56,8%, women 43,2%). Its occurrence predominates in men aged 40–59 years (43,6%) and in women aged 60–79 years (83,4%). Heart rhythm and conduction disorders were detected in 74/107 (69,1%) ACS and in 63/82 (76,8%) STEMI. As obserevd, there was a statistically sigificant association between heart rhythm and STEMI (79,8%, $p<0,05$) (method of parametric Spearman correlation) (Table 1). Conduction disorder detected in 22/107 (21,5%) patients with ACS (Table 1) presents a significant association of conduction disorder with STEMI (68,2%, $p<0,05$). However, by comparing the frequency of heart rhythm and conduction disorders between the patients with STEMI and other groups, i.e. non-STEMI (NSTEMI), unstabile angina pectoris (UAP) and reinfarction (ReInf) there were no statistically significant differences ($p>0,05$) (Table 2). Therefore, in a further study heart rhythm and conduction disorders were under follow-up, independently of the type of ACS.

By analyzing the occurrence of supraventricular rhythm disorder in STEMI during the first 4 hrs and in the period from 5–12 hrs from AMI onset, the trend of SB (247,7%) and ST (40,9%) development during the first 4 hrs was observed, while AF (registered in 9; 64.3% of patients) was most frequent in the period from 5–12 hrs (Figure 2). The occurrence of SVES and AFL was not registered in the period of 12 hrs from the AMI onset.

Among ventricular disorders in STEMI, VT was most frequent (35,3%) during the first 4 hrs. VF and single VES were equally frequent (23,5%), while VES in pairs was present in 17,7% patients. In the period 5–12 hrs from AMI onset, single VES were most frequent, in 6/9 patients with ventricular rhythm disorders. Polymorphic VES and VES with R/T phenomenon were not registered in the observed group of patients during the first 12 hrs from AMI onset (Figure 3).

By analyzing heart conduction disorders in STEMI a statistically more significant frequency of bundle branch blocks (BBB) was observed in relation to AV blocks (10:5). AV blocks occurred only during the first 4 hrs, while the frequency of BBB was statistically more significant during the first 4 hrs in 8 (80,0%) patients. Figure 4 presents the frequency of each form of heart rhythm and conduction disorders where it can be observed that SB was the most frequent rhythm disorder in STEMI (24,2%) followed by ST with 20,2%.

In the first 4 hrs there was 74,75% rhythm and conduction disorders, while in the 5–12 hrs period there was 25,25% disorders (Figure 5).

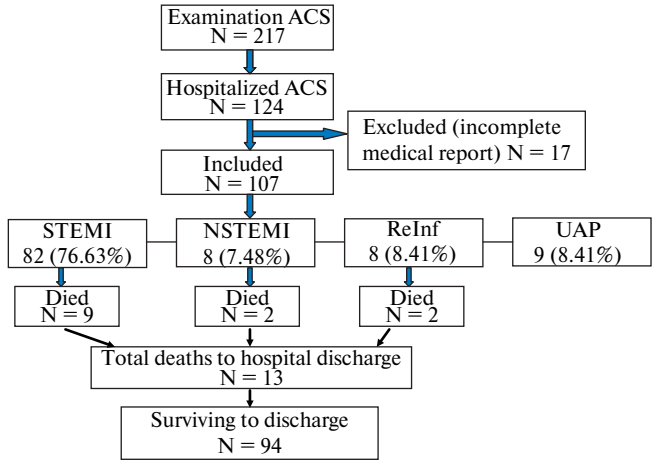

Figure 1. Flow diagram of patients with acute coronary syndrome.

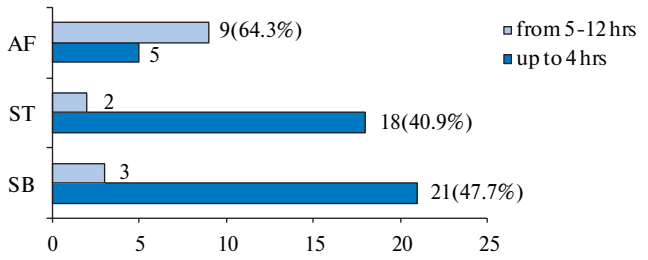

Figure 2. Supraventricular rhythm disorders in STEMI according to onset occurrence.
Abbreviations: AF — atrial fibrillation, ST — sinus tachycardia, SB — sinus bradycardia.

Table 1

Frequency of rhythm and conduction disorders in relation to single forms of ACS

Rhythm disorder	STEMI (n)	NSTEMI (n)	UAP (n)	ReInf (n)	Total (n)
Supraventricular	39	2	5	4	50
Ventricular	6	-	-	-	6
Combined	14	3		1	18
Total	59	5	5	5	74
Conduction disorder	STEMI (n)	NSTEMI (n)	UAP (n)	ReInf (n)	Total (n)
Atrioventricular (AV)	5	-	1	-	6
Bundle brunch block (BBB)	10	-	2	3	15
Combined	-	1	-	-	1
Total	15	1	3	3	22

Follow-up of each form of bradyarrythmia in relation to STEMI localization revealed that SB was the most frequent rhythm disorder associated with diaphragmal MI, with statistical significance of p<0,05, while BBB was highly significantly associated with anterior STEMI, with statistical significance of p<0,05, while BBB was highly statistically significantly associated with anterior STEMI (p<0,01). A statistically significant frequency was revealed regarding the occurrence of AV blocks in diaphragmal STEMI.

In the anterior STEMI, among bradyarrhythmias only SB and AV blocks were present in the first 4 hrs, while the occurrence of BBB was statistically more significant in the first 4 hrs in relation to the period of 5–12 hrs. Using the method of two-factor ANOVA to analyze proportions, we tested the significance of difference in the frequency of various categories of rhythm disorders in relation to the AMI localization and time of onset; consequently, we detected that the most frequent and most expected form in the first 4 hrs was SB rhythm disorder and that it was associated with diaphragmal STEMI (p<0,05), while AV blocks occurred only during the first 4 hrs, whereas BBB did not occur in STEMI of diaphragmal localization.

The analysis of each form of tachycardia in the anterior and diaphragmal localization of AMI revealed that tachyarrhythmias were more frequent in the anterior STEMI, i.e. that ST was most frequent of rhythm disorders associated with anterior localization of infarction with statistical significance of p<0,05. Single VES were more frequent in the diaphragmal STEMI. Almost identical frequency was that of VT in both localizations, while VF was statistically significantly present in the anterior STEMI (Figure 6).

By observing the frequency of tachyarrythmias in relation to the localization of AMI according to the time of onset, we revealed that in the first 4 hrs ST occurred exclusively in 14 patients and that it was significantly associated with STEMI (p<0,05). VT was present in 4 patients in the anterior STEMI during the first 4 hrs only, while AF was more present in the 5–12 hrs period. By analyzing the frequency of certain forms of tachyarrhythmias in diaphragmal STEMI, it was revealed that in the first 4 hrs ST was more frequent and that single VES were more frequent in the period 5–12 hrs. The occurrence of VF in the diaphragmal STEMI was registered in the first 4 hrs only.

Thirteen (12,1%) ACS patients died before being discharged from hospital, of whom 9 with STEMI (6 with anterior and 3 with diaphragmal localization), 2 with NSTEMI and 2 with ReInf, while in the UAP group there was no lethal outcome (Figure 7). In STEMI, total mortality rated 11%. Most lethal endings were in patients

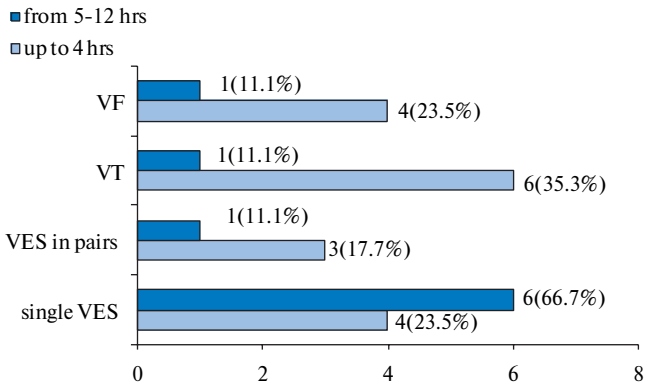

Figure 3. Ventricular heart disorders in STEMI according to onset.
Abbreviations: VF-ventricular fibrillation, VT-ventricular tachycardia, VES-ventricular extrasystole.

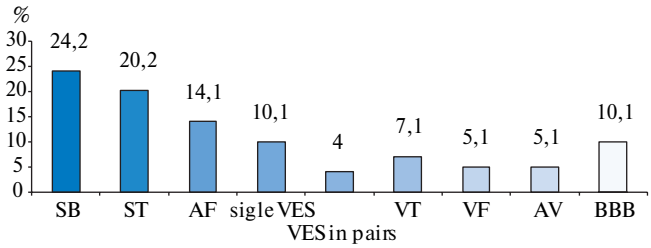

Figure 4. Distribution of heart rhythm and conduction disorders in STEMI.
Abbreviations: BBB-Bundle Brunch Blocks, AV-atrioventricular.

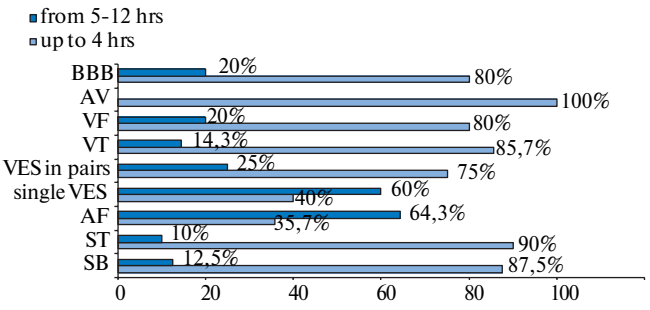

Figure 5. Distribution of rhythm and conduction disorders according to the time of onset in STEMI.

Table 2

Frequency and statistical significance of rhythm and conduction disorders in relation to STEMI and other groups

Heart rhythm and conduction disorders	STEMI		Other groups	
	No	%	No	%
With	63	76.80	19	76
Without	19	23.20	6	24
Total	82	100	25	100

with BBB (33.3%), and slightly less in those with VF and ST (22/2% in each). In the group of patients with NSTEMI and ReInf who died, those with AF and BBB were equally represented (one of each). In 13 ACS patients who died, supraventricular rhythm disorders were present in 4 (30,8%), ventricular in 3 (23%), and conduction disorders in 6 (46,2%) patients. The most frequent rhythm disorder registered in 5 patients who died BBB.

Discusion

Prehospital healthcare of patients with ACS is an essential element that influences the survival of patients and the outcome of disease. Most lethal outcomes occur within the first hour since AMI onset, and usually the cause is some of rhythm (VF) or conduction (asystole) disorders. In our paper, of the total number of ACS 76,63% had STEMI. According to the database of the National Registry for ACS (REACS), in 2003 there was 52,7%, in 2004 51,8% [5] and in 2005 50/7% of STEMI patients on admission, which is considerably lower in relation to our study results. Although according to this registry the rate of STEMI indicates the tendency of mild decrease, it is still significantly higher as related to the data of the European countries registry, for example in the GRACE study [6] there is about 42% of STEMIs. This most severe form of ACS has also the highest hospital mortality rate. Better diagnostics and organization of healthcare services would probably also decrease the number of patients with STEMI and increase the number of NSTEMIs.

In our study there was more men than women (60,7%:39.3%) with ACS. Similarly to our results, according to the data of REACS in Serbia the number of men with ACS was higher: in 2003 62,7%, in 2004 63,1%, and in 2005 63%. In EHS-ACS-II study [7], there were 70% of men with ACS, and in the GRACE study 72% [6].

The frequency of ACS development rises with age. In persons aged 40–70 years ACS is diagnosed more frequently than in women, while in those aged over 70 years the rate in both gender is mostly identical.

Heart arrhythmias are usually manifested during ACS, while the type of arrhythmia depends on the form of ACS. In almost 90% of patients who survived AMI, some of the forms of rhythm disorder were disclosed; while according to a study by Perron et al. [8] 25% had conduction disorder in the first 24 hrs since the onset of AMI. In our study 69,1% (74/107) of patients with ACS had heart rhythm and conduction disorders, while heart rhythm and conduction disorders occurred in 76,8% (63/82) of STEMI patients. Conduction disorder was present in 18,3% (15/82) of patients, and rhythm disorder in 72%, which is similar to Meltzer s results according to which the frequency of rhythm disorders in AMI was 72–96% [9], while Perron et al [8] obtained much lower rate results.

In STEMI patients 74,75% of rhythm and conduction disorders occurred within the first 4 hrs, and 25.25% from

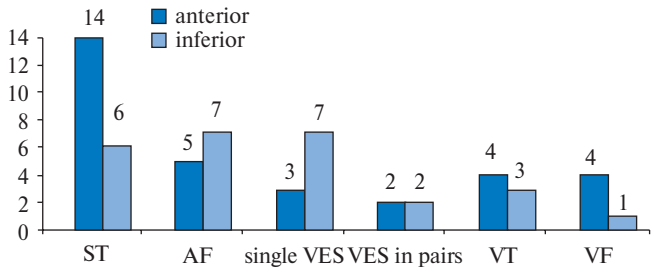

Figure 6. Distribution of tachyarrhythmia in STEMI of anterior and diaphragmal localization.

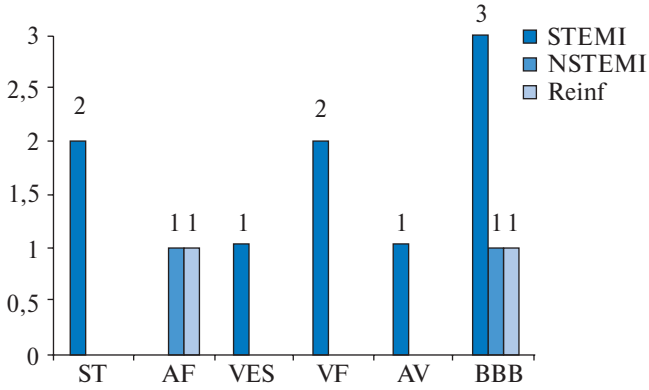

Figure 7. Distribution of lethal outcome in relation to rhythm and conduction disorders.

5–12 hrs after AMI onset. Supraventricular rhythm disorders developed in 64,6% (53/82) of patients with STEMI. By analyzing the frequency of supraventricular rhythm disorders in relation to the time elapsed since AMI occurrence, the most frequently registered were SB with 47,7% (21/44) and ST with 40,9% (18/44) of patients in the first 4 hrs, while AF was most frequent rhythm disorder within 5–9 hrs with 63,3% (9/44) registered patients. Branwald [10] reported that SB occurred in 25–40% of patients within the first hour after infarction and in 15–20% within the first 4 hrs.

In our study rhythm and conduction disorders in STEMI were registered in 14.1% of patients, while data from the literature vary from 10–20% [10], i.e. 5–23% [11]. According to the data from the GISSI-3 study [12] the incidence of AF is 7,8% and it is associated with the indicators of poor prognosis: patient s age (>70 years), female gender, Killip class III/IV, previous AMI, hypertension, high systolic arterial pressure on admission, diabetes mellitus as well as VT and VF. Sugi [13] recommends the application of amiodarone in the prevention of AF episode relapses after cardioversion. In their study on atrial arythmias during the first hours of AMI, Kyriakidis et al. [14] reported that most supraventricular arrhythmias was ischemia of the left and right atrium, and all cases had blood vessel occlusion with compromised blood supply to AV node. Ischemia of sinoatrial (SA) node was one of the basic causes of AF. None of the patients with SB had arte-

rial occlusion of the SA node. Bradycardia was the result of increased vagal tone.

Ventricular rhythm disorders were recorded in 24,4 (20/82) of STEMI patients, while ventricular rhythm disorders were most frequent in single VES with 38.5% (10/26) of patients, then VT in 26,9% (7/26) and VF in 19,2% (5/26). By the analysis of ventricular rhythm disorders we confirmed that they were most frequent in the first 4 hrs since AMI onset. At that period there were 65,4% (17/26) ventricular rhythm disorders, among which VT was most frequent with 35,3% (6/17) of patients. According to Braunwald, about 60% of VF episodes occur within the first 4 hrs and about 80% within 12 hrs from AMI onset, while non-sustained paroxysmal VT, either monomorphic or polymorphic, and occur in 67% of patients monitored within the first 12 hrs after infarction [10]. In our study there were 80% of VF episodes in the first 4 hrs, which is in accordance with the results by Vasiljević-Pokrajčić Z. and Stefanović B. [15].

Primary VF occurs suddenly and unexpectedly in patients with or without minimal signs of cardiac failure; it also occurs in over 10% of hospitalized patients with AMI [11]. Antman [10] reports that primary VF occurs in 3–5% of patients during hospitalization [10], which is similar to the results by Perron et al. (4,5%) [8]. GISSI-1 study [12] VT is registered in 3,5% and VF in 4,1% of patients, while in our study VT was registered in 7.1% and VF in 5,1% of patients.

Conduction disorders were present in 18,3% (15/82) of STEMI patients, while BBB were most frequent particularly in the first 4 hrs after AMI onset, i.e. in 53,3% (8/15) of patients. AV bundle blocks occurred only during the first 4 hrs, i.e. in 33,3% (5/15) of patients.

The occurrence of bradycardia in diaphragmal STEMI is 30%, while in our study it was 57,9% (22/38) [17]. By analyzing the occurrence of single forms of bradyarrhytmia in STEMI related to the MI localization and onset time, the most frequent form of rhythm disorder in the infarction of diaphragmal localization was SB as well as the most expected one within the first 4 hrs. According to data from the literature it occurs in 10–15% of MI patients, i.e. in up to 40% of infarction with diaphragmal localization, while in our study it occurred in 78,2% (18/22) of diaphragmal STEMI. SB is a more frequent rhythm disorder in infarctions of inferior and posterior localization, which explains the fact that a higher number of receptors responsible for cholinergic stimulation are localized in the inferoposterior wall of the left ventricle which, when stimulated, triggers bradycardia and hypotension. These are manifestations of Bezold-Jarisch reflex which is induced by vagal stimulation, particularly in occlusion of the right coronary artery. SB can be occasionally caused by pain or morphine usage and lead to vasovagal syncope. SB occurring 6 hrs after AMI onset is most often transitory and caused by sinus node dysfunction or atrial ischemia. In a very early phase of AMI this arrythmia can lead to the development of repetitive ventricular arrhythmias and hypotension on one hand and on the other to the reduction in myocardial oxygen demand.

In the TIMI II Trial, which analyzed the occurrence of bradyarrhythmia in diaphragmal localization of MI treated with thrombolytic therapy, the frequency of AV block was 12%, and in prethrombolytic phase even 20%. In our study the frequency of AV blocks in diaphragmal localization of MI was slightly lower, i.e. 10,52% (4/38). BBB occurred only in MI of anterior localization and more frequently in the first 4 hrs.

According to Uznańska-Loch et al. [18], in diaphragmal infarction AV block can suddenly occur without the introduction of first degree AV block, and within the first 6 hours after the onset of symptoms, while the block itself usually reacts well to atropine administration. Patients with a later AV block development, usually after 24 hrs, are resistant to atropine and require the application of electrostimulation. The authors consider that the early AV block is the result of vagotomy, while the late one is caused by ischemia and it can be resolved gradually concurrently with the decrease of ischemia.

Myocardial ischemia can cause blocks at any level of the conduction system, atrioventricular and/or intraventricular. According to data from the literature, BBB can occur in 5–10% of AMI patients [10], while in our study they occurred only in patients with anterior infarction (10% of cases of the total number of patients with rhythm and conduction disorders).

By analysis of each form of tachyarrhythmia in the anterior and diaphragmal localization of infarction, it was shown that tachyarhythmias were more frequent in the anterior STEMI, i.e. that ST was the most frequent form of rhythm disorder associated with the anterior localization of infarction that occurs exclusively within the first 4 hrs. According to data from the literature, in about 1/3 of patients with AMI ST usually occurs within the first days after infarction, and particularly in patients with anterior infarction [19]. This leads to the increased demand of the myocardium for oxygen as well as to a reduced time necessary for coronary perfusion. Persistent ST results in the development of weak heart. Single VES are more frequent in the diaphragmal localization. The frequency of VT in both localizations is almost identical, while VF is statistically significantly more frequent in infarction of anterior localization. The occurrence of VF in the diaphragmal STEMI was recorded only in the first 4 hrs. AF is a rhythm disorder that develops significantly in the period from 5–12 hrs.

Coronary arterial disease is the leading cause of death worldwide [1]. It is the cause of death in 45,6% of cases in the developed countries and in 24.5% of cases in the developing countries. The analysis of the cause of death has shown that infarct complications, primarily severe ventricular arrhythmias and weak heart, are still the main reason of such a high mortality rate. In our study 13

(12/1%) of ACS patients died, of whom 70% (9/13) were those with STEMI. Most frequent disorders, which were registered in 5 lethal cases, were those with BBB. Of the total number of lethal cases with STEMI there were 6 with anterior and 3 with diaphragmal localization. Most lethal cases were those with BBB (33.3%), while the patients with VF and ST were represented by identical rates. Peters et al. [20] also detected increased mortality rate in patients with conduction and supraventricular rhythm disorders. Thus increased mortality rate in patients with ACS associated with BBB is more associated with extensive myocardial damage than with the block itself.

According to data from the literature, a total mortality rate due to STEMI in Serbia in 2004 was 12,4%, and in 2005 11,7%, hospital mortality due to ACS was 8.2%, and UAP 1,6% [5]. Also, as reported in the literature, it is well known that in patients with MI mortality rate is highest during the first hours, most often before hospital admission and it ranges between 30–50%, while hospital mortality rate ranges from 10–15%, and within the first year from 5–10%.

Conclusion

As presented in our paper, heart rhythm and conduction disorders are one of the leading causes of death in patients with ACS during the first hours after the onset of complaints. In order to decrease mortality rate, it is necessary to apply some of the measures regarding the education of risk population, i.e. patients with some of the forms of coronary disease, but it is also necessary to have available educated teams in the sector of emergency medicine. Future researches should be directed toward the determination of highly methods for early prehospital screening of heart rhythm and conduction disorders in ACS so as to act on time preventively and therapeutically.

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SAFETY OF TIROFIBAN FOR PATIENTS WITH ACUTE ISCHEMIC STROKE IN ROUTINE CLINICAL PRACTICE

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Aim. This work aims to study the safety of tirofiban alone and in combination with various treatments in acute ischemic stroke (AIS).
Material and methods. 120 AIS patients were included in this study. There were 3 groups as below: Group A (tirofiban alone, n=68), Group B (tirofiban plus thrombolytic therapy, n=26), and Group C (tirofiban plus bridging therapy, n=26). Risk factors, stroke severity, initial imaging, treatment regimens, complications and long-term outcomes were analyzed.
Results. Eight patients (6,7%) in Group A, 6 patients (23,1%) in Group B and 2 patients (7,7%) in Group C had hemorrhage during or after treatment. Sixteen patients (6 in Group A, 8 in Group B and 2 in Group C) died during hospital admission. The mortality rate was 13,3% (8,8% for Group A, 30,7% for Group B and 7,7% for Group C, respectively) in the acute phase. A favorable outcome (mRS 0–2) at the first three months after stroke was only observed in 43,3% of patients (44,1% in Group A, 46,7% in Group B and 36,4% in Group C). The average Barthel index was 72,3 in Group A, 84,4 in Group B and 56,8 in Group C (total score: 71,0).
Conclusion. The stroke treatment with tirofiban is safe in AIS. A large randomized controlled trial in the future will be needed to decrease the minor bleeding complication of tirofiban therapy.

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Key words: Tirofiban, acute ischemic stroke, safety.

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AIS — acute ischemic stroke, BI — Barthel Index, CCTs — cerebral CT-built, CEA — carotid endarterectomy, CTA — CT angiography, DSA — digital Subtraction angiography, GFAP — glial fibrillary acidic protein, ICA — internal carotid artery, MRA — magnetic resonance angiography, mRS — Modified Rankin Scale, NIHSS — National Institutes of Health Stroke Scale, PTCA — percutaneous transluminal coronary angioplasty, tPA — plasminogen activator, UFH — unfractionated IV heparin.

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БЕЗОПАСНОСТЬ ТИРОФИБАНА ДЛЯ ПАЦИЕНТОВ С ОСТРЫМ ИШЕМИЧЕСКИМ ИНСУЛЬТОМ В РУТИННОЙ КЛИНИЧЕСКОЙ ПРАКТИКЕ

Yan-Jun Zhang, Qing Liu, Qin Zhan, Qiong Li

Цель. Данная работа направлена на исследование безопасности применения одного тирофибана и в сочетании с различными препаратами в острый период ишемического инсульта (ОИИ).
Материал и методы. 120 пациентов с ОИИ были включены в это исследование. Они были разделены на 3 группы: Группа А (тирофибан, n=68), группа б (тирофибан плюс тромболитическая терапия, n=26), и группа С (тирофибан плюс сопутствующее лечение, n=26). Факторы риска, степень тяжести инсульта, первичное обследование, схемы лечения, осложнений и долгосрочные результаты были проанализированы.
Результаты. Восемь пациентов (6,7%) в группе, у 6 (23,1%) в группе В и 2 пациентов (7,7%) в группе С, были кровотечения во время или после лечения. Шестнадцать пациентов (6 в группе А, 8-в группе В и 2 в группе С) умерли во время госпитализации. Уровень смертности составил 13,3% (8,8% для группы А, 30,7% для группы В и 7,7% для группы С, соответственно) в фазе обострения. Благоприятный исход (mRS 0–2) в первые три месяца после инсульта наблюдался только в 43,3% пациентов (44,1% в группе А, 46,7% в группе В и 36,4% в группе С). Средний Barthel index был 72,3 в группе А, 84,4 в группе В и 56,8 группы С (Общая оценка: 71,0).
Вывод. Лечение инсультов с применением тирофибана безопасно при ОИИ. Большие рандомизированные контролируемые испытания будут необходимы в будущем для уменьшения незначительных кровотечений как осложнений терапии тирофибаном.

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Ключевые слова: тирофибан, острый ишемический инсульт, безопасность.

Acute ischemic stroke (AIS) is a common cause of morbidity and mortality worldwide. Thrombolysis with recombinant tissue plasminogen activator is the only proven beneficial therapy in AIS which is received by less than 2% of patients [1]. The reasons include lack of adequate transport facilities, high cost of tissue plasminogen activator, lack of proper infrastructure including facilities for thrombolysis in most centers, and lack of awareness among public and doctors [2]. Moreover, there is a slight increase in hemorrhagic complications with thrombolysis.

Glycoprotein IIb/IIIa inhibitors, after their initial success in patients with acute coronary syndromes, has led to increasing interest to treat AIS over the past decade [3–7]. Highly selective platelet antagonists, the glycoprotein (gp) IIb/IIIa inhibitors, block the fibrin binding receptors reversibly and effectively prevent platelet aggregation. Tirofiban is a fast-acting, highly selective nonpeptide gpIIb/IIIa antagonist for the treatment of acute coronary syndrome up to 48 hours after onset [5].

However, the exact effect of tirofiban in patients with AIS, including risk factors, stroke severity, treatment regimens, complications, symptomatic or asymptomatic hemorrhage and long-term outcomes are unclear at the moment. The aim of this research was to study the safety of tirofiban alone and in combination with various treatments in AIS.

Materials and methods

Patients. A total of 120 patients with AIS, 70 men and 50 women, in the context of individual treatment trial with tirofiban were included in the study. Patient Inclusion and Exclusion Criteria-Patients with ischemic stroke between

18 and 82 years who were not eligible for thrombolysis and within a timeframe of 45 to 72 hours after onset of symptoms with National Institutes of Health Stroke Scale (NIHSS) scores between 4 and 18 were recruited. Patients were excluded if platelet level was <100 000/μL or there were contraindications to anticoagulants/thrombolytic agents. Prophylactic doses of low-molecular-weight heparin as deep vein thrombosis prophylaxis are allowed but higher doses were not. Pregnant women, subjects disabled before the recent stroke (modified Rankin Scale>2), recently treated with thrombolysis, or with recent major bleedings, surgery, or trauma were excluded. All patients received a first brain imaging (CT or MRI), blood pressure monitoring as well as laboratory tests (platelet counts, partial prothrombin time, creatinine, hemoglobin) before randomization. Hypertension was defined as on prior medication or elevated initial blood pressure during screening (systolic blood pressure >160 mm Hg). Hypercholesterolemia was classified as patients on lipid-lowering substances as well as diabetes on antidiabetics.

This study was approved by Ethics Committee of Zhengzhou People's Hospital in accordance with the declaration of Helsinki. Written informed consent was obtained from all participants.

Treatment. An initial dose of 0.4 mg/over 30 kg, and then continued at 0.1 mg/kg body weight per hour. The recommended infusion duration was 24 hours. Here, both patients receiving tirofiban alone and patients receiving tirofiban and other recanalisations methods were included. There were 3 groups: Group A (tirofiban monotherapy), Group B (tirofiban in combination with an intravenous or intra-arterial thrombolysis) and Group C (tirofiban as "bridging therapy", an additional recanalisation measure started before and continued during and after the intervention known as the PTCA and coronary stent implantation).

Data collection. Vascular risk profile, stroke localization, treatment duration, cumulative dose and time of Tirofibandosis were recorded. Modified Rankin Scale (mRS) was used to describe the severity of the stroke.

Pretreatment imaging including cerebral CT-built (CCTs) and stroke MRIs were performed to evaluate infarct demarcation, and early signs of infarction. In patients who had finished angiography before treatment, it should be noted whether a vascular occlusion had happened.

CCTs and MRIs were scored for bleeding complications during and after tirofiban application. To determine the severity of bleeding, ECASS II criteria were used: hemorrhagic infarction 1 (HI1) with small hemorrhages along the infarct margins; hemorrhagic infarction 2 (HI2) on confluent hemorrhage within infarct area but without space-occupying effect; parenchymal bleeding 1 for a bleeding that affects up to 30% of the infarct area and shows a possibly small space-occupying effect; parenchymal bleeding 2 at a blood flow, which affects more than 30% of the infarct area and has a significant space-occupying effect. Symptomatic intracerebral hemorrhage was defined as bleeding in any region of the brain accompanied by a significant clinical deterioration [8]. Among the patients in whom an initial vascular occlusion was documented, were, after treatment by means of representations guided vascular CT angiography (CTA), magnetic resonance angiography (MRA) or digital Subtraction angiography (DSA) evaluated for recanalisation. NIHSS, mRS and Barthel Index (BI) were used to assess the outcomes at discharge.

Statistical analysis. All experiments were performed at least three times. Data were expressed as mean ± standard deviation. One-way ANOVA was used to analyze data. A p value less than 0.05 was considered statistically significant.

Results

General characteristics. There were a total of 120 patients, 70 men and 50 women, who were treated with tirofiban in the context of individual treatment trial. Overall baseline characteristics were similar in all groups; no significant difference was found for age, baseline NIHSS at screening, time between symptom onset, screening, and start of infusion. The proportion of men was higher than that of women in all groups. The vascular risk profile of patients was summarized in Table 1.

Patient groups. Many patients (n=68) received tirofiban as monotherapy and were assigned to Group A. A clot lysis by tissue plasminogen activator (tPA) here was no longer in question mainly because of a lapse three-hour time window. Because the remaining 18 patients were treated within the window time, there were different exclusion criteria for lysis treatment. Two patients suffered from ulcerative colitis, two had an alcohol abuse and another four patients already had the tirofiban treatment. 26 patients above were assigned to Group B. And these 26 patients were also divided into subgroups according to who received tirofiban following a systemic or intra-arterial thrombolysis.

The rest 26 patients were assigned to group C, in which to initiate other recanalisation or bridging IV therapy during the tirofiban therapy. In one case, the bridge was combined with a Carotid endarterectomy (CEA). The young patient was previously treated systemically because of a medium infarction. Since the symptoms were not improved, she was brought to our hospital, where a stenosis of the internal carotid artery (ICA) and a thrombus just distal to the stenosis were determined at the day after admission. Eight patients received IA thrombolysis, which was in the middle period from onset of symptoms until 2.5 hours after the start of treatment. In three patients, however, the time of symptom onset was unclear. The intra-arterial embolectomy was performed in three patients. The time to initiation of treatment with tirofiban was on average 6.25 hours, until another 35 minutes at the

beginning of the intervention. One patient received IV lysis and tirofiban practically and simultaneously, the time of treatment was 2.5 hours. In all patients undergoing neuro-interventional radiology measure, the infusion was maintained during and after treatment by coronary angiography or by percutaneous transluminal coronary angioplasty (PTCA) with or without stent implantation in patients with acute coronary syndrome. The distribution of stroke localization in the different groups was shown in Table 2.

Imaging findings. Prior to treatment, all of the patients received cerebral imaging CT, even MRI in two cases to rule out intracerebral hemorrhage. Thirty-two patients were found the demarcated infarcts in imaging studies; another 24 patients had at least early infarct signs.

93,3% of the patients had also a vascular imaging with CTA, MRA or DSA. Transcranial Duplex Sonography was carried out in two cases. 68 patients (56,7% of total population) had a complete or nearly complete vessel occlusion.

Clinical outcomes and complications. The application of tirofiban was recommended for duration of 24 hours. However, the infusions were generally continued until a stable situation had been established in 12 cases. And there was even a second dose for fluctuating symptoms, so that the total application time significantly extended. The mean treatment duration was 30,5 hours (ranging from 4 to 106 hours). The mean cumulative dose was 15,7 mg tirofiban (ranging from 2,5 to 71,9 mg). The infusion had to be terminated prematurely in 18 patients because of complications. Two cases showed a contrast medium extravasation injury in the basal ganglia by CT imaging after thrombolysis, so that the infusion was stopped because a potential bleedingd by the contrast agent can be masked. Four patients developed a large space-occupying infarction and had to receive hemicraniectomy. There were concerns whether the treatment continue in two cases, since the patient was suffering from colon cancer. Thrombocytopenia occurred in two cases. Two patients had a haematemesis and another four patients had a control parenchymal bleeding at the end of CT.

The time from symptom onset to tirofiban administration was very different and ranged from 45 to 72 hours, especially because many patients in group A were treated only with tirofiban and the fluctuation in symptoms was noticeable. In ten patients, the time of symptom onset could not be determined because the patient woke up with symptoms. The median time was the time to start similar treatment in groups A and C (Table 3).

The four patients, who had been waived on an imaging, had an excellent outcome with complete resolution of symptoms. In the total population, only 8 (6,7%) out of all patients suffered hemorrhage. All hemorrhages were classified as parenchymal bleeding first, and symptomatic bleeding had not occurred. Table 4 shows the frequency of bleeding in each group.

14 patients (11,7%) experienced extracerebral bleeding complications. 10 cases included a gastrointestinal hemorrhage, a hematoma of the abdominal wall, a compartment syndrome after hemorrhage in the thigh. None of the patients required a blood transfusion. 2 out of 14 patients had received tirofiban after a systemic lysis with tPA, the rest 12 patients were treated in group A. The one patient observed in group A had not clinically significant thrombocytopenia.

A complete or nearly complete vessel occlusion had been detected in 68 patients. 38 of them were subjected to transcranial duplex sonography. 24 cases had recanalisation of the occluded vessel (Table 5).

Stoke severity. To assess the severity of the stroke, patients were assessed by modified mRS and NIHSS at admission, shown in Figure 1. The median NIHSS was 11 points in the overall, 8 points, in group A, 16 points in Group B and 12 points in Group C. Overall, the variation was very large, but most cases were the heavy ones.

16 patients (6 in group A, 8 in group B, 2 in group C) died during the hospital stay, which the mortality was 13.3% (8,8% for group A, 30,7% for group B and 7,7% for group C, respectively) in the acute phase. These 16 patients had a mRS 5 at admission. 48 Of the 52 patients or their relatives were interviewed. The follow-up was

Table 1

Vascular risk profile of patients

Risk factors	n (%)
Diabetes mellitus	16 (13,3)
Arterial hypertension	74 (61,7)
Arteriosclerosis	68 (56,7)
Heart rhythm disorders	30 (25,0)
Other cardiac source of embolism	26 (21,7)
Hyperlipidemia	52 (43,3)
Obesity	52 (43,3)
Previous stroke	28 (23,3)
Smoking (current and former)	30 (25,0)

Table 2

The distribution of stroke in the different groups

Infarct	Total, n	Group A, n	Group B, n	Group C, n
Anterior circulation Infarct	36	20	2	14
Posterior circulation Infarct	80	46	22	12
Watersheds Infarct	4	2	2	-

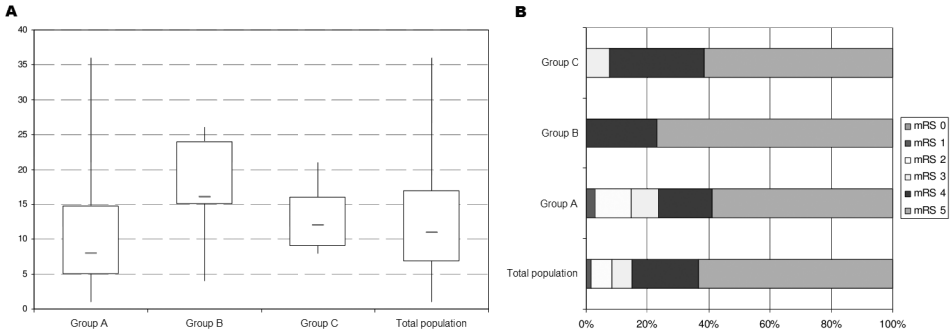

Figure 1. The stoke severity in each group at admission. A) NIHSS; B) mRS.

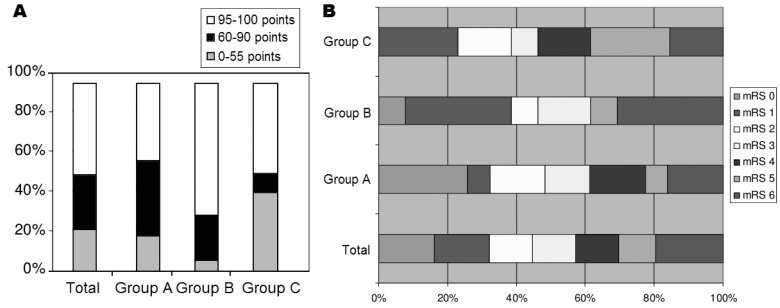

Figure 2. Outcome of patients in each group three months or longer after stroke. A) Barthel Index; B) mRS.

between three and 14 months after the stroke, and Barthel index and mRS were queried. The results were shown in Figure 2.

A favorable outcome (mRS 0–2) at the earliest three months after stroke was only observed in 43,3% of patients (44,1% in group A, 46,7% in group B and 36,4% in group C). The average Barthel index was 72,3 points in group A, 84.4 points in Group B, 56,8 points in Group C and 71,0 points in the overall.

Discussion

In this retrospective study, it was shown that in certain selected cases, the treatment of acute ischemic stroke with the GPIIb/IIIa antagonist tirofibans. This opens up the next thrombolysis with rTPA further treatment options such as a bridge between diagnosis and specific measures for revascularization. The present study is retrospective, however, not controlled and considered various treatment strategies simultaneously, so that we urgently needed to confirm the results of larger prospective, controlled studies.

The studied patient population can be well with group B of the present study compared, in which no symptomatic and only 3% of patients with asymptomatic hemorrhages occurred, although both rtPA and tirofiban was not used in a reduced dose. A follow-up study with rTPA 0.6 mg/kg plus eptifibatide versus standard-lysis in the pipeline. Then will then decide whether it will be a Phase III efficacy study [9].

Interesting results were also found in experimental stroke research in rodents. A dose-dependent relationship between intracerebral hemorrhage risk and use of an anti-mouse GPIIb/IIIa F (ab) 2 fragments could be detected for the dose that resulted in a receptor blockade of more than 95%, but not for the dose at which a receptor blockade was achieved by 67.8% [10]. Choudhri et al. found significant bleeding in maximum doses following administration of non-peptidic substance SDZ GPI 562 in a mouse model of acute ischemic stroke. After administration of lower doses was found after staining with triphenyltetrazolium chloride, a significantly smaller infarct volume than expected [11]. Other studies in experimental stroke models in guinea pigs and squirrel monkeys with the non-peptide GPIIb/IIIa blocker FK419 could uncover no bleeding complications, but showed reduced infarct volume as an indication of their effectiveness [12, 13].

The GPIIb/IIIa receptor (integrin aIIbb3) has the same β3 subunit as the vitronectin receptor (integrin αvβ3) that is present on resting endothelial cells in small numbers. However, the expression of αvβ3 by angiogenic stimuli such as hypoxia, transforming growth factor (TGF) -β3 and thrombin, as they occur in the context of regional cerebral ischemia, upregulated. The expressed on endothelial cell vitronectin receptor is responsible for the adhesion of monocytes to the endothelium, conveys a permeability the blood-brain barrier and contributes as well as the vascular endothelial growth factor (VEGF) on proliferation and migration of inflammatory cells into the perivascular tissue

Table 3

Time to initiation of treatment with tirofiban (hours)

	Total	Group A	Group B	Group C
Average	9,5	11,6	9,3	3,6
Median	4,5	4,25	7,0	2,5

Table 4

The frequency of bleeding in groups

	Total bleeding, n (%)	HI1, n (%)	HI2, n (%)	PH1, n (%)	PH2, n (%)	SICH, n (%)
Total	8 (6,7)	-	-	8 (6,7)	-	-
Group A	-	-	-	-	-	-
Group B	6 (23,1)	-	-	6 (23,1)	-	-
Group C	2 (7,7)	-	-	2 (7,7)	-	-

Table 5

Arterial recanalization rate for all patients diagnosed with vascular occlusion

Therapy	Recanalization, n (%)
Tirofiban-Monotherapy (n=8)	2 (25%)
IV thrombolysis (n=8)	4 (50%)
IA thrombolysis (n=16)	14 (88%)
IV and IA. thrombolysis (n=2)	0 (0%)
Embolectomy (n=4)	2 (50%)
Early CEA (n=2)	2 (100%)
All (n=40)	24 (60%)

during angiogenesis in [14, 15]. Possibly by the binding of GPIIb/IIIa receptor blockers on the vitronectin receptor and the permeability of the blood-brain barrier and thus influences the occurrence of intracerebral hemorrhage. This should bring a dose-dependent study of the effects of GPIIb/IIIa blockers on activated endothelial cells further insight.

While the link between fibronectin receptor interference and occurrence of ICB is currently more of a theoretical nature, the favorable relationship between vascular occlusion and reperfusion after ICB has been shown in several studies [16]. The use of biomarkers in blood-brain barrier provides in predicting intracranial hemorrhagic complications after stroke and especially after thrombolysis followed by additional help. Especially for matrix metalloproteinase-9, cellular fibronectin, S100β and glial fibrillary acidic protein (GFAP) has been shown that they can contribute to the prediction of intracranial hemorrhage [17].

These biomarkers could also be used to study the different GPIIb/IIIa antagonists in regard to bleeding complications. Since the individual substances in structure and mode of action show quite lower vagina, could thus those that are particularly suitable for treating cerebral ischemia, are highlighted. Mangiafico et al. published a paper in which they described 21 patients with acute ischemic stroke who have an aggressive treatment regimen consisting obtained from iv tirofiban for 24 to 48 hours, iv heparin, a local lysis with urokinase and in most patients undergoing percutaneous transluminal angioplasty [18]. However, note that the comparability is limited due to low patient numbers. There have been two studies that the combination of tirofiban with unfractionated IV heparin (UFH) or with IV rtPA in the treatment of acute stroke in approach. Junghans et al. have prospectively 18 patients within 24 hours after onset of stroke symptoms included in a study in which they initially with UFH, with a target PTT 50–70 seconds and then tirofiban in the PRISM-PLUS dosage of funds received in 46 hours [19]. Intracerebral hemorrhage is not any way this occurred, however, only a low recanalization rate of 25% will be retained.

Neither tirofiban, heparin still possess thrombolytic properties. The rationale of treatment is rather the time it takes for an endogenous mediated by endothelial cells remains to extend thrombolytic therapy to prevent further thrombus and to prevent reocclusion already re-opened vessels. In addition to the narrow time window that is another problem is that in the sole rTPA administration vessels re-opened in about a third of re-occluded cases [20], which speaks well for it, as in group B of our work in a place lysis treatment, even in terms to follow up re-opened despite the major tribes still limited microcirculation [11], further therapy with a GPIIb/IIIa inhibitors.

Comparing the present data with the results of the already mentioned in the introduction satis study, the only previous completed investigation with tirofiban in a larger cohort of stroke patients, then the long-term outcome in Group A is not as advantageous as for the satis population described. The Barthel Index was in the present study at least three months after stroke on average 71 points (median 90), in Satis-study funds at 1.

Overall, the safety of tirofiban in monotherapy or in combination with various Rekanalisations methods in the treatment of patients with acute ischemic stroke by the present investigation is based. Because of the retrospective, non-controlled study design and the relatively low numbers of patients with heterogeneous treatment approaches, the data must be interpreted with caution, but they give a good insight into the safety of the use of tirofiban in clinical practice.

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EFFECT OF PREOPERATIVE TIROFIBAN ON POSTOPERATIVE MYOCARDIAL PERFORMANCE IN PATIENTS WITH LEFT MAIN CORONARY ARTERY DISEASE UNDERGOING CABG SURGERY

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Aim. In this study, we investigated the impact of tirofiban on ventricular performance in patients who were diagnosed with acute coronary syndrome, found to have left main coronary artery stenosis during coronary angiography, and administered tirofiban prior to coronary artery bypass to prevent the recurrence of an acute coronary syndrome during the preoperative period.

Material and methods. The patients were divided into two groups. Group 1 included patients who were pre-diagnosed with acute coronary syndrome and administered tirofiban infusion in another hospital and subsequently sent to our center for advanced examination and treatment, where they exhibited left main coronary artery disease during coronary angiography and were submitted to surgery (n=28). Group 2 included patients who arrived at our emergency service with chest pain, were pre-diagnosed with acute coronary syndrome in the cardiology clinic, exhibited left main coronary artery disease during coronary angiography, and were submitted to urgent surgery without receiving tirofiban infusion (n=29). Standard and tissue Doppler echocardiography were applied to each patient in the preoperative and postoperative periods.

Results. After bypass surgery, the mean postoperative left ventricular myocardial performance index (0.84±0.30) was significantly lower than the mean preoperative left ventricular myocardial performance index (1.10±0.35) (p=0.001). The left lateral myocardial performance index was lower in group 1 (0.76±0.31) than in group 2 (0.92±0.27) (p=0.050*), but the ejection fraction was higher in group 1 (61.46±7.74) than in group 2 (52.87±11.64) (p=0.003*).

Conclusion. Preoperative administration of tirofiban improved postoperative left ventricular performance compared to pretreatment with aspirin alone in patients with left main coronary artery disease undergoing coronary artery bypass surgery. Therefore, we recommend the preoperative administration of tirofiban as an antithrombotic agent to patients who are undergoing coronary artery bypass for left main coronary artery disease.

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Key words: left main coronary artery disease, CABG, tirofiban, ventricular performance.

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LIMA — Left internal mammarian artery, LAD — left anterior descending artery.

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ВЛИЯНИЕ ПРЕДОПЕРАЦИОННОЙ ТЕРАПИИ ТИРОФИБАНОМ НА ПОСЛЕОПЕРАЦИОННЫЕ ПОКАЗАТЕЛИ МИОКАРДА У БОЛЬНЫХ ПЕРЕНЕСШИХ ОПЕРАЦИЮ АОРТО-КОРОНАРНОГО ШУНТИРОВАНИЯ

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Цель. В этой работе изучено влияние тирофибана на желудочковые показатели у больных, которым был поставлен диагноз «острый коронарный синдром» (ОКС), обнаружен стеноз левой коронарной артерии при коронарной ангиографии и введен тирофибан до операции коронарного шунтирования, чтобы не допустить повторения ОКС в предоперационном периоде.

Материал и методы. Больные были разделены на две группы. В группу 1 были включены пациенты, которым был предварительно поставлен диагноз ОКС, введен тирофибан в другой больнице; затем они были направлены в наш центр, им было проведены современное обследование и лечение, подтвержден стеноз левой коронарной артерии при коронарной ангиографии, и пациенты были отправлены на хирургическое лечение (n=28). 2 группа — пациенты, доставленные в наш центр бригадами экстренной помощи, с болью в области груди; им был предварительно поставлен диагноз ОКС в клинике кардиологии, подтвержден стеноз левой коронарной артерии при коронарной ангиографии, и была назначена срочная операция, без получения инфузии тирофибана (n=29). Метод стандартной и тканевой допплер-эхокардиографии был применен к каждому пациенту в предоперационном и послеоперационном периодах.

Результаты. После шунтирования, значение индекса послеоперационного миокарда левого желудочка (0,84±0,30) был значительно ниже, чем значение индекса предоперационного миокарда левого желудочка (1,10±0,35) (p=0,001). Показатель индекса левого латерального миокарда был ниже в группе 1 (0,76±0,31), чем в группе 2 (0,92±0,27) (p=0,050*), но фракция выброса была выше в группе 1 (61,46±7,74), чем в группе 2 (52,87±11,64) (p=0,003*).

Вывод. Предоперационное введение тирофибана улучшает состояние послеоперационного левого желудочка, по сравнению с предварительным приемом аспирина у больных с заболеванием левой коронарной артерии, перенесших аорто-коронарное шунтирование. Поэтому, мы рекомендуем предоперационное введение тирофибана как антитромботического агента для пациентов, перенесших аортокоронарное шунтирование при заболевании левой коронарной артерии.

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Ключевые слова: заболевание левой коронарной артерии, аорто-коронарное шунтирование, тирофибан, производительность желудочка.

Introduction

Early surgical intervention is preferred for patients who are diagnosed with acute coronary syndrome and found to have left main coronary artery stenosis during coronary angiography. In hospitals where angiography cannot be used, anti-aggregant and anticoagulant drugs, such as clopidogrel, aspirin, low molecular-weight heparin, and glycoprotein IIb/IIIa antagonists, can be administered to patients who are diagnosed with acute coronary syndrome. The short action time of the glycoprotein IIb/IIIa inhibitor tirofiban, which facilitates its use up to four hours before surgery, is a distinct advantage over other drugs [1, 2]. Batyraliev et al. reported

that the use of tirofiban after coronary angiography in patients with coronary syndrome with ST elevation improved the left ventricular ejection fraction compared to patients who were not administered tirofiban [3]. Tissue Doppler echocardiography in combination with echocardiography is a practical, reliable and well-defined non-invasive diagnostic method for investigating left and right ventricular systolic and diastolic function [4, 5]. In this study, we used this method to investigate postoperative left and right ventricular performance in patients who were admitted directly to our hospital with acute coronary syndrome, diagnosed with left main coronary artery disease using coronary angiography, and submitted to urgent surgery. We compared the results of this group to those of patients who were pre-diagnosed with acute coronary syndrome and administered tirofiban infusion in another hospital and subsequently sent to our center for advanced examination and treatment, where they were diagnosed with left main coronary artery disease using coronary angiography and submitted to surgery.

Materials and Methods

Subjects and Study Design. In this study, we analyzed 57 consecutive patients between the ages of 40 and 85 years who had been diagnosed with acute coronary syndrome and exhibited left main coronary artery disease during coronary angiography. Gender differences were not considered when selecting patients. The patients were divided into two groups. Group 1 included patients who were pre-diagnosed with acute coronary syndrome and administered tirofiban infusion (the patients were given 0.4 μg/kg/min of tirofiban for loading and were randomized to receive maintenance infusion at 0.1 μg/kg/min for 24 or 48 h) in another hospital and sent to our center for advanced examination and treatment, where they exhibited left main coronary artery disease during coronary angiography and were submitted to surgery (n=28). Group 2 included patients who came to our emergency service with chest pain, were pre-diagnosed with acute coronary syndrome in the cardiology clinic, exhibited left main coronary artery disease during coronary angiography, and were submitted to urgent surgery without receiving tirofiban infusion (n=29). In addition, all patients in the study received only upstream aspirin treatment.

The exclusion criteria excluded patients who were in a state of cardiogenic shock, who were classified as Killip class 3 or 4, who used clopidogrel preoperatively, who were undergoing repeat coronary artery bypass surgery, who had incomplete revascularization, who underwent off-pump coronary bypass surgery, who developed mechanical complications of coronary artery disease (e.g., post- myocard infarction ventricular septal defect or rupture of the free ventricular wall), who underwent heart valve surgery combined with coronary artery bypass (e.g., mitral valve replacement, aortic valve replacement or tricuspid valve repair), and who were administered high-dose inotrope infusion and/or fitted with an intra-aortic balloon to treat poor postoperative ventricular function.

This study was approved by the Ethics Board and the Institutional Review Board (Project no: KA13/105) of Baskent University and supported by the Baskent University Research Fund. This study was conducted according to the recommendations contained in the Declaration of Helsinki on Biomedical Research Involving Human Subjects.

Surgical Procedure. Median sternotomy was applied to all patients under general anesthesia. Systemic heparinization was performed to ensure an activated clotting time of 600–800/second. The cardiopulmonary bypass was done via aorta-caval cannulation. Non-pulsatile cardiopulmonary bypass was used with a roller pump and a membrane oxygenator. The patients were routinely cooled to 28–30°C. After the installation of the cross-clamp, a crystalloid cardioplegic solution (St. Thomas II solution) was applied every 20 minutes to protect the myocardium. Topical cooling was performed using a crystalloid ice slush solution in all patients. At the same time, two surgeons routinely removed the saphenous vein from under the right knee, the radial artery from the left arm, and the left internal mammarian artery (LIMA). Using 7/0 propylene, distal anastomoses were made initially to the right coronary artery or to its posterior descending branch, subsequently to the circumflex coronary arterial system, and finally to the left anterior descending artery (LAD) and the diagonal arterial system. The LIMA was preferred as a graft for the anastomoses to the LAD artery, the saphenous vein was used for the anastomoses to the right coronary artery and the diagonal arterial system, and the radial artery was preferred for the anastomoses to the circumflex artery and its branches. The proximal anastomoses were sewn onto the aorta, installing a side-clamp. Coronary endarterectomy was not applied to any of the included patients. The patients were weaned from cardiopulmonary bypass when the rectal temperature reached 37°C.

Echocardiographic Evaluation. During the preoperative and postoperative (i.e., 4–8 weeks after the operation) periods, standard and tissue Doppler echocardiography were applied to each patient in the lateral decubitus position, using the Acuson Sequoia C256 Echocardiography System (Acuson, Mountain View, CA, USA), The echocardiographic images were recorded in video. Using M-mode imaging, the diastolic and systolic thicknesses of the intraventricular septum, the thickness of the posterior wall, and the end-diastolic and end-systolic diameters of the left and right ventricles were measured on the parasternal long axis. The ejection fraction was calculated.

To assess right ventricular diastolic function using pulsed wave Doppler (PW) in apical 4-chamber view, the sample volume was placed over the tips of the tricuspid valve and the right ventricular inflow samples were recorded. This procedure facilitated measurements of the early diastolic flow rate (E), the late diastolic flow rate (A), the E/A ratio, and the deceleration period of the E wave (Edz). The mean of three cardiac cycles was calculated for each value.

Tissue Doppler Imaging. To accurately determine myocardial speeds, the gain adjustment of the instrument was reduced

Table 1

The demographic and baseline echocardiographic measurements of the patient and control groups

	Group1 (n=28)	Group2 (n=29)	p
Gender (Female/male)	21	24	0,481
Age (years)	63,71±9,71	66,52±9,14	0,267
SBP (mm Hg)	138,86±21,15	142,59±19,33	0,527
DBP (mm Hg)	83,64±11,77	87,41±9,03	0,224
Total cholesterol (mg/dL)	184,94±52,63	181,36±41,03	0,663
HDL (mg/dL)	39,12±7,31	42,21±11,44	0,274
LDL (mg/dL)	116,82±45,63	108,00±39,70	0,514
Triglyceride (mg/dL)	160,35±62,94	154,79±78,51	0,795
Heart rate (beats/minute)	72,59±11,92	67,13±9,62	0,131
Preoperative blood sugar (mg/dL)	161,56±152,81	124,86±51,04	0,337
Height (cm)	156,65±39,58	165,08±7,72	0,405
Weight (kg)	77,39±8,35	77,69±12,53	0,867
Hypertension	14	20	0,109
Preoperative ejection fraction	59,73±9,81	58,83±15,09	0,797

Abbreviations: SBP — systolic blood pressure, DBP — diastolic blood pressure, HDL — high density lipoprotein, LDL — low density lipoprotein.

Table 2

The operation data for both groups, comparison of drainage, blood and blood products

	Group1 (n=28)	Group2 (n=29)	p
The number of distal anastomoses	3,48±0,79	3,41±0,80	0,754
LAD	1,00±0,00	1,00±0,00	0,221
Diagonal artery	0,56±0,51	0,63±0,49	0,682
intermedial Cx artery	0,22±0,43 1,06±0,24	0,10±0,31 0,93±0,62	0271 0,380
RCA artery Average x-clamp period (minute)	0,67±0,59 46,00±10,08	0,67±0,48 42,00±10,11	1,0 0,201
Average CPB period (minute)	110,50±30,95	94,59±23,26	0,073
Full Blood	3,36±1,43	4,16±1,84	0,173
ES	4,55±2,11	2,64±1,98	0,032*
FFP	5,24±2,31	4,62±2,32	0,396
Chest tube drainage/24 h, day 0 (ml)	517,86±235,02	562,50±278,19	0,602
Chest tube drainage/24 h, day 1 (ml)	366,67±349,89	301,09±146,45	0,545
Chest tube drainage/24 h, day 2 (ml)	200,00±150,00	210,00±135,50	0,924

Abbreviations: LAD — left descending coronary artery, Cx — circumflex coronary artery, RCA — right descending coronary artery, X–Clamp — cross-clamp CPB — cardiopulmonary bypass, ES — erythrocyte suspension, FFP: fresh frozen plasma.

to the lowest possible value. Throughout the procedure, the Doppler velocity was maintained at 0.5 m/sec and the sample volume interval was maintained at 5.9 mm. Apical 4-chamber view was used to record the myocardial speeds at the tricuspid and septal annuli. The tissue Doppler sample was recorded by positioning the PW sample volume above the myocardium at the basal septum and at the right ventricular lateral tricuspid annulus. This method makes it possible to assess the longitudinal movements of the right ventricle and the mutual interaction of both ventricles through a single selected window.

At these regions, we measured the systolic myocardial velocity (Sm), the early (Em) and late (Am) diastolic velocities and their ratio (Em/Am), as well as the isovolumetric relaxation times (IVRZm). The mean of these values for three consecutive heart beats was calculated.

The interval from the onset to the cessation of left ventricular outflow was used to measure the left ventricular ejection time (LVET). The interval from the onset to the end of right ventricular outflow was used to measure the right ventricular ejection time (RVET). The interval from the cessation of mitral inflow to the onset of left ventricular outflow was used to measure the isovolumetric contraction time of the left ventricle (IVCTL).

The isovolumetric relaxation time of the right ventricle (IVRTR) was defined as the interval from the cessation of right ventricular outflow to the onset of tricuspid inflow. The interval from the cessation of tricuspid inflow to the onset of right ventricular outflow was used to measure the isovolumetric contraction time of the right ventricle (IVCTR). The myocardial performance index of the right ventricle was calculated using the formula (IVCTR+IVRTR) /RVET. The myocardial performance index of the left ventricle was calculated using the formula (IVCTL+ IVRTL) /LVET.

The left ventricular Sm and ejection fraction values were used to evaluate left ventricular systolic function. The right ventricular Sm was used to evaluate right ventricular contractile function. The trans-mitral and trans-tricuspid E-wave velocity, the A-wave velocity, the E/A ratio, Em, Am, the Em/Am ratio, IVRT, IVCT, ET and myocardial performance index values were used to evaluate right and left ventricular relaxation (i.e., diastolic) function. The echocardiographic evaluation was performed by a cardiologist who was not informed about the clinical data or the echocardiographic analysis.

Statistical Analyses. SPSS software (SPSS Ver. 10.0) (SPSS Inc., Chicago IL, USA) was used to perform the statistical analyses. The numeric values were expressed as the mean±SD. The independent samples t-test or the Mann-Whitney U test was used for continuous variables, and the Chi-square test was used for categorical variables. Continuous variables were tested for normal distribution using the Kolmogorov-Smirnov test. Values of $p<0.05$ were accepted as statistically significant. According to the power analysis, if a 20% change in a certain variable was considered clinically significant with a two-tailed $\alpha=0.05$ and a statistical power of 80%, the adequate subject count was 17. This result indicated that a sample size of 57 participants would be sufficient. With this sample size, the statistical power was 0.930.

Results

Clinical Features of the Study Group

The preoperative demographic characteristics are presented in Table 1. No differences in gender, age, systolic blood pressure, diastolic blood pressure, total cholesterol,

high density lipoprotein cholesterol, low density lipoprotein cholesterol, triglycerides, preoperative blood sugar, heart rate (beats/minute), height, weight, preoperative ejection fraction, or hypertension were observed between the two groups.

Surgical Data

The surgical data are presented in Table 2. A statistically significant difference in erythrocyte suspension was observed between the two groups. No significant differences in the other parameters were observed between the study groups.

Morbidity, Mortality and the Length of Stay in the Intensive Care Unit

Throughout the study period (i.e., the six months following the day of hospitalization), no mortality was encountered among the patients included in the study. No differences in atrial fibrillation, pleural effusion, acute renal failure, stroke or pulmonary infection during the length of stay in the hospital (i.e., the first seven days of the study period) were observed between the two groups (p >0.05). In addition, no differences in the length of stay in the intensive care unit or the length of stay in the hospital were observed between the two groups (p >0.05) (Table 3).

Left Ventricular Relaxation Data

No differences in the preoperative left ventricular relaxation parameters were observed between the two groups (Table 4). In the postoperative period, no differences in the mitral E/A ratio (p=0.939), left ventricular Em (cm/s) (p=0.064), left ventricular Am (cm/s) (p=0.737), the left ventricular Em/Am ratio (p=0.265), left ventricular IVCT (ms) (p=0.102), or left ventricular ET (ms) (p=0.658) were observed between the two groups. Tissue Doppler IVRT (ms) was greater in group 2 than in group 1 (p=0.018*) (Table 5).

Right Ventricular Relaxation Parameters

No differences in the preoperative right ventricular relaxation parameters were observed between the two groups (Table 4). In the postoperative period, no differences in the right ventricular Em (cm/s) (p=0.167), right ventricular Am (cm/s) (p=0.583), the right ventricular Em/Am ratio (p=0.179), right ventricular IVRT (ms) (p=0.682), right ventricular IVCT (ms) (p=0.593), or right ventricular ET (ms) (p=0.201) values were observed between the two groups (Table 6).

Left and Right Ventricular Systolic Function

No differences in the preoperative left and right ventricular systolic function parameters were observed between the two groups (Table 4). In the postoperative period, no differences in the left ventricular Sm were detected between the two groups (p=0.182) (Table 5). Similarly, no differences in the right ventricular Sm value for the contractile function of the right ventricle were observed between the two groups (p=0.879) (Table 6). Among these parameters, the left ventricular ejection (cm/s) in the postoperative period was higher in group 1 than in group 2 (p=0.003*) (Table 5).

Myocardial Performance Index Values for the Left and Right Ventricles

No differences in the preoperative myocardial performance index values for the left and right ventricles were observed between the two groups (Table 4). In the postoperative period, the left lateral myocardial performance index was lower in group 1 than in group 2. This difference was statistically significant (p=0.050*) (Table 5). No difference in the right lateral myocardial performance index was detected between the two groups (p=0.617) (Table 6). After bypass surgery, the mean postoperative left ventricular myocardial performance index (0.84±0.30) was significantly lower than the mean preoperative left ventricular myocardial performance index (1.10±0.35) (p=0.001). However, no difference was observed between the mean preoperative right ventricular myocardial performance index (0.91±0.36) and the mean postoperative right ventricular myocardial performance index (0.89±0.35) (p=0.783).

Table 3

Comparison of the two groups with regard to the rates of morbidity, mortality and length of stay in the ICU

	Group 1	Group 2	p
AF	1	6	0,161
Pleural effusion	1	2	0,856
ARF	1	0	0,204
Sternum infection	0	1	0,431
Stroke	1	0	0,204
Pulmonary infection	1	0	0,204
Length of stay in the ICU (days)	2,94±1,16	2,59±0,97	0,296
Length of stay in the hospital (days)	13,17±7,37	9,93±4,45	0,107

Abbreviations: AF — atrial fibrillation, ARF — Acute renal failure.

Table 4

Preoperative left and right ventricular systolic and diastolic function measurements

	Group1	Group2	p
Right ventricular Sm (cm/s)	10,57±4,18	10,52±3,68	0,959
Right ventricular Em (cm/s)	9,64±3,84	10,79±4,09	0,275
Right ventricular Am (cm/s)	12,89±4,68	13,72±5,89	0,557
Right ventricular IVRT (ms)	117,99±50,89	113,03±32,82	0,665
Right ventricular IVCT (ms)	97,61±49,25	98,21±31,05	0,959
Right ventricular ET (ms)	241,26±55,19	256,93±49,85	0,275
Right ventricular MPI	0,94±0,34	0,88±0,38	0,501
Left ventricular Sm (cm/s)	7,89±3,36	9,17±2,66	0,121
Left ventricular Em (cm/s)	7,93±3,62	9,83±4,74	0,096
Left ventricular Am (cm/s)	13,04±4,42	13,72±5,93	0,623
Left ventricular IVRT (ms)	124,25±32,56	135,75±33,03	0,195
Left ventricular IVCT (ms)	113,02±44,42	127,78±35,20	0,174
Left ventricular ET (ms)	238,78±47,27	234,74±33,34	0,713
Left ventricular MPI	1,05±0,39	1,15±0,31	0,276

Abbreviations: Sm — systolic peak velocity, Em — early peak velocity, Am — atrial peak velocity, IVRT — isovolumetric relaxation time, IVCT — isovolumetric contraction time, ET — ejection time, MPI — myocardial performance index.

Discussion

To our knowledge, our study is the first investigation of the impact of tirofiban use prior to coronary artery bypass on the ventricular performance of patients with left main coronary artery disease. In this study, the left ventricular myocardial performance index was significantly lower in group 1 than in

Table 5

Postoperative left ventricular systolic and diastolic function measurements

	Group1	Group2	p
Mitral Emax (cm/s)	79,76±25,26	73,62±20,86	0,404
Mitral Amax (cm/s)	77,47±29,63	72,66±20,69	0,560
Mitral E deceleration time (ms)	255,75±69,02	234,60±48,97	0,297
Mitral E/A ratio	1,10±0,38	1,09±0,47	0,939
LVM	223,56±44,72	243,43±80,92	0,314
LVMI	123,59±19,14	139,96±46,59	0,288
left ventricular Sm (cm/s)	8,92±3,67	10,12±2,91	0,182
left ventricular Em (cm/s)	9,09±3,82	11,34±5,08	0,064
left ventricular Am (cm/s)	11,50±4,58	11,97±5,77	0,737
left ventricular E/A ratio	1,21±0,51	1,38±0,62	0,265
left ventricular IVRT (ms)	96,21±35,56	117,71±30,07	0,018*
left ventricular IVCT (ms)	90,26±41,38	107,93±37,99	0,102
left ventricular ET (ms)	256,82±47,45	253,04±37,74	0,742
left ventricular MPI	0,76±0,31	0,92±0,27	0,050*
LVEF	61,46±7,74	52,87±11,64	0,003*

Abbreviations: LVM — left ventricular mass, LVMI — left ventricular mass index, Sm — systolic peak velocity, Em — early peak velocity, Am — atrial peak velocity, IVRT — isovolumetric relaxation time, IVCT — isovolumetric contraction time, ET — ejection time, MPI — myocardial performance index, LVEF — left ventricular ejection fraction.

Table 6

Postoperative right ventricular systolic and diastolic function measurements

	Group1	Group2	p
Right ventricular Sm (cm/s)	11,46±4,25	11,62±3,80	0,879
Right ventricular Em (cm/s)	10,14±4,06	11,66±4,13	0,167
Right ventricular Am (cm/s)	12,11±4,66	12,86±5,59	0,583
Right ventricular Em/Am ratio	0,87±0,36	1,03±0,53	0,179
Right ventricular IVRT (ms)	116,28±50,67	111,55±33,95	0,682
Right ventricular IVCT (ms)	97,04±48,88	97,66±31,09	0,955
Right ventricular ET (ms)	242,25±55,57	260,86±50,64	0,201
Right ventricular MPI	0,93±0,34	0,86±0,37	0,433

Abbreviations: Sm — systolic peak velocity, Em — early peak velocity, Am: — atrial peak velocity, IVRT — isovolumetric relaxation time, IVCT — isovolumetric contraction time, ET — ejection time, MPI — myocardial performance index.

group 2 (p=0.050*) and the ejection fraction was higher in group 1 than in group 2 (p=0.003). Also, after bypass surgery, the mean postoperative left ventricular myocardial performance index (0.84±0.30) was significantly lower than the mean preoperative left ventricular myocardial performance index (1.10±0.35) (p=0.001). This result indicates that tirofiban exerts a protective effect on the performance of the left ventricle.

After cardiopulmonary bypass, the left and right ventricular functions are adversely affected by factors such as myocardial ischemia, reperfusion injury and vasoconstriction induced by hypothermia [6]. Left ventricular diastolic function begins to improve immediately after coronary artery bypass and returns to preoperative levels in the long term. In contrast, right ventricular dysfunction does not completely resolve and is encountered after both on-pump and off-pump surgery [7]. Left ventricular dysfunction and cardiac failure are important independent risk factors for surgical mortality after coronary artery bypass [8, 9].

The use of glycoprotein IIb/IIIa inhibitors after coronary interventions is currently common. Glycoprotein IIb/IIIa inhibitors prevent platelet aggregation and thrombus formation by blocking the glycoprotein IIb/IIIa receptors on the surface of platelets that promote aggregation. Among the drugs in this group, tirofiban takes effect rapidly, exerts an antiplatelet effect that disappears shortly after discontinuation, and is highly specific for glycoprotein IIb/IIIa receptors. The efficiency of tirofiban was demonstrated in three large scale studies: Platelet Receptor Inhibition for European Journal of Cardio-thoracic Surgery (PRISM), PRISM-Patients Limited by Unstable Signs and Symptoms (PRISM-PLUS) and Randomized Efficacy Study of Tirofiban for Outcomes and Restenosis (RESTORE) [10–12]. The increased use of coronary stents and glycoprotein IIb/IIIa inhibitors has markedly reduced the incidence of emergent and urgent coronary artery bypass graft surgery for unsuccessful percutaneous coronary intervention [13]. Moreover, a number of studies demonstrated that the use of tirofiban after unsuccessful percutaneous coronary angioplasty does not increase the incidence of bleeding after urgent coronary artery bypass operations [14–15]. However, no previous studies of the impact of tirofiban on myocardial performance after heart surgery are currently available.

Tissue Doppler imaging combined with echocardiography is a practical, reliable and well-defined, non-invasive diagnostic method that has recently been used to investigate left and right ventricular systolic and diastolic function [4, 5]. Echocardiographic evaluation of the right ventricle is very difficult due to its geometry and its position immediately below the sternum. The myocardial performance index obtained via tissue Doppler imaging is used to evaluate the non-geometrical systolic and diastolic functions. This parameter has been reported to be reliable for evaluating right [16,17] and left [18] ventricular performance. Myocardial performance is not affected by the pulse rate or blood pressure [19, 20]. High myocardial performance values are associated with adverse cardiac events [21, 22]. In our study, the left ventricular myocardial performance index value was significantly lower in group 1 than in group 2 (p=0.050*).

Microvascular obstruction is present in one-quarter to one-third of patients in whom TIMI 3 has been achieved using mechanical or pharmacological methods [23, 24]. Microvascular obstruction has been reported to cause intracardiac hemorrhage [25] and myocardial rupture [26]. A previous study on the use of abciximab, which is also a glycoprotein IIb/IIIa inhibitor, after acute myocardial infarction demonstrated that this drug is more effective than classical fibro analytical therapy against microvascular obstruction [27].

Clopidogrel is routinely administered to patients with acute coronary artery disease who seek emergency services. This drug has a long half-life; thus, if a coronary artery dis-

ease, such as left main coronary artery stenosis, is detected in such patients during coronary angiography and a surgical operation is necessary, surgery cannot be performed immediately due to the previous use of clopidogrel. An initial waiting period is necessary after the discontinuation of clopidogrel; in the absence of a waiting period, bleeding and mortality [28] rates increase in the postoperative period. In contrast, an acute coronary syndrome may redevelop if clopidogrel is not administered. As a glycoprotein IIb/IIIa antagonist, tirofiban is a drug that inhibits platelet aggregation. This drug is used increasingly in intensive care units because it can be used up to 4–6 hours before coronary artery bypass surgery.

However, no studies of the impact of this drug on ventricular function in the postoperative period are available. We found that preoperative administration of tirofiban improved postoperative left ventricular performance in patients with left main coronary artery disease undergoing coronary artery bypass surgery compared to pretreatment with aspirin alone. Therefore, we recommend the preoperative administration of tirofiban as an antithrombotic to patients who are undergoing coronary artery bypass for left main coronary artery disease.

Study Limitations

This study included a small registry of patients and has all of the limitations of a non-randomized trial. We found that tirofiban exerts a positive effect on left ventricular performance. However, the mechanism that underlies this effect is not fully known. The effectiveness of this drug might be linked to its ability to reduce microvascular obstructions. Additional large-scale studies that use more effective methods to evaluate microvascular obstruction are needed.

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CLINICAL ANALYSIS OF ASSOCIATION OF CYSTATIN C AND ATRIAL FIBRILLATION

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Some studies have disclosed atrial fibrillation (AF) is associated with inflammation. Cystatin C is not only inflammatory markers but also an independent predictor of cardiovascular events.

Aim. We sought to investigate the relationship between serum levels of cystatin C and the occurrence and development of AF.

Material and methods. 134 paroxysmal and persistent AF (AF1 group) and 121 permanent AF (AF2 group) patients in AF group and 154 healthy people in control group were prospectively measured for cystatin C, other inflammatory markers, biochemical indicators, left atrial diameter (LAD), left ventricular diameter (LVD) and left ventricular ejection fraction (LVEF).

Results. (1) Compared with control and AF1 groups, AF2 group had higher values of cystatin C, high sensitivity C reactive protein (hsCRP), LAD and LVD whereas lower values of LVEF (P<0.05). (2) After adjust for age, gender and body mass index (BMI), correlation analysis showed that serum level of cystatin C was closely related to hsCRP, LAD, systolic blood pressure (SBP) and creatinine, the correlation coefficient were respectively 0.658, 0.502, 0.475 and 0.530 (P<0.01), but negatively associated with LVEF (P=0.011) in AF group. (3) Multivariate regression analysis showed the hsCRP, cystatin C, LAD and LVEF entered finally into the regression equation (cystatin C, OR: 3.41, 95%CI: 1.09–11.08, P=0.009).

Conclusion. The serum levels of cystatin C has significant correlation with AF, which indicates cystatin C may play an important role in the process of AF development.

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Key words: cystatin C, atrial fibrillation, inflammation, inflammatory markers.

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AF — Atrial fibrillation, BUN — Blood urea nitrogen, BMI — Body mass index, ECG — Electrocardiogram, EDTA — Ethylenediamine tetraacetic acid, FBG — Fasting blood glucose, GFR — Glomerular filtration rate, hsCRP — High sensitivity C reactive protein, HDL–C — High-density lipoprotein cholesterol, LAD — Left atrial diameter, LVD — Left ventricular diameter, LVEF — Left ventricular ejection fraction, LDL–C — Low-density lipoprotein cholesterol, Cr — Serum creatinine, SBP — Systolic blood pressure, DBP — Diastolic blood pressure, TC — Total cholesterol, TG — Triglycerides, WBC — White blood (cell) count.

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КЛИНИЧЕСКИЙ АНАЛИЗ АССОЦИАЦИИ ЦИСТАТИНА С И ФИБРИЛЛЯЦИИ ПРЕДСЕРДИЙ

Ping Liu, Shujian Sui, Dongling Xu

В некоторых исследованиях было выявлено, что фибрилляция предсердий (ФП) связана с воспалением. Цистатин С является не только воспалительным маркером, но и независимым предиктором сердечно-сосудистых событий.

Цель. Мы попытались выяснить отношения между уровнем цистатина С в сыворотке крови и возникновением и развитием ФП.

Материал и методы. 134 пациента с пароксизмальной и персистирующей ФП (ФП1 группа), 121 пациент с постоянной ФП (ФП2 группа) и 154 здоровых людей в контрольной группе были под наблюдением для измерения цистатина С, других воспалительных маркеров, биохимических показателей, диаметра левого предсердия (LAD), диаметра левого желудочка (LVD) и фракции выброса левого желудочка (ФВ ЛЖ).

Результаты. (1) В сравнении с группой контроля, группы ФП1 и ФП2 имели более высокие значения уровня цистатина С, высокую чувствительность С реактивного белка (hsCRP), LAD и LVDб в тоже время — низкие значения ФВ ЛЖ (P<0,05). (2) После ранжирования по возрасту, полу и индексу массы тела (ИМТ), корреляционный анализ показал, что сывороточный уровень цистатина С тесно связан с hsCRP LAD, систолическим артериальным давлением (САД) и креатинином, коэффициенты корреляции были, соответственно, 0.658, 0.502, 0.475 и 0.530 (P<0.01), но отрицательно ассоциированы с ФВ ЛЖ (P=0,011) в группе с ФП. (3) Многофакторный регрессионный анализ показал, что hsCRP, цистатин С, LAD и ФВ ЛЖ в конечном счете входят в уравнение регрессии (цистатин С, OR: 3.41, 95%CI: 1.09–11.08, P=0.009).

Заключение. Уровень цистатина С в сыворотке крови имеет значимые корреляции с ФП, которая указывает на то, что цистатин С, может играть важную роль в процессе развития ФП.

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Ключевые слова: цистатина С, фибрилляция предсердий, воспаление, маркеров воспаления.

Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia and increases in prevalence with aging [1–3]. It has become one of the leading causes for hospitalized patients with AF because AF may induce stroke, heart failure and increases case fatality [1, 2, 4]. Unfortunately, its fundamental pathological mechanisms are not fully clear. Recent evidence is accumulating that AF may be closely interrelated with inflammation and inflammatory biomarkers [2, 4–6]. Some studies confirmed that diverse inflammatory factors participate in pathogenesis and development of AF [6–8].

Cysteine protease inhibitors-C (cystatin C) is a member of protease inhibitor superfamily. cystatin C is not only a relatively more sensitive indicator of evaluating renal function than creatinine but also an independent and strong predictor of cardiovascular events [7, 9]. Recently studies find cystatin C is closely related to the inflammatory process or other inflammation factors [7, 10]. However, it remains challenged whether or not there is correlation between cystatin C and AF. In this study, the correlation between cystatin C and AF was investigated and its possible pathogenesis was preliminarily discussed and elucidated.

Materials and methods

Subjects. A total of 255 consecutively hospitalized patients with AF (assigned to group AF) were prospec-

tively recruited between June 2008 and December 2010 from the Second Hospital of Shandong University and Qilu Hospital of Shandong University, which included 134 cases of paroxysmal and persistent AF (placed to group AF1), 66 males and 68 females with mean age of 67.58±12.4 years old. There were 121 cases of permanent AF (put to group AF2), 58 males and 63 females, averaged (68.09±11.7) years old. All cases of AF diagnosed were verified by medical history, physical examination, electrocardiogram (ECG) or dynamic electrocardiogram. The control group had 154 cases of adults after health examination in the Second Hospital of Shandong University, selected from outpatients without diseases or with minor illnesses from cardiac or other departments following the same exclusion criteria. Of which, there were 71 male cases, 83 female cases with a mean age of 64.43±11.2 years old. ECG showed sinus rhythm in control group. There were not statistically significant differences (P>0.05) but comparability in comparison with age, sex and etiological composition among the three groups.

AF was defined and classified according to the management of atrial fibrillation of the European Society of Cardiology (ESC, 2010 edition) [11]. Paroxysmal AF is self-terminating usually within 48 hours, and may continue for up to 7 days. Persistent AF is present when an AF episode either lasts longer than 7 days or requires termination by cardioversion, either with drugs or by direct current cardioversion. Permanent AF is said to exist when the presence of the arrhythmia is accepted by the patient (and physician). Patients with any of the following conditions were excluded from the study: infectious diseases, malignant tumors; hyperthyroidism; hypokalemia, hypomagnesemia, hypocalcemia and acidosis; pneumonia and pulmonary embolism; moderate and severe anaemia; intracranial hemorrhage; liver and renal abnormal function and other organs dysfunction; immune system and endocrine metabolic diseases; pregnant women and breastfeeding women; taking some medicines such as statins and angiotensin-converting enzyme-inhibitors and/or angiotensin II receptor blockers. This research was conducted in accordance with the ethical principles stated in the "Declaration of Helsinki". The study protocol and written informed consent were approved by the Ethics Committee of Clinical Research, the Secondary Hospital of Shandong University.

Methods. Peripheral vein blood were obtained from all participants early in the day after a 12 h fast, immediately transferred into a glass tube containing disodium EDTA, and centrifuged for 10 min at 3000 round/min, separated in aliquots and then stored at −80 °C. Cystatin C and hsCRP were respectively measured by means of a particle-enhanced turbidimetric immunoassay with commercial kits (Serum cystatin C, Beijing Leadman Biochemistry Co., Ltd. Beijing, China; hsCRP, Diagnostic System Laboratory Inc, Webster, TX, USA). Its normal reference value is 0−3mg/L.

Fasting blood glucose (FBG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL−C), high-density lipoprotein cholesterol (HDL−C), triglycerides (TG), blood urea nitrogen (BUN) and serum creatinine (Cr) were measured in automatic biochemical analyzer (Hitachi 7600, Tokyo, Japan) with enzymic method in all subjects. Blood routine was tested in a Sysmex XE-2100 hematology analyzer (Sysmex corporation, Kobe, Japan). Every participant received the test of a 12-lead MAC1200 electrocardiogram system (GE Healthcare, Milwaukee, WI, USA). Left atrium diameter (LAD), left ventricular diameter (LVD) and left vetricular ejection fraction (LVEF) were recorded using a Philips iE33 ultrasonocardiograph (Philips Medical Systems, Bothell, WA, USA).

Statistical treatment. Continuous variables were expressed as mean ± SD and categorical variables were presented as percentages. Continuous variables were compared using one-way ANOVA, and categorical variables were compared with chi-square test. The relationship between variables was evaluated by significance calculation of partial correlation analysis after adjusting classical risk factors (age, sex and body weight). The overall influence of selected risk factors on the AF was assessed using binary logistic regression. Predictors of AF were determined by the multivariate regression analysis. The association between variables and the occurrence of AF was represented by odds ratio (OR) and their accompanying 95% confidence interval (95% CI). SPSS 17.0 (SPSS Inc., Chicago, IL, USA) was used for all calculations. P<0.05 was considered significant.

Results

Comparison of baseline data between AF and control groups

Baseline characteristics are shown in Table1. Compared with control group, AF1 and AF2 groups did not have statistical significance in age, gender, TG, TC and HDL (P>0.05), but had higher values of BM, SBP, FBG and Cr (P<0.05 or P<0.01). Values of BUN and LDL were significantly higher whereas those of DBP were significantly lower in AF2 group than in control group, while there were not significant differences in the values of BP, BUN and LDL between AF1 group and control group (P>0.05). Furthermore there were not statistical differences in baseline datum between AF1 group and AF2 group (all P>0.05).

Comparison of inflammatory indicators between AF and control groups

As shown in Table 2**,** white blood cell counts were showed no significant difference (P>0.05) whereas there were significant difference in the values of cystatin C and hsCRP among these groups (P<0.05 or P<0.01). Compared with control group, AF1 and AF2 groups had higher values of cystatin C and hsCRP (P<0.05 or P<0.01). Furthermore AF2 group had higher values of cystatin C and hsCRP than those in AF1 group (P<0.05 or P<0.01).

Table 1

Comparison of baseline data between AF and control groups

Variables	control group	AF1 group	AF2 group
Age (year)	64.44±11.20	66.08±12.45	65.37±11.83
Male (n,%)	71 (46.10)	66 (49.25)	60 (47.93)
BMI	26.32±4.42	28.40±4.78*	28.95±5.07*
SBP	132.36±13.26	143.59±14.05*	144.18±15.63*
DBP	82.94±10.70	79.66±11.32	78.80±11.05*
FBG (mmol/l)	5.88±1.24	6.28±2.20*	6.35±2.48**
BUN (mmol/l)	5.95±2.26	6.30±3.07	6.57±3.12**
Cr (umol/l)	60.79±12.58	87.65±25.84*	88.19±26.36**
TG (mol/l)	1.18±0.53	1.20±0.46	1.24±0.60
TC (mol/l)	4.46±0.95	4.29±0.74	4.51±0.70
HDL (mol/l)	1.32±0.33	1.26±0.26	1.20±0.30
LDL (mol/l)	2.59±0.63	2.63±0.58	2.70±0.68*

Compared with control group, * P<0.05, **P<0.01.

Table 2

Comparison of inflammatory indicators between AF and control groups

Variables	control group	AF1 group	AF2 group
WBC (×109/L)	5.89±1.88	6.07±1.91	6.12±2.03
hsCRP (mg/l)	1.28±1.09	2.76±1.18**	3.90±1.25**##
cystatin C (mg/l)	0.84±0.17	1.05±0.28*	1.35±0.41**#

Compared with control group, * P<0.05, **P<0.01; Compared with AF1 group, # P<0.05, ## P<0.01

Comparison of echocardiogram parameters between AF and control groups

As outlined in Table 3**,** Echocardiogram showed AF1 and AF2 groups had higher values of LAD and LVD but lower values of LVEF than those of control group (P<0.05 or P<0.01). Compared with AF1 group, AF2 group had higher values of LAD and LVD but lower values of LVEF (P<0.05 or P<0.01).

Analysis for correlation between cystatin C and high risk factors of AF

As demonstrated in Table 4**,** after adjusting age, gender and body weight, cystatin C was closely related to hsCRP, LAD, SBP and Cr, and their correlation coefficient respectively were 0.658, 0.502, 0.475 and 0.53 (P<0.05 or P <0.01) whereas cystatin C was inversely related to LVEF (P=0.01).

Multivariate Analysis of AF risk factors

As presented in Table 5, all selected variables from AF and control groups were analysed by stepwise regression analysis and the related indicators were picked out. Finally, hsCRP, cystatin C, LAD and LVEF by turns entered the regression equation, showed in Table 4, included respectively hsCRP (OR: 3.76; 95% CI: 1.18–13.90; P=0.015), cystatin C (OR: 3.41; 95% CI: 1.09–11.08; P=0.008), LAD (OR: 1.84; 95% CI: 0.91–5.75; P=0.037), SBP (OR: 1.78; 95% CI: 1.05–4.32; P=0.006) and LVEF (OR: 1.26; 95% CI: 0.85–3.09; P=0.043).

Discussion

Cystatin C is a cysteine protease inhibitor having a molecular weight of 13kD, synthesized in all nucleated cells at a constant rate and present in an unglycosylated protein form, which extensively exists in animals and plants tissue and participate in proteolytic regulation between the interior and the exterior of the cell [7,12]. Due to its free filtration in the glomerulus, nearly complete reabsorption and catabolism in the proximal tubule, and lack of tubular secretion, serum cystatin C concentrations are closely related to the glomerular filtration rate (GFR) reflecting renal function [7, 9, 12]. So cystatin C is thought to be a specific, accurate and more sensitive marker than creatinine clearance rate.

In recent years, a large number of studies have confirmed that cystatin C is likely to be an independent risk factor of cardiovascular disease [7, 12]. The close relationship between cystatin C and cardiovascular disease is not only involved to kidney function but also is mediated by inflammatory mechanism [7, 13, 14]. The unique association of AF with renal dysfunction could be explained by the fact that AF and renal dysfunction share a number of risk factors [15]. Although mechanical stress on atrium due to volume overload could be the mediating factor that

Table 3

Comparison of ultrasound parameters of left heart between AF and control groups

Variables	control group	AF1 group	AF2 group
left atrial diameter (LAD, mm)	33.67±3.40	43.54±10.61**	47.09±11.75**#
Left ventricular diameter (LVD, mm)	49.49±7.33	52.63±11.29*	54.14±11.38**#
LVEF	54.82±8.46	50.07±10.50*	47.31±12.13**#

Compared with control group, * P<0.05, **P<0.01; Compared with AF1 group, # P<0.05, ## P<0.01

Table 4

Analysis for correlation between cystatin C and AF high risk factors

	hsCRP	LAD	LVD	LVEF	SBP	FBG	Cr	BMI	LDL
r	0.658	0.502	0.246	-0.353	0.475	0.213	0.53	0.153	0.164
P	0.00	0.000	0.044	0.010	0.035	0.048	0.009	0.057	0.036

leads to development of AF in patients with renal dysfunction, this may not be the case in earlier phases. One possible mechanism for a higher prevalence of AF in early stages of renal insufficiency could be relevant to inflammation [15]. In this study, only cystatin C among indicators reflecting renal function in multivariate analysis had strong connection with AF. It is explained that cystatin C is more sensitive than other markers to reflect renal function. Some researchers also disclosed that cystatin C is a more reliable marker of renal function compared to creatinine or estimated GFR as it is less affected by age, gender, and ethnicity [9].

Many researchers have verified that cystatin C has a linear positive interrelation with a variety of inflammatory cytokines such as hsCRP and reflects the severity of inflammatory activity in a renal function-independent manner [12]. Cystatin C and its fragments may also affect the phagocytic and chemotactic functions of granulocytes and participate in the inflammatory process [9, 12]. In atrial tissue of the patients with atrial fibrillation, inflammation results in inflammatory cell infiltration, oxidative stress and damage. Then fibrous tissue repairs the local tissue damage. As a result, the pathological process leads to the atrial remodelling [6–8]. It is worth mentioning that Targoński et al. found the serum concentration of hsCRP is closely positive correlation with the diameter size of left atrium [16]. This study result was consistent with Targoński 's conclusion and showed the serum concentration of cystatin C also coincided with LAD.

This study confirmed that atrial fibrillation groups had higher values of cystatin C, hsCRP and LAD than those in control group. Furthermore, persistent atrial fibrillation group had significantly higher values of cystatin C, hsCRP and LAD than those in paroxysmal AF and control groups. At the same time, correlation analysis showed that cystatin C is closely related to hsCRP and LAD of patients with atrial fibrillation. Therefore it is speculated that the inflammatory cytokines such as cystatin C and hsCRP should modulate process of inflammatory, participate in the hypertrophic degeneration of atrial muscle fiber, and induce atrial structural abnormalities in patients with atrial fibrillation, thus lead to atrial electrical remodelling [6–8]. Inflammation is closely associated to atrial fibrillation [6] and may be the important medium (such as high blood pressure and obesity, etc.), which links with known risk factors for atrial fibrillation and results in the occurrence and development of atrial fibrillation [1, 3, 17]. Even the atrial pathoanatomy in lone atrial fibrillation showed inflammatory infiltration, muscle cell necrosis and fibrosis [1, 17]. Modern research confirmed that chronic inflammation has arrhythmogenic effect giving rise to the development of AF in susceptible populations. Inflammatory markers could be the result of atrial fibrillation rather than the cause of atrial fibrillation [18]. Conen et al. found the augment of hsCRP increased the risk of AF by 31% in the elderly [18]. In this study, monofactorial analysis showed

Table 5

Multiple logistic regression analysis of predictive factors for AF

Variables	β	SE	OR	P	95%CI
hsCRP	0.73	2.90	3.76	0.015	1.18–13.90
cystatin C	0.60	2.35	3.41	0.009	1.09–11.08
LAD	0.34	1.12	1.84	0.037	0.91–5.75
SBP	0.58	0.91	1.78	0.006	1.05–4.32
LVEF	0.56	0.81	1.26	0.043	0.75–3.09

that the serum levels of hsCRP and cystatin C in 2 atrial fibrillation groups were higher than those in control group, and they were closely related to each other. Multifactor analysis showed that both cystatin C and hsCRP entered the regression equation and had higher OR values (3.41 and 3.76, respectively). It was demonstrated that atrial fibrillation is closely associated with inflammation regardless of the duration of atrial fibrillation. However, this study showed no significant relationship between white blood cell count and risk of incident atrial fibrillation, which differs from the result of the Framingham Heart Study [19].

Cystatin C is not only an independent risk marker of predicting cardiovascular risk but also is an independent risk factor of MetS [7]. As mentioned above, Cystatin C was not only related to inflammation but also was associated with the risk factors of atrial fibrillation, and these risk factors were properly the components of metabolic syndrome. Compared with no metabolic syndrome, the generating possibility of atrial fibrillation in patients of metabolic syndrome increased by 88% [3]. Atrial fibrillation and metabolic syndrome share common risk factors: obesity, hypertension, hyperglycemia and hyperlipidemia. The patients with higher level of cystatin C have higher metabolic state: higher BMI, blood pressure, blood sugar and lipid levels [12]. Researchers have shown that cystatin C is closely related to the metabolic syndrome [3, 7]. Insulin resistance is not only the pathogenesis of metabolic syndrome but also may be the pathological process that connects cystatin C with metabolic syndrome [7, 20]. Presumably, from another perspective, atrial filbrallation and the metabolic syndrome may have a common pathological relationship mediated by inflammtory biomakers such as cystatin C. This study confirmed that BMI, SBP, FBG and LDL in AF groups, especially in permanent atrial fibrillation group (AF2), were higher than those in the control group. Blood pressure is the most common risk factor of atrial fibrillation. Moreover SBP is the better predictor of atrial fibrillation than DBP [3]. This study also revealed that SBP closely correlated to cystatin C as showed in the univariate analyse. Linssen, et al. pointed out that AF facilitate the progression of HF in several ways. Due to rapid heart rates, an irregular ventricular rhythm, loss of atrioventricular synchrony, and an increase in mitral and tricuspid regurgitation, AF may further decrease cardiac

output and aggravate HF [21]. As shown in this study, LVEF was also independently aligned with AF. Some studies have validated that obesity is an independent risk factor for predicting atrial fibrillation [3]. But this study showed that BMI did not enter the regression equation in the multivariate analysis.

Study limitations

There were several limitations in this study. Our sample size, although small, was sufficient to display differences between the control group and the AF group, however further studies with larger scale of cohorts are needed to confirmed these results. Additionally, some inflammatory indicators such as interleukin-6 and tumor necrosis factor -α were not applied in this study. Although these indicators maybe do not affect the conclusion of this study, which possibly made an impact on the estimate for action degree of hsCRP and cystatin C in this study. Furthermore, the relationship between cystatin C and atrial fibrillation was not verified by pathological and molecular biological methods. Finally, we did not progressively group the patients with paroxysmal and persistent atrial fibrillation into two parts according to AF duration.

Conclusion

In summary, as a new inflammatory factor, cystatin C is intimately associated with atrial fibrillation, may play an important role in the occurrence and development of atrial fibrillation. However, the specific relationship and precise mechanism between cystatin C and atrial fibrillation will need to be verified by a lot of further basic and clinical study.

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MODERN ELECTROCARDIOGRAPHIC METHODS OF ESTIMATION OF CORONARY REPERFUSION AT THROMBOLYSIS IN ACUTE PERIOD OF MYOCARDIAL INFARCTION

Belaya I. Ye.

In the article the sensitivity of new vectorcardiographic research method of patients on the cardiodiagnostic complex MTM-SKM in the process of thrombolytic therapy is proved by clinical example.

Clinical case. In a patient with acute myocardial infarction of anterior wall of the left ventricle vectorcardiogram results give the opportunity to confirm a significant diminution of the area of myocardial damage with concomitant deterioration of conductivity and preserving of ischemic events due to reduction of electromotive force of the heart in the anterior wall of the left ventricle. In addition, the dynamic decrease of the electrical activity of the atria with a significant slowing of the pulse and repolarization disorder may indicate involvement of atriums in the pathological process with a considerable blood flow disorder in them.

Conclusion. This method allows to make a quality and quantitative evaluation of the efficiency of the reperfusion therapy, as well as to obtain the information about the electromotive force of the heart both in the necrobiosis zone and out of myocardium affection zone.

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Key words: acute myocardial infarction, cardiodiagnostic complex MTM-SKM, vectorcardiography, thrombolytic therapy.

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ECG — electrocardiography, EMF/H — electromotive force of the heart, LV — left ventricle, MI — myocardial infarction, PCI — percutaneous coronary intervention, STEMI — ST elevation myocardial infarction.

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СОВРЕМЕННЫЕ ЭЛЕКТРОКАРДИОГРАФИЧЕСКИЕ МЕТОДЫ ОЦЕНКИ КОРОНАРНОЙ РЕПЕРФУЗИИ ПРИ ТРОМБОЛИЗИСЕ В ОСТРОМ ПЕРИОДЕ ИНФАРКТА МИОКАРДА

Belaya I. Ye.

В статье доказана чувствительность нового векторкардиографического метода исследования пациентов на кардиодиагностическом комплексе МТМ–СКМ в процессе проведения тромболитической терапии на клиническом примере.

Клинический случай. У пациентов с острым инфарктом миокарда передней стенки левого желудочка результаты векторкардиограммы дают возможность подтвердить значительное сокращение площади повреждения миокарда с одновременным ухудшением проводимости и сохранения ишемических событий из-за снижения электродвижущей сила сердца в передней стенке левого желудочка. Кроме того, динамичное снижение электрической активности предсердия с существенным замедлением пульса и расстройством реполяризации может означать участие предсердий в патологическом процессе со значительным расстройством кровяного потока в них.

Вывод. Этот метод позволяет дать качественную и количественную оценки эффективности реперфузионной терапии, а также получить информацию об электродвижущей силы в сердце, как в зоне некробиоза, так и в зоне повреждения миокарда.

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Ключевые слова: острый инфаркт миокарда, кардиодиагностический комплекс МТМ–СКМ, векторкардиография, тромболитическая терапия.

According to Euro Heart Survey I, in the last decade, the 30-day mortality in acute ST elevation myocardial infarction (STEMI) in Europe has decreased from 8,4% to 6,4% [1]. This happened owing to the introduction into clinical practice of methods of recanalization of the culprit coronary artery, which was the key to restoring of blood flow to the heart and preventing necrosis, or at least significantly reducing the damage of the heart muscle. According to the guidelines of the European Society of Cardiology (2008), with a confirmed diagnosis of STEMI, there are two real ways to restore patency of the culprit coronary artery — it is thrombolytic therapy and/or primary percutaneous coronary intervention (PCI) [2].

Primary PCI has an advantage over thrombolytic therapy, initiated in hospital. Invasive approach contributes to further reduce of the death risk by 30%, non-fatal recurrent MI — by 58%. In addition, there is a lower rate of intracranial bleeding. Currently, PCI is preferred if implemented no later than 90 minutes after the onset of myocardial infarction, prior to contact with the medical staff [3]. This advantage is also evident in terms of operations with highly qualified personnel in appropriate conditions [4]. In Europe and in the United States the number of invasive procedures in STEMI has increased: coronary angiography — 52–63%, PCI — 25–37%, aortocoronary bypass — 12% [1].

Dr. Goldstein Patrick from Lille University Hospital, France, stressed that saving of patient with MI is a race against time. However, access to timely and optimal primary PCI is limited worldwide. Thus, about 20–30% of those with STEMI in Europe still do not receive reperfusion therapy in any form, and for many of those with reperfusion it goes beyond the recommended “therapeutic window” [5]. Even in the United States, only 20% of the population lives in areas where there is a possibility of PCI [6]. At the same time, fibrinolytic therapy is universally available and can be scheduled in a timely manner by general practitioners and emergency care to patients in the first hours of STEMI

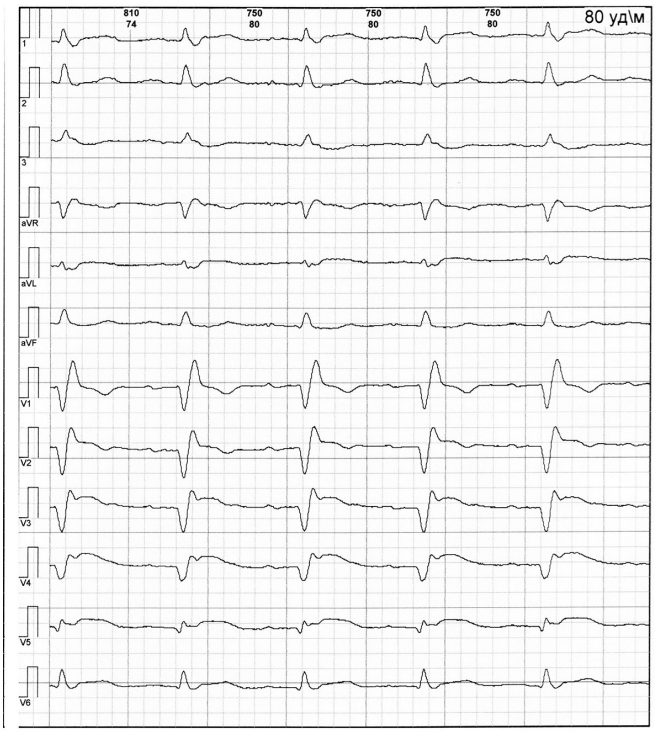

Figure 1. Electrocardiogram of patient R. before thrombolysis

[7]. Obviously, if invasive treatment is impossible or is conducted with a significant delay in time and cannot be executed under appropriate conditions, it is necessary to give fibrinolytics and subsequently, if necessary, to consider the possibility of revascularization [8]. In the first 2–3 hours of ischemia MI mortality in the thrombolytic therapy and PCI is comparable [4].

The main aim of the culprit coronary artery opening is not the restoration of its patency, but firstly the resumption of blood flow at the tissue level, which is achieved with thrombolytic therapy in 30–40% of cases [9]. In clinics with modern equipment it is possible to estimate myocardial reperfusion using coronary angiography (index MBG), myocardial scintigraphy with 99mTc, Doppler echocardiography and magnetic resonance imaging with contrast, positron emission tomography, and electrocardiography (ECG) [4, 10] which is used in the practice of infarct compartments as the most accessible method. However, in some cases, to control the dynamics of thrombolytic therapy, ECG failed to disclose all aspects of change in the electromotive force of the heart (EMF/H). Its vector analysis is a promising area in detecting myocardial electrical instability. In recent years, in case of acute coronary pathology researchers use adjusted orthogonal systems of leads, including those according to Frank and Mac Fi-Parunhao, not only in Ukraine [11] and Russia [12], but also in many countries of European Union (Sweden [13], Bulgaria [14]), as well as in the United States [15] Canada [16] Singapore [17]. I. T. Akulinichev methodic does not have the faults of vector analysis of ECG due to the location of electrodes near the heart instead of geometric shapes building. VCG projections reflect the potential of certain areas of myocardium, which is especially important in case of its focal damage: first projection reflects the electrical activity of the anterior region of the heart, the second — the posterior-lateral areas of left ventricle (LV), third — right lower diaphragmatic area, the fourth — of the apex, and the fifth — base of the heart. M. B. Tartakovskij made some changes to the I. T. Akulinichev precardiac system by placing the electrode from the back to V_7 ECG position, with the recording of three chest leads according to Neb [18]. Five leads system by I. T. Akulinichev leads in Tartakovskij modification gives an advantage in examining of critically ill patients with acute cardiovascular disorders due to better electrodes location. Comparing the results of ECG and VCG allows to expand diagnostic capabilities of both methods. In the 50–70s of the last century in the USSR the study of VCG features in MI on the VEKS-O1 device (constructed by Akulinichev I. T.) was conducted, which was very difficult because of the lack of automated material handling, multi-stage analysis, a large scatter of results, lack of time characteristics. Diagnostic errors were the result of low resolution of the device, which made the analysis of loops track, and differential diagnosis of convergence and loops intersection harder, and almost insufficient information content in the isoelectric point. Since 2003 Sieverodonetsk Scientific and Production Enterprise "Microterm" together with the Lugansk State Medical University and Volodimir Dal East-Ukrainian National University have developed a new advanced polygraph MTM-SCM [19]. This device makes it possible to obtain, with high resolution (up to 3000 times) additional indicators of electrical activity of the heart, that were not previously possible to research; real-time analysis of received topographic information and automatic processing of the results, including in the process of reperfusion therapy control [20].

The new method has been worked out and tried on 181 patients with acute MI, icluding14 patients with STEMI in thrombolysis. A clinical case may be an example of the use of highly sensitive polycardiography in the dynamics of thrombolytic therapy evaluation.

Purpose of the research — to evaluate the electrical activity of the myocardium in acute MI with thrombolytic therapy using a modification of electro-vectorcardiography.

Clinical case

Patient R. was taken to the infarction department of Luhansk City Clinical Multihospital № 1 with complaints of precordial discomfort in 2 hours after the beginning of growing pressing pain in chest, that were stopped by ambulance crew before the patient was brought to hospital. Blood pressure — 160/90 mm Hg.

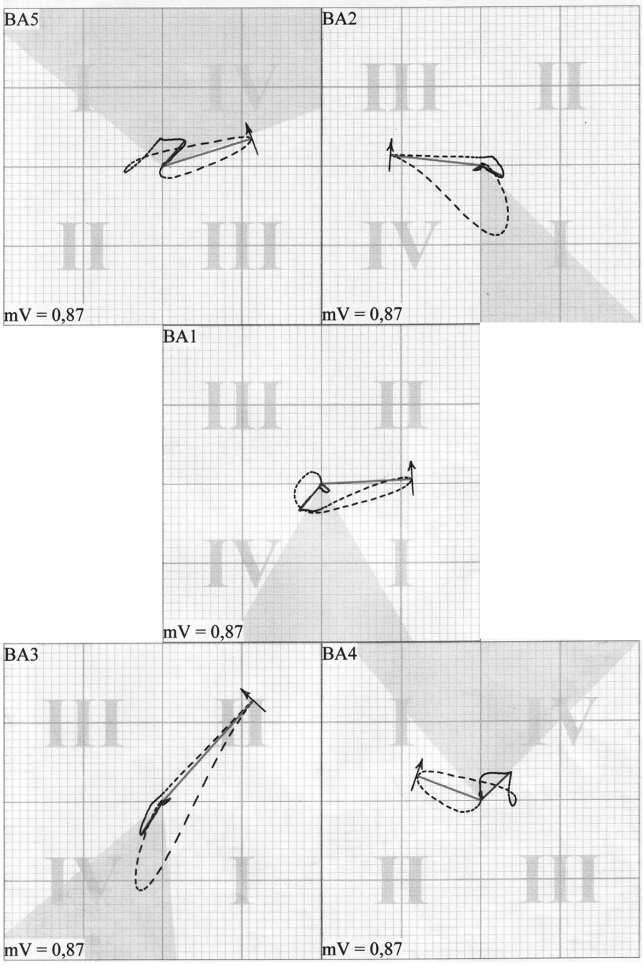

Figure 2. Vectorcardiogram of patient R. before thrombolysis

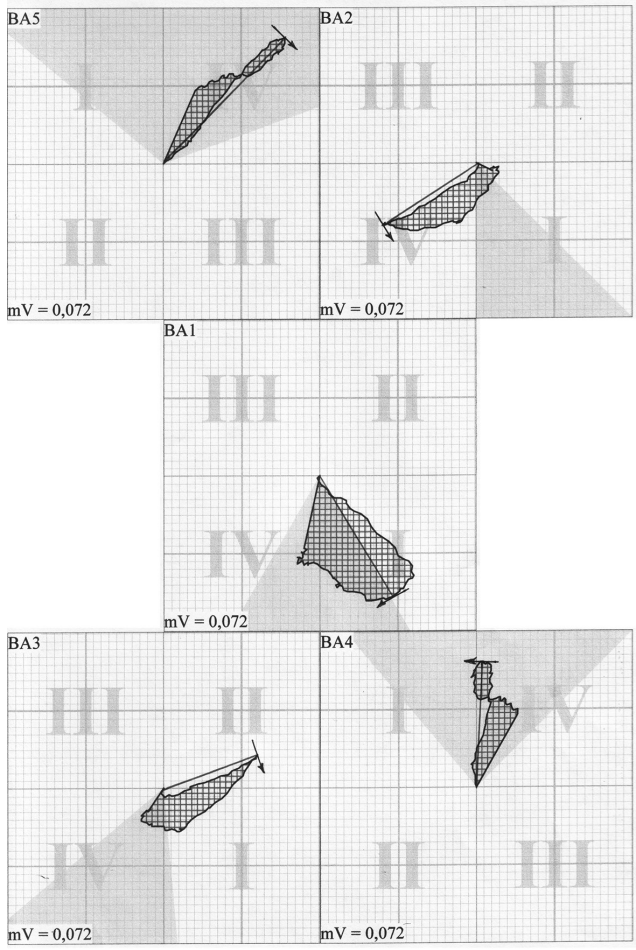

Figure 3. P loops of vectorcardiogram, enlarged up to 2000 times, before thrombolysis

Discussion

The ECG on admission showed right sinus rhythm, 78 per minute, the voltage is reduced to the chest leads, electrical axis of the heart is normal (a +67° angle). QR in $V_{2-}5$ are registered with ST-segment elevation in $V_{2-}6$ and I, avL with a dominant in V_4 to 0.4 mV with total right bundle branch block as a reflection of damage and necrosis of anteroseptal-apical-lateral region of the LV and the reciprocal changes in III, avF as segment ST depression (Figure 1). Taking into account the time of admission from the beginning of anginal attack, the ECG data, and the lack of absolute and relative contraindications, the patient was assigned 1.5 million units of streptokinase intravenously on a background of basic therapy according to the protocol of care for patients with MI with Q wave.

With the help of vector analysis additional information about the EMF/H was provided (Figure 2). QRS loop is shifted to the left and up a little forward, because electrical forces, directed forward, are decreased [21]. In the first projection QRS loop has a sharp shift upwards and to the left, the initial part is increased and directed upwards and to the right. Local symptoms of intraventricular blockade are seen in the initial location of the QRS loop in the III quadrant in first projection and in the IV quadrant in the third projection, and loops are crossed in $BA_{4,5}$. At the same time QRS loop in BA_1, with a start in the upper half of the coordinate system moves to the bottom; in в BA_2 the main part of QRS loop is located in quadrants I and IV; in BA_3 the initial part of the loop is in the lower half of the coordinate system, which is typical for nontransmural spread MI [18]. In the second and third projections QRS loops are asymmetrical, apexes are pointed, in the initial part there is an additional pole [21], they change their direction: the projection of the second loop moves clockwise, and the third projection — counterclockwise. Phase relations disorder manifests itself a peculiar direction of QRS loop in BA_2: it begins in the I quadrant, and the main part is located on the left (in space — behind) from the isoelectric center [22], which confirms the anterior localization of MI. At the same time, the location of most of the QRS loop in the IV quadrant in BA_2 indicates that the side wall of the left ventricle is involved in the pathological process. QRS loops orientation changes in the in projection IV shows apex damage: initial part of the

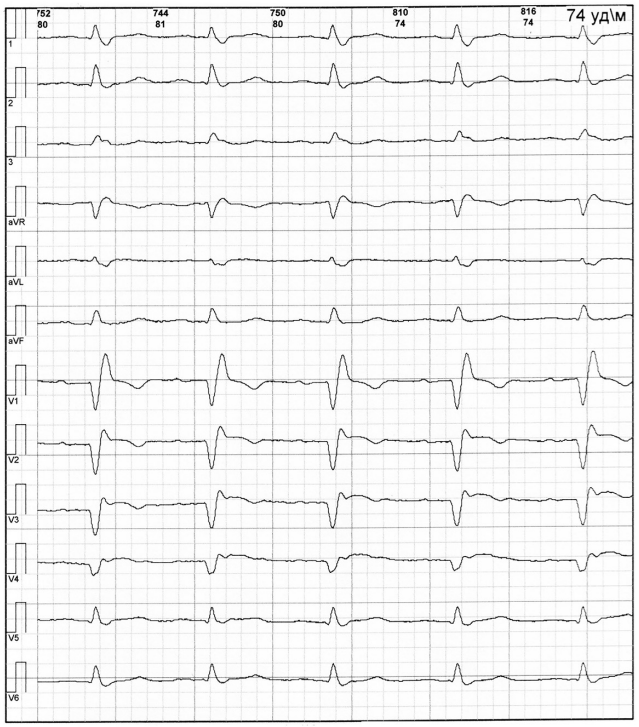

Figure 4. Electrocardiogram of patient R. 90 minutes after thrombolysis

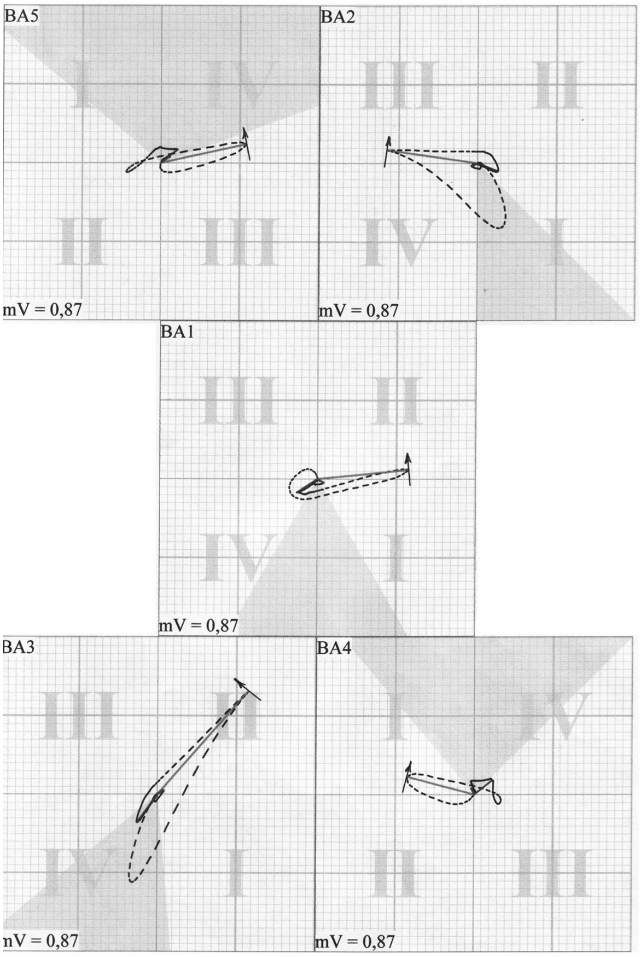

Figure 5. Vectorcardiogram of patient R. 90 minutes after thrombolysis

loop is located in the lower half of the coordinate system [18].

The formation of additional pole with a cross in the final part of the QRS loop in projections 4 and 5, that is recorded with a slow movement of the recording beam and is directed upwards and to the right, recording of the initial part of QRS loop with fast movement of the beam in projections 2, 3 and 4 confirm the presence of a complete right bundle branch block, and indicates that the zone of ischemia and/or necrosis is spread to the heart septum [21].

Reduction of the total area of QRS loops happened due to 2–2,5 times decrease in the area of 1, 4 and 5, without significant changes in projections of maximum vector. Timestamps thickening is observed throughout QRS loop in $BA_{1,4,5}$, and also in the final deviation vector in IV and V projections. T loops are directed to the right and down, they are rounded and situated outside the QRS loops of all projections, their maximum vector is reduced in 1, 4 and 5 projections. In these projections, there is thickening of the time stamp of the loop T. The area of T loops is increased in all projections with maximal changes in $BA_{4,5}$. Recording of broadened T loops and QRS loops in projections 1, 4 and 5 is in the opposite direction. The angular divergence of loops QRS and T is increased in BA_{1-5} (Table 1–3). Loops QRS and T are not closed: in BA_1 to — 0.32 mV, in $BA_{2,3-}$ 0.08 mV, in BA_4–0.46 mV and in BA_5–0.33 mV. The vector ST is directed forward, to the left and downwards as the equivalent of damaged anterior septum-apical-lateral wall of the LV.

Thus, in addition to the ECG information about damage and necrosis of the anterior septum-apical-lateral wall of the left ventricle, vectorcardiography allowed to obtain data about the disorder of myocardial blood supply in the basal parts of the ventricles, which is confirmed by a disorder of the interrelation of QRS and T loops and qualitative changes of the loop T in projection 5, and about pulse slowing in the anterior wall of the left ventricular apex and basal parts of the ventricles due to the change in speed markers in $BA_{1,4,5}$. In addition, the increase in the of P loops area in the first three projections at 1,3–1,8 times at unchanged indicators of their maximum vectors show hemodynamic overload of the atria (Figure 3). Cove-like P loops route, their cross at the base of $BA_{4,5}$ with a change in the loops rotation direction, thickening of the time markers on the P loops in all projections indicate excitation spread slowing of the atrial myocardium, concentrated mainly in the posterior-lateral wall of the left atrium and posterior wall of the right atrium. The increase in the angular divergence of the loops in the QRS-P in projections1, 4 and 5 shows repolarization disorder in front of the atrial posterior-lateral wall of the left atrium and posterior wall of the right atrium (Table 1, 4).

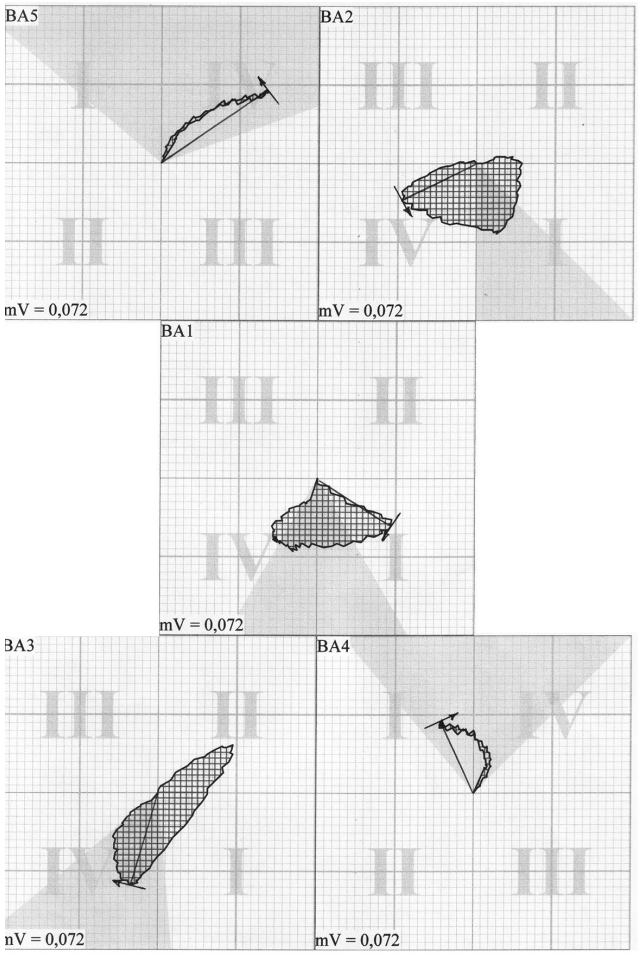

Figure 6. P loops of vectorcardiogram, enlarged up to 2000 times, 90 minutes after thrombolysis

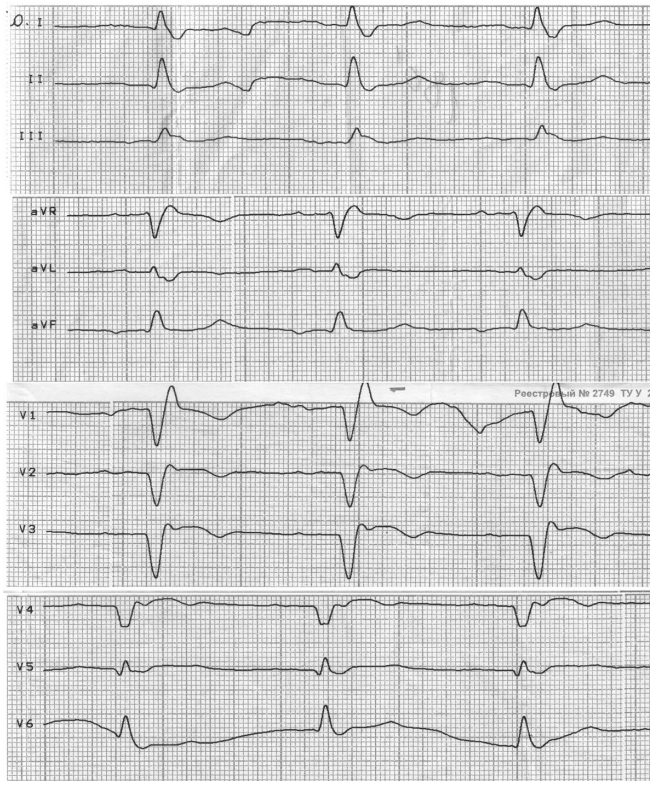

Figure 7. Electrocardiogram of patient R. 180 minutes after thrombolysis

90 minutes after thrombolysis ST-segment depression by 50% or more from baseline in the V_{2-4} and reperfusion arrhythmias are not registered on the ECG, but in $V_{5,6}$ ST segment is decreased to contour and R wave amplitude is increased (Figure 4). VCG-study showed a slight decrease in the dynamics of QRS area in all projections, decrease of the total area of T loops in projections 1, 4 and 5, the increase in the angular divergence of QRS and T loops in $BA_{1-4,}$ decrease in the disjunction of QRS and T loops in projection 1 to 0.13 mV, in projection 4 — to 0.25 mV and in projection 5- to 0.15 mV (Figure 5). At the same time, R loops area was increased in projections 2 and 3 together with decrease in the angular divergence of QRS and P loops and multidirectional changes of speed markers in all projections. However, in the $BA_{4,5}$ significant decrease in P loops area was followed by two loops crosses (Figure 6). So, as a result of vector analysis together with decrease in the electrical activity of the LV myocardium reduction of damage zone is registered (1,8–2,5 times decrease of the QRS and T loops opening) in the anterior septum-apex-side area with persistent left ventricular ischemia around damage zone. In addition, the decrease in the EMF/H in the posterior atrial wall is registered, together with a local blockade (P loops cross in $BA_{4,5}$) with hemodynamic overload of the atria against the functional heterogeneity of the myocardium due to ischemic manifestations (Table 1, 4).

180 minutes after the start of thrombolytic therapy ECG showed signs of effective reperfusion therapy in the form of ST-segment decrease in V_2 by 0,10 mV, in V_3–0,15 mV, in V_4–0,25 mV, which corresponds to a reduction in ST-segment to 50% or more from the initial number. Reperfusion arrhythmias are not registered (Figure 7).

VCG shows QRS loop cross in projection 1 together with the reduction of its area, T loops cross in projections 1, 4 and 5, and decrease of T loops area in all projections (in $BA_{2,3}$ parameter was normalized), thickening of the time markers in T loops in projections 2 and 3, some increase in the angular divergence of QRS and T loops in projection 1, 1,3–1,8 times more decrease of QRS and T loops opening value: in BA_1 to 0.07 mV, in BA_2 — to 0.06 mV, in BA_3 — to0.05 mV, in BA_4 — to 0,16 mV, and in BA_5 — to 0,11 mV (Figure 8). In all projections the cross of P loops can be seen, with the change of their rotation direction, a progressive decrease in their area, multidirectional changes of the angular divergence of P and QRS loops, and time markers thickening in the dynamics of the loop P in BA_{1-5} (Figure 9, Table 1, 3, 4). Thus, VCG results allow to confirm a significant reduction in the

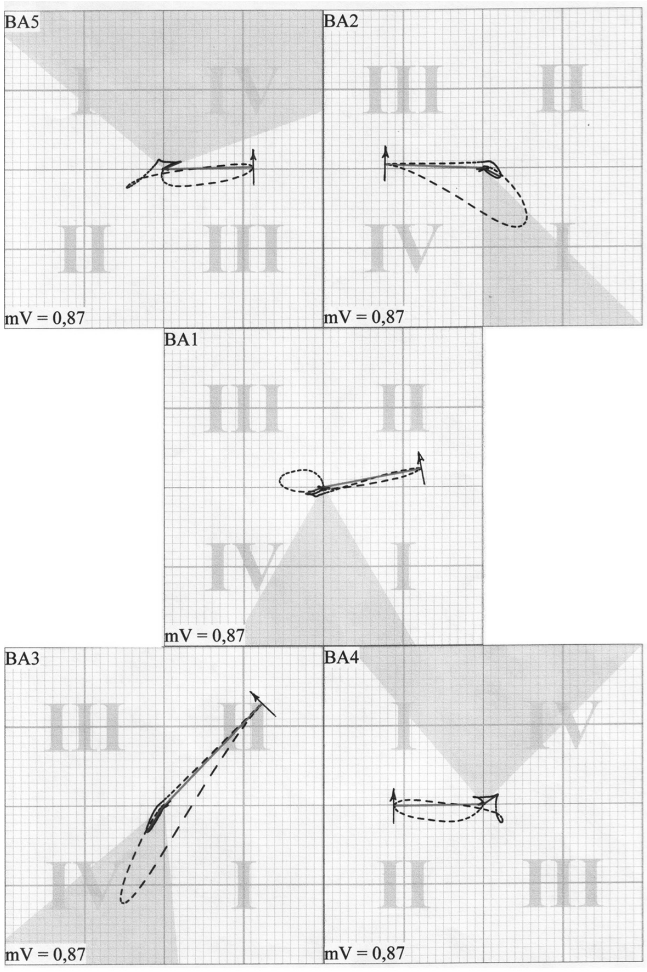

Figure 8. Vectorcardiogram of patient R. 180 minutes after thrombolysis

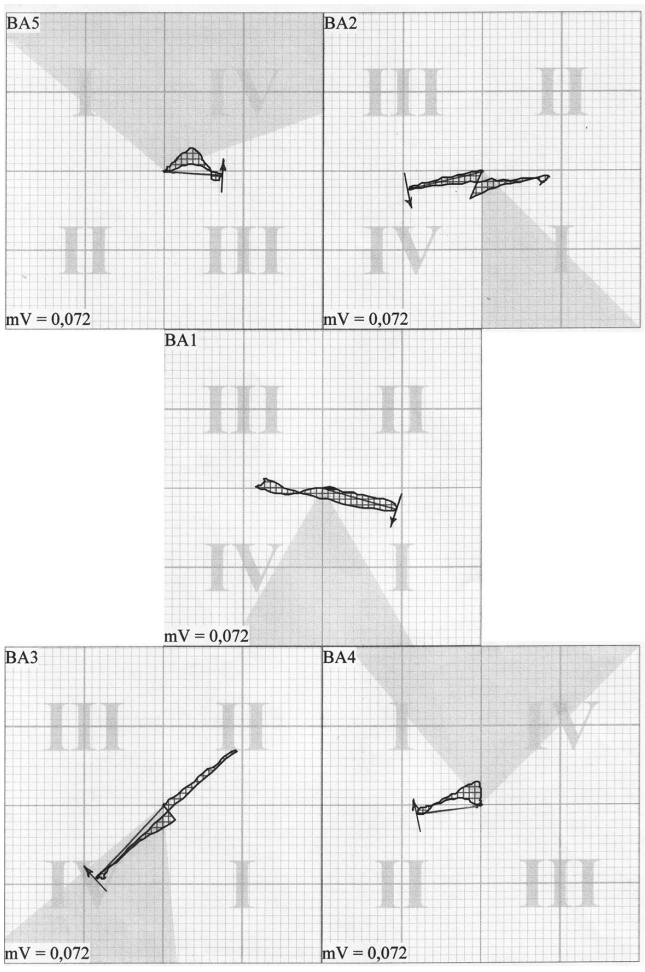

Figure 9. P loops of vectorcardiogram, enlarged up to 2000 times, 180 minutes after thrombolysis

myocardial injury zone with a concomitant deterioration of conductivity on the front wall of the left ventricle and the resumption of ischemic events together with EMF/H decrease. Dynamic reduction in the electrical activity of the atria with a pulse slowing and the repolarization disorder may indicate that the atria are involved into pathological process with a major blood supply disorder in them.

Conclusion

Modern VCG method of EMF/H study on the new MTM-SCM polygraph allows not only to evaluate the effectiveness of thrombolytic therapy in high-resolution, in real-time, and in dynamics, but also to obtain information about the electrical activity in the affected area of the myocardium, and outside necrobiotic changes of the heart muscle.

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A TIME-DOMAIN HYBRID ANALYSIS METHOD FOR DETECTING AND QUANTIFYING T-WAVE ALTERNANS

Xiangkui Wan[1], Kanghui Yan[1], Jun Zhang[1], Yanjun Zeng[2]

T-wave alternans (TWA) in surface electrocardiograph (ECG) signals has been recognized as a marker of cardiac electrical instability, and is hypothesized to be related with patients at increased risk for ventricular arrhythmias. A novel time-domain TWA hybrid analysis method (HAM) utilizing the correlation method and least squares regression technique is described in this paper. Simulated ECGs containing artificial TWA (cases of absence of TWA and presence of stationary or time-varying or phase-reversal TWA) under different baseline wanderings are used to test the method, and the results shows the HAM has a better ability to quantifying TWA amplitude compared with the Correlation Method (CM) and Adapting Match Filter Method (AMFM). The HAM is subsequently used to analyze the clinical ECGs, and results produced by the HAM have, in general, demonstrated the consistency with those produced by the CM and the AMFM, while the quantifying TWA amplitudes by the HAM are universally higher than those by the other two methods.

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Key words: electrocardiograph, T-wave alternans, hybrid analysis method, correlation method, adapting match filter method, least squares regression.

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AMFM — Adapting Match Filter Method, CM — Correlation Method, ECG — electrocardiograph, HAM — hybrid analysis method TWA — T-wave alternans.

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ГИБРИДНЫЙ МЕТОД АНАЛИЗА ВРЕМЕННОГО ДОМЕНА ДЛЯ ВЫЯВЛЕНИЯ И КОЛИЧЕСТВЕННОЙ ОЦЕНКИ ИЗМЕНЕНИЙ Т-ВОЛН

Xiangkui Wan[1], Kanghui Yan[1], Июнь Zhang[1], Yanjun Zeng[2]

Изменения Т-волн (TWA) в сигналах электрокардиографии (ЭКГ) были признаны маркером электрической нестабильности сердца, и гипотетически связаны с пациентами, у которых повышен риск развития желудочковых аритмий. Новый гибридный метод анализа временного домена TWA (HAM) использующий метод корреляции и методики регрессии наименьших квадратов, описан в этой статье. Симулируемые ЭКГ, содержащие искусственные TWA (в случаях отсутствия TWA и присутствия стационарных или изменяющихся во времени или фаза-восстановление TWA) при различных блужданиях исходных показателей используются для тестирования метода, и результаты показывают, что HAM имеет лучшую возможность количественной оценки амплитуды TWA, по сравнению с корреляционным методом (CM) и методом адаптации матч-фильтрации (AMFM). HAM в дальнейшем используется для анализа клинических ЭКГ, и результаты, полученные HAM, в целом, показали согласованность с теми, что были получены при проведенных CM и AMFM, а количественная оценка амплитуд TWA при HAM является повсеместно выше, чем при использовании двух других методов.

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Ключевые слова: электрокардиограф, изменения Т-волн, гибридные методы анализа, метод корреляции, метод адаптации матч-фильтрации, метод регрессии наименьших квадратов.

Introduction

The T-wave alternans (TWA) has been considered as one of the most promising markers of sudden cardiac death (SCD) over past 10 years. TWA is a phenomenon appearing in the surface electrocardiograph (ECG) as a consistent fluctuation in the repolarisation morphology on an “every-other-beat” basis (2:1 behaviour). This fluctuation refers to a beat-to-beat variability in the amplitude, morphology and/or polarity of the T-wave. Numerous clinical studies have demonstrated TWA is associated with ventricular arrhythmias. Nowadays TWA has been considered an independent predictor for cardiac arrhythmias.

Several signal processing methods have been proposed to detect and estimate TWA in the ECG on a single-lead or multi-lead basis [1–8]. And a comprehensive and systematic discussion of methods for TWA detection and analysis is reported in [9]. Most widely used TWA detection methods work in two different domains: time and frequency.

The disadvantage of the frequency based methods is that they treat the alternans signal as a stationary wave with the constant amplitude and phase, which is not true in general. They cannot detect non-stationary characteristics of the signal.

The time domain methods can detect TWA in short-time, non-stationary ECG signal, and they have also been used on Holter data. Correlation Method (CM) [6, 7] as a well known time-domain method performs well under different conditions, but it is sensitive to noise, especially the baseline wandering. In the presence of baseline oscillations at TWA frequency, a strong overestimation of TWA mean amplitude, and even TWA detection from TWA-free ECG tracings, is produced by the CM. And in the presence of higher frequency baseline fluctuations, the CM is not able to identify TWA [10]. An adapting match filter method (AMFM) was proposed by the same authors of the CM to overcome the CM limitations [11]. The AMFM yielded a significant improvement in algorithm-based identification of duration and amplitude of TWA from ECG tracings with frequency of baseline oscillations both lower and higher than that of TWA. Nevertheless, in the presence of baseline fluctuations at the TWA frequency, it produced erroneous TWA detection from ECG tracing

with no TWA, and even strong overestimation of TWA amplitude, when present.

Based on above background, we propose a hybrid approach for the TWA detection, which is based on correlation method and least squares regression technique. The study aims to develop a novel TWA detector to overcome the CM limitations, which can detect and measure transient TWA with more accuracy in the time domain, even in the presence of higher frequency baseline fluctuations.

The rest of the paper is organized as follows. In Section II, we present a novel method of TWA detection, simulated cases and clinical cases are also prepared. Then, in Section III, we report the results of its validation on the simulation database and clinical database, and compare the results to that of the CM and the AMFM. Next, in Section IV, we give the discussion. Finally, we summarize the conclusions of this work in Section V.

Material and methods

1. The hybrid analysis method (HAM) using correlation method and least squares regression technique. The hybrid analysis method consists of three different blocks: pre-processing, TWA detection and TWA evaluation. The whole TWA analysis process is described as below:

1) Data pre-process.

Before detecting TWA, the clinical ECG used here are required to be submitted to a preliminary pre-processing stage. This consists of various steps, which are: baseline wandering suppression, QRS complex detection and segmentation of the T-wave.

• Baseline wandering suppression: this is performed using a cubic spline interpolation technique [12].

• QRS complex detection: it is determined using a wavelet-based algorithm [13].

• T-wave segmentation: it is done by selecting intervals of 300 ms, beginning at a distance from the QRS fiducial point dependent on the RR interval. The interval onset for the *ith* beat, b_i, is given by the expression:

$$b_i = 0 + 1.3R^{1/2} \text{ (ms)}$$

• T-wave alignment: after T-wave segmentation, 128 consecutive T-waves present in the ECG are used to compute the median T-wave (T_m, which has each sample point given by the median value of the corresponding sample points of the 128 available T-waves), which is used as a template. Synchronization of the *ith* T-wave is performed according to a recursive procedure that keeps the segmented T-wave window length constant but varies its position ±30ms from the original position, with a time increment of one sample point. For each position of the T-wave window, the windowed *ith* T-wave is cross-correlated against the template. Optimal alignment occurs when maximum correlation is reached.

2) Qualitative detection of TWA.

After the data pre-processing, TWA is detected by looking for an alternating trend in the T-wave morphology quantified by a correlation index. To this aim, an alternans correlation index (ACI) is computed to measure morphological changes of each of the consecutive T_i waves in comparison to T_m [12], which is as shown in equation (1)

$$ACI_i = \frac{\sum_{j=1}^{N} T_i(j)T_m(j)}{\sum_{j=1}^{N}[T_m(j)]^2} \quad i = 1,2,\cdots,128 \quad (1),$$

where T_m is the median T wave computed using 128 T waves available in each ECG tracing. N is the number of samples in each T wave.

ACI_i is defined as the ratio of the maximum value of the cross-correlation function of T_i and T_m over the maximum value of the auto-correlation function of T_m. T_i is classified as alternating.

The presence of TWA is considered when the value of ACI strictly oscillates (not necessary around one) in the case of monophasic TWA at least 7 consecutive beats. Figure 1 shows an example of alternating values of ACI_i, indicating the presence of TWA.

To limit false detections caused by noise, a local threshold criterion, with Th_{ACI} equal to 0.06 [6], is considered, such that ACI values alternations have to exceed 0.12 for at least seven consecutive beats to be detected as TWA.

3) Quantitative estimation of TWA.

The odd and even beats of above detected consecutive beats are labelled as *A* and *B*, respectively. The odd T waves are obtained from *A* series and the even T waves are obtained from *B* series. The odd T waves constitute a matrix:

$$T_{A_{m\times n}} = (T_{A_0}, T_{A_1}, \cdots, T_{A_n}) = \begin{bmatrix} T_{A_{0,0}} & T_{A_{0,1}} & \cdots & T_{A_{0,n}} \\ T_{A_{1,0}} & T_{A_{1,1}} & \cdots & T_{A_{1,n}} \\ \cdots & \cdots & \cdots & \cdots \\ T_{A_{m,0}} & T_{A_{m,1}} & \cdots & T_{A_{m,n}} \end{bmatrix}$$

Where $T_{A_{m,n}}$ is the *nth* point of the *mth* odd T wave. Analogously the even T-wave matrix $T_{B_{m,n}}$ can be constituted.

The amplitude corrections of odd and even T waves are performed using the first-degree polynomial as shown in equation (2).

$$f(i) = aT_{i,k} + b \quad (2),$$

where $T_{i,k}$ is the *ith* row and *kth* column point of odd (or even) T-wave matrix. And the coefficients *a, b* are estimated by the linear least squares fitting process.

Each column vector T_{A_k} of $T_{Am\times n}$ is divided into 7-point epochs, and the equation (2) is recursively applied to each epoch throughout the entire T_{A_k}. Denote θ_i as the *ith* deviation point of T_{A_k} from the fitting line:

$$\theta_i = \left| T_{i,k} - f(i) \right| \quad (3).$$

Then the mean deviation value of T_{A_k} can be expressed as equation (4):

$$\bar{\theta} = \frac{\sum_{i=0}^{m} \theta_i}{m} \quad (4).$$

If $\max x(\theta_i) \geq 3 \times \overline{\theta}$, then the θ_i is considered to be corrected and replaced by the *ith* column mean value $\overline{T}(k)$ (as shown in equation (5)) of odd (or even) T-wave matrix.

$$\overline{T}(k) = \frac{\sum_{i=0}^{m} T_{i,k}}{m} \quad (5).$$

And the amplitude correction of entire T_{A_k} is recalculated, until the $\max x(\theta_i) \leq 3 \times \overline{\theta}$ or $\max x(\theta_i) \prec 2\mu V$.

A specific example of amplitude correction of odd T wave matrix using linear fitting function is shown as Figure 2. The Figure 2 (a) represents the uncorrected T waves, and the Figure 2 (b) represents the corrected T waves.

Measure TWA_k as the maximum absolute value of the difference between $\overline{T_{A_k}}$ and $\overline{T_{B_k}}$:

$$TWA(k) = \max_{i=T_{onset}}^{i=T_{offset}} \left| \overline{T_{A_k}}(i) - \overline{T_{B_k}}(i) \right| \quad (6),$$

where *TWA(k)* denotes the *kth* local TWA (i.e. relative to a single odd (or even) beat), $k = 1,2\cdots,m$.

The TWA of the analyzed consecutive ECG segment (segment TWA) is measured as the mean value of measured local TWAs:

$$TWA_{seg} = \frac{\sum_{k=1}^{m} TWA(k)}{m} \quad (7).$$

And the global TWA (i.e., relative to the entire ECG tracing analyzed) is measured as the mean value of segment TWAs:

$$TWA = \frac{\sum_{i=1}^{l} TWA_{seg}(i)}{l} \quad (8)$$

Above process can be described as the block diagram (Fig. 3).

2. Simulated cases. There is no generally accepted TWA-measuring criterion to be used as a gold-standard. Therefore, a simulation approach was used in the present study in different controlled cases.

A realistic, clean simulated ECG was obtained as a K-fold repetition of a single beat extracted from a real ECG [14].This guarantees that all the T waves of the simulated ECG are identical, so no TWA can be present in the original signal. In particular, we used a 0.7-s beat sampled at 500 samples per second. Length of each simulated ECG tracing was assumed to count 128 consecutive heart beats. Our choice relies on the fact that 128 consecutive beats were originally used for SM applications, and later on, this became the standard ECG length [5] for TWA detection and quantification. A constant RR interval of 0.7 s was assumed, so that TWA fundamental frequency was 0.71 Hz (that is, $1/(0.7 \times 2s)$ or 0.5 cycles per beat). TWA was simulated by varying T-wave amplitude (10, 50 and 100 μV) in a time window of 160 ms centered around the T-wave apex.

Four different sets of ECG simulation were considered, respectively reproducing the cases relative to the absence of TWA, the presence of stationary TWA, the presence of time-varying TWA and the phase-reversal TWA, which are described below.

1) Case 1: simulated ECG tracing with no TWA.

The simulated ECG tracing with no TWA (N_TWA) is assumed not to be affected by any kind of noise. This simulated signal is thought to test the ability of recognizing the absence of TWA, which is represented in Figure 4 (a).

2) Case 2: simulated ECG tracings with stationary TWA.

The simulated ECG tracings with stationary TWA (S_TWA) are designed to test the ability of quantifying TWA amplitude in the presence of stationary alternating T-wave profiles. Three kinds of simulated ECG tracings were considered; namely, a tracing with a 10 μV TWA (S_TWA10), a tracing with 50 μV TWA (S_TWA50), and a tracing with 100 μV TWA (S_TWA100). An example of a tracing with 50 μV TWA is represented in Figure 4 (b).

3) Case 3: simulated ECG tracings with time-varying TWA.

ECG with visible TWA clearly shows the non-stationary nature of this phenomenon, whose variability often shows on-off or cyclic trends. Evaluation of dynamic aspects of TWA is important in clinics since transient TWA has been observed during acute ischemia [15]. To test the ability of the HAM in detecting non-stationary TWA, two simulated ECG tracings were considered, each one incorporating a specific beat-to-beat varying (and then, time-varying) A (n) sequence. A sinusoidal A (n) sequences, with 128 beats period, were affecting the first (TV_TWA1) ECG tracing, while An A (n) varying from 50 μV to 20 μV, following a smoothed (24 beats transition) step pattern, was affecting the second ECG tracing (cascaded TWA, TV_TWA2). The two simulated tracings were characterized by a uniform profile of TWA, which are represented in Figure 5 (a) and (b). The examples of TV_TWA1 and TV_TWA2 are represented in Figure 6 (a) and (b), respectively.

4) Case 4: simulated ECG tracing with phase-reversal TWA.

Arrhythmias can sometimes trigger a phase reversal so that the alternans pattern changes from ABABAB to BABABA [5]. The simulated ECG tracing with phase-reversal TWA (PR_TWA) is designed to test the ability of the method in detecting phase-reversal TWA. PR_TWA tracing incorporates a stationary 10 μV TWA, which changes phase twice, at beats 40 and 80, respectively. This simulated case may also be used to help the interpretation of realistic cases in which a beat is missed (false negative QRS detection) or wrongly inserted (false positive QRS detection). An example is represented in Figure 6 (c).

Finally the noise is also considered to be added to above simulated ECG tracings in this study. In clinical settings, power line interfere is generally eliminated by hardware filter. When computing the ACI indexes (equation (1)) the white noise is already taken into account. So baseline wandering is

considered to the present simulated cases which might cause erroneous detection of TWA. Baseline wandering can be eliminated by pre-processing stage, whereas ECG amplitude modulation may survive, and elimination by pre-processing of ECG modulation related to T-wave variability should be prevented because TWA is a specific case of it [4]. Based on these considerations, ECG simulations with baseline wandering are considered. Baseline wanderings are simulated with a sinusoid of 0.1 mV amplitude and various frequencies: 0.30, 0.71 and 1.50 Hz, respectively, which we denote as bw030, bw071 and bw150. These frequencies are, respectively, lower, equal and greater than TWA frequency. The frequency of 0.30 Hz relates to usual breathing pattern in patients. And the baseline fluctuations are simply added to each simulated ECG tracing. Two representative examples of our simulated ECG tracings, with and without baseline fluctuations, are displayed in Figure 7.

3. Clinical cases. Two clinical data sets are considered in this study: ECG tracings from healthy subjects (H_subjects) and that from patients.

ECG tracings from H_subjects belong to the Digital Electrocardiology Study databases of Liuhuaqiao Hospital, Guangzhou, which includes 320 Holter ECG tracings from H_subjects. The study was approved by the institutional research ethics committee of Guangzhou Medical College, and it was conducted following required rules for human subjects' research principles, according to the Declaration of Helsinki, as well as to Title 45, U. S. Code of Federal Regulations, Part 46, Protection of Human Subjects, Revised November 13, 2001, effective December 13, 2001. Each subject underwent 10-min ECG recording in resting conditions. Nine standard leads (V1-V6, I, II, and III) were recorded using equipment by Siemens-Elema AB and digitized at a sampling rate of 500 Hz with amplitude resolution of 0.6 μV. Leads aVF, aVR, and aVL were derived from leads I. II, and III.

ECG tracings from patients belong to the T-Wave Alternans Challenge Database (TWACD) [16], which contains 100 multichannel ECG records sampled at 500 Hz with 16 bit resolution over a ± 32 mV range. The subjects include patients with myocardial infarctions, transient ischemia, ventricular tachyarrhythmia, and other risk factors for sudden cardiac death, as well as healthy controls and synthetic cases with calibrated amounts of T-wave alternans. the databases is chosen for two reasons: one is that previous studies found T-wave alternans episodes, some of them related to annotated ischemic episodes. Another is that the databases are well-known and available by many research groups.

In the specific, a group of fourteen healthy subjects was compared with a group of fourteen patients. A subject was classified as belonging to the H-group when fulfilling the following criteria [17]:

1). no overt cardiovascular disease or history of cardiovascular disorders (including stroke, TIA, and peripheral vascular disease);

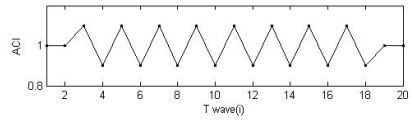

Figure 1. An example of the presence of TWA.

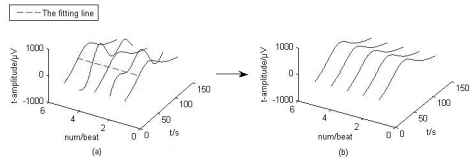

Figure 2. A specific example of amplitude correction of odd T wave matrix. The corrected matrixes for odd and even T waves are known as $\overline{T}_A$ and $\overline{T}_B$, respectively.

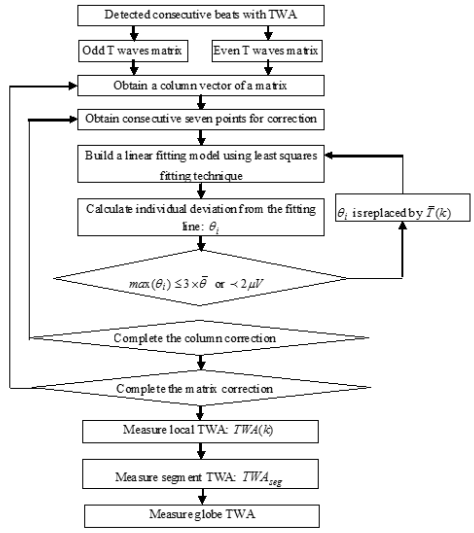

Figure 3. The block diagram of T-waves amplitude correction and TWA estimation.

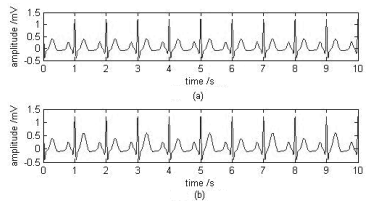

Figure 4. An example of simulated ECG tracings with/without TWA. (a) simulated ECG tracings not affected by TWA (N_TWA); (b) simulated ECG tracings with stationary 50μV TWA (S_TWA50).

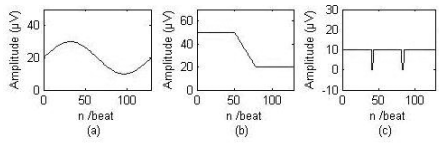

Figure 5. The different cases of nonstationary TWA. (a) sinusoidal trend of TWA amplitude signals; (b) cascaded TWA amplitude signals; (c) phase-reversal TWA.

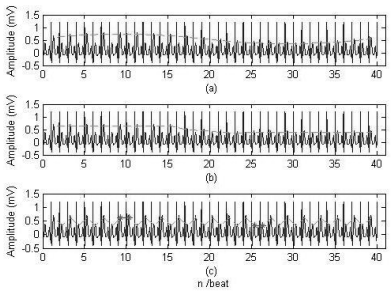

Figure 6. The simulated ECG tracings with different nonstationary TWA. (a) TV TWA1; (b) TV_TWA2; (c) PR_TWA.

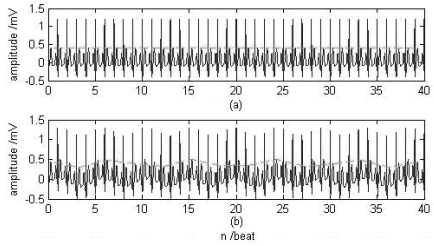

Figure 7. Two examples of the simulated tracings affected by baseline wanderings. (a) The simulated tracings without baseline; (b) The simulated tracings with 0.3Hz baseline.

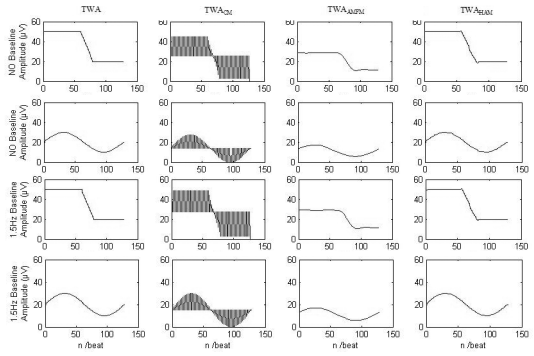

Figure 8. The time-varying TWA measurement results under different baseline conditions.

2). no history of high blood pressure (>150/90 mmHg);

3). not taking medication;

4). no other chronic illness (e.g. diabetes, asthma, chronic obstructive pulmonary disease, etc.);

5). diagnosed as being healthy if evaluated by a physician for cardiovascular-related syndrome (chest pain, palpitation, syncope);

6). normal physical examination;

7). sinus rhythm in 12-lead ECG without any suspicious abnormalities (e.g. signs of ventricular hypertrophy, inverted T-wave, intraventricular conduction disturbances);

8). normal echo and normal ECG exercise testing in presence of suspicious ECG changes;

9). no pregnancy.

4. Statistics. To evaluate the ability of the presented method to quantify TWA, the other two related time-domain methods, which are the CM and the AMFM, are used here for comparison.

In our simulation study, the root mean square error (*RMSE*) in the estimate of TWA amplitudes are computed [13]:

$$RMSE_M = \sqrt{\frac{\sum_{n=1}^{N}\left(TWA_M(n) - A(n)\right)^2}{N}} \quad (9),$$

where N is the total number of beats in an ECG tracing, and $A(n)$ (relative to the *nth* beat) is assumed equal to the absolute value of the maximum difference between the *nth* and the *(n+1)th* T-wave sample amplitude, and $TWA_M(n)$ is the estimated local TWA (relative to the *nth* beat) by the three competing methods. Subscript M is for either the HAM or the CM or the AMFM. In this study, the resolution of *RMSE* is $0.1\mu V$, and the predefined $A(n)$ are considered as constitutive reference TWA-amplitude signals (gold-standard).

When analyzing clinical data, the Lilliefors test was used to evaluate the hypothesis that estimated TWA had a normal distribution (significance was set at 5% level) over a population. Comparisons between normal distributions were performed using Student's test, whereas distributions that could not be considered normal would be compared using the Wilcoxon rank sum test. Statistical significant differences were assumed for $P<0.05$.

Results

For the simulated data and clinical data set, ECG segments of 128 consecutive beats were randomly extracted and directly submitted to the AMFM, which does not require pre-processing [11]. Rather, a data preprocessing stage, described in 2.1 section, was performed prior to submit the CM and the HAM.

1. Simulated cases. For the simulated cases, results obtained from TWA analysis, by applying the CM, the AMFM and the HAM respectively, are reported in below tables.

In Table 1 are reported the results obtained from the simulated ECG tracing with no TWA (N_TWA). These three methods applying to tracings with no baseline yielded accurate identification of TWA amplitude. In the presence of 0.30 and 1.50 Hz baseline wandering, a slight overestimation of TWA amplitude was produced by the CM. In the presence of baseline fluctuations with frequency equal (0.71 Hz) to that of TWA, the strong overestimations of TWA amplitude were produced by the three methods.

In Table 2 are reported the results obtained from the simulated ECG tracing with stationary TWA (S_TWA). In the presence of 0.30 and 1.50 Hz baseline wandering, the CM and the AMFM produced underestimation of TWA amplitude for different stationary TWA, while the HAM yielded an accurate identification of TWA ($RMSE_{HAM}=0\mu V$). In the presence of baseline fluctuations at the TWA frequency of 0.71 Hz, the CM produced underestimation of TWA amplitude, and the AMFM still produced

Table1

TWA amplitude measurements and errors evaluation for N_TWA case

	TWA_{CM}	TWA_{AMFM}	TWA_{HAM}	$RMSE_{CM}$	$RMSE_{AMFM}$	$RMSE_{HAM}$
N_TWA (no bw)	0	0	0	0	0	0
N_TWA (bw030)	2	0	0	4.6	0	0
N_TWA (bw071)	34	200	23	34.4	385.9	22.6
N_TWA (bw150)	1	0	0	5.2	0	0

Table 2

TWA amplitude measurements and errors evaluation for S_TWA case

	TWA_{CM}	TWA_{AMFM}	TWA_{HAM}	$RMSE_{CM}$	$RMSE_{AMFM}$	$RMSE_{HAM}$
S_TWA10 (no bw)	6.5	5.7	10.0	3.2	4.23	0
S_TWA10 (bw030)	6.5	5.8	10.0	4.7	4.2	0
S_TWA10 (bw071)	12	219.7	10.1	21.6	209.7	0.2
S_TWA10 (bw150)	7.2	5.9	10.0	2.6	4.2	0
S_TWA50 (no bw)	36	28.6	50.0	14.3	21.4	0
S_TWA50 (bw030)	36	28.8	50.0	14.8	28.9	0
S_TWA50 (bw071)	17.3	198.8	32.0	32.4	198.8	18.4
S_TWA50 (bw150)	38.2	29	50.0	11.7	29	0
S_TWA100 (no bw)	74.9	57.7	100.0	25.3	42.3	0
S_TWA100 (bw030)	74.9	57.5	70.0	25.6	42.4	0
S_TWA100 (bw071)	54.7	176.2	100.0	45.0	76.0	29.5
S_TWA100 (bw150)	79.2	57.6	100.0	21.1	42.4	0

strong overestimation of TWA amplitude. While the HAM, even produced a slight underestimation of TWA amplitude, showed a better ability to quantifying TWA amplitude with more accuracy in this case, and $RMSE_{HAM}$ obtained $0\mu V$ for S_TWA10, $18.4\mu V$ for S_TWA50, $29.5\mu V$ for S_TWA100, respectively.

For TV_TWA1 and TV_TWA2 cases, the local TWA comparisons are considered because of time-varying amplitudes. A graphical representation of the results obtained from ECG simulations with presence of time-varying TWA (TV_TWA1 and TV_TWA2) is depicted in Figure 8. The columns of panels from left to right display simulated TWA-amplitude signals (128 beats), and detected TWA-amplitude signals provided by the CM, the AMFM and the HAM, respectively. For the cases of the simulated ECG tracing with 0.30 and 0.71 Hz baseline wandering, analogous results are obtained.

The root mean square errors obtained are reported in Table 3. The three methods were able to track the time course of TWA. But the local TWA-amplitude signals provided by the CM showed vigorous amplitude fluctuation, and $RMSE_{CM}$ are higher then $RMSE_{AMFM}$ and $RMSE_{HAM}$ uniformly. The CM and the AMFM produced underestimation of TWA amplitude, which are same to the above mentioned cases, while the HAM provided a good estimate of TWA ($RMSE_{HAM}<1.5\mu V$, except the case of frequency of baseline equal to that of TWA)

In Table 4 are reported the results obtained from the simulated ECG tracing with phase-reversal TWA

Table 3

TWA errors evaluation for TV_TWA1 and TV_TWA2 cases

	$RMSE_{CM}$	$RMSE_{AMFM}$	$RMSE_{HAM}$
TV_TWA1 (no bw)	13.8	12.7	0.9
TV_TWA1 (bw030)	16.1	10.9	1.2
TV_TWA1 (bw071)	25.5	296.9	14.9
TV_TWA1 (bw150)	16.1	12.6	1
TV_TWA2 (no bw)	6.9	2.8	0.5
TV_TWA2 (bw030)	10.1	2.2	1.3
TV_TWA2 (bw071)	19.9	342.1	15.1
TV_TWA2 (bw150)	7.5	3.0	0.5

(PR_TWA). The AMFM produced underestimation of TWA amplitude (40%) in the presence of 0.30 and 1.50 Hz baseline wandering, while the CM and the HAM produced a good results ($RMSE_{CM}=0\mu V$, $RMSE_{HAM}=0\mu V$). In the presence of baseline fluctuations at the TWA frequency of 0.71 Hz, the three methods produced strong overestimation of TWA amplitude, but obviously the results provided by the HAM are more close to the simulated TWA ($TWA_{HAM}=19.7\mu V$, $RMSE_{HAM}=13.1\mu V$).

2. Clinical cases. TWA levels quantified by the three competing methods in the H-subjects and patients data are reported in Table 5, The CM, the AMFM, and the HAM detected various levels of TWA in same H-subjects and all patients. TWA was detected in two H-subjects by the CM and the AMFM, while only one H-subjects was affected by TWA according to the HAM (Table 5). And the three

methods detected the presence of TWA in all patients. TWA showed a normal distribution over patients' populations. Mean TWA values estimated by the HAM in H-subjects ($0.5\pm1.9\mu V$) and patients ($10.8\pm3.7\mu V$) were higher than the corresponding mean TWA estimates provided by the AMFM (H-subjects: $0.4\pm1.9\mu V$; patients: $8.6\pm3.3\mu V$) and the CM (H-subjects: $0.5\pm1.3\mu V$; patients: $9.5\pm3.5\mu V$). All these methods provided mean TWA estimates which showed significant differences between H-subject and patient groups.

The CM, the AMFM and the HAM detected the presence of TWA in all patients, and provided similar TWA estimates. The CM and the AMFM tend to underestimate TWA (Fig. 9 and simulation study results), and this finding is confirmed by our clinical result.

Discussion

In this study four simulated cases were generated with characters of: absence of TWA; presence of different kinds of stationary TWA; presence of two kinds of non-stationary (time-varying) TWA; and presence of phase-reversal TWA. The other two time-domain methods, namely the CM and the AMFM, are compared with the HAM in detection TWA. Results of our simulation study indicate that the HAM allows detection and quantification of TWA better than the CM and the AMFM.

The CM was found to underestimate TWA amplitude in the simulated ECG tracing, since it assumed TWA being distributed along the entire length of the T wave [18]. And in the case of ECG simulations with presence of time-varying TWA, the CM produced the worst results compared with other method (Figure 9 and Table. 3).

The AMFM showed a good performance of time-varying TWA detection, due to its heart-rate adaptive-match-filter yielded the suppression of all ECG and interferences frequency components, while it produced strong overestimation of TWA amplitude in the presence of baseline fluctuations at the TWA frequency, and the reason and a potential solution were given in literature [10].

We can find that the HAM yielded, in general, a more accuracy TWA estimation in the simulated cases, although in the presence of baseline fluctuations with frequency equal to that of TWA the deviation from TWA amplitude was produced which are also produced by the CM, and the reason is that the accuracy of isoelectric line estimation by the cubic spline interpolation technique reduces. And all simulation cases showed $RMSE_{HAM}$ were systematically smaller than TWA_{CM} and TWA_{AMFM}, even in

Table 4

TWA amplitude measurements and errors evaluation for PR_TWA cases

	TWA_{CM}	TWA_{AMFM}	TWA_{HAM}	$RMSE_{CM}$	$RMSE_{AMFM}$	$RMSE_{HAM}$
PR_TWA (no bw)	10	6	10	0	2.8	0
PR_TWA (bw030)	10	6	10	5.1	3.1	1.3
PR_TWA (bw071)	32	230	19.7	22.5	348.3	13.1
PR_TWA (bw150)	9	6	10	0	3.2	0

Table 5

TWA amplitude measurements of clinical data applying the CM, the AMFM and the HAM

H-subjects	TWA_{CM}	TWA_{AMFM}	TWA_{HAM}	TWACD	TWA_{CM}	TWA_{AMFM}	TWA_{HAM}
1	0	0	0	Twa06	6.55	5.73	7.05
2	0	0	0	Twa09	6.91	6.21	8.11
3	0	0	0	Twa10	7.05	5.93	7.65
4	3.02	2.11	0	Twa18	3.75	3.23	4.25
5	0	0	0	Twa22	14.17	12.56	15.10
6	0	0	0	Twa23	12.91	10.83	13.47
7	0	0	0	Twa41	12.08	11.10	14.48
8	0	0	0	Twa46	5.95	4.91	7.55
9	4.12	4.08	7.11	Twa61	11.83	11.06	13.06
10	0	0	0	Twa71	7.12	7.10	8.80
11	0	0	0	Twa85	10.88	10.06	13.16
12	0	0	0	Twa92	13.10	12.55	14.21
13	0	0	0	Twa94	13.79	12.94	15.41
14	0	0	0	Twa99	7.16	6.38	8.23
	0.5±1.3	0.4±1.9	0.5±1.9		9.5±3.5*	8.6±3.3*	10.8±3.7*

*P < 0.05 when comparing H-subjects vs. patients with the t-test for normal distributions.

the presence of baseline fluctuations at the TWA frequency of 0.71 Hz.

The HAM performs a amplitude corrections procedure based on the linear least squares fitting technique before calculating the local TWA, which further suppresses the interferences, and the local threshold criterion, integrated in the HAM, appears to help improving detecting accuracy. The limitation of the CM is that then computing the ACI, the exact location of the maximum amplitude difference between the two waves is lost, so that a mean (over T wave) TWA amplitude value is provided (assumption of uniformly distributed TWA), while in our method TWA is measured by the maximum absolute value of the difference between the corrected matrixes for odd and even T waves, which also improves the accuracy of TWA estimation. The baselines with various frequencies are considered in the simulated cases, and the test results also show the HAM is robust to the noise.

Our results relative to the clinical data highlighted consistency in the detection and quantification of TWA by the three different methods, and significant differences between H-subject and patient groups are manifested, as shown in Table 5. While the TWA amplitudes measured by the CM and the AMFM are slight lower than that by the HAM. The results of our simulation test help interpretation of TWA data obtained from clinical cases.

Conclusions

A novel time-domain TWA detector is presented in this paper based on the correlation method and linear least squares fitting technique. Although the method is simple, it was validated using simulated ECG test signals with artificial TWA of various amplitudes and baseline wanderings, and achieved a good performance under reasonable levels of noise. The results of our simulation study indicate that the HAM provides a more accurate TWA estimation than the CM and the AMFM.

Results of TWA detection produced by the three methods in real clinical ECG records show high consistency, which confirms the TWA detection power of the hybrid method for clinical data, although the quantifying TWA amplitudes by the HAM are universally higher than that by the CM and the AMFM.

Declarations

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Competing Interests: All authors of the present work exclude any financial and personal relationships with other people or organizations that could inappropriately influence this job.

Ethical approval: The study was approved by the institutional research ethics committee of Liuhuaqiao Hospital, Guangzhou, and the Approved No. of ethic committee is No. 20111212. Informed consent was obtained from each subject.

The study protocol conforms to the ethical guidelines of the World Medical Association, Declaration of Helsinki — Ethical Principles for Medical Research Involving Human Subjects adopted by the 18th WMA General Assembly, Helsinki, Finland, June1964, as revised in Tokyo 2004, as reflected in a priori approval by the appropriate institutional review committee. Declaration of Helsinki-Ethical Principles for Medical Research Involving Human Subjects adopted by the 18th WMA General Assembly, Helsinki, Finland, June1964, as revised in Tokyo 2004, as reflected in a priori approval by the appropriate institutional review committee.

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MINNESOTA LEISURE TIME PHYSICAL ACTIVITY QUESTIONNAIRE AS AN ADDITIONAL TOOL IN CLINICAL ASSESSMENT OF PATIENTS WITH CORONARY ARTERY DISEASE TREATED WITH ANGIOPLASTY

Zbigniew Nowak, Agata Nowak

Out of many methods used for assessment of physical activity, a questionnaire seems to be a simple and affordable method of assessing the risk of occurrence of coronary insufficiency. However the number of clinical studies done on the application of physical activity questionnaires is limited.

Aim. The objective of the present study was to analyze the suitability of Minnesota Leisure Time Physical Activity Questionnaire (MLTPAQ) in assessment of physical activity in patients after percutaneous coronary intervention (PCI)

Material and methods. Design: prospective analysis — before and 6 months after PCI and correlation between level of physical activity and physical capacity assessed with treadmill exercise test (ET), ejection fraction (LVEF%) Setting: Upper Silesia Medical Center. Department of cardiology. Population: One hundred fiftieth four inpatients (mean of 56 y), among which there were patients with acute myocardial infarction (MI), with history of past MI and with IHD without MI. All subjects underwent coronarography procedure with optional PCI. All patients underwent phase I and II cardiac rehabilitation. The MLTPAQ was administered to all patients at the time of PCI and then 6 months later, so was the treadmill stress test (TST) and echocardiography (ECHO).

Results. Total energy expenditure calculated with the MLTPAQ remained at the same level and was of low intensity (<4 MET, <2000 kcal/week) 6 months after the PCI. There was an increased physical capacity noted 6 months after initial PCI: increased metabolic cost (MET); maximal oxygen consumption (VO_{2max}); maximal heart rate (HR_{max}) obtained during the TST and decreased resting heart rate (HR_{rest}). ECHO examination showed improved LVEF%.

Clinical Rehabilitation Impact: the helpfulness of the research may be used in the work of cardiologists or physiotherapists. The research will allow to estimate the actual level of physical activity and physical endurance of patients that were treated by angioplasty. Moreover, this is the simple and cheap method of estimation.

Conclusion. Despite increased physical capacity and improved heart hemodynamic resulting most likely from PCI procedure, patients presented with similar level of leisure time physical activity 6 months after the PCI.

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Key words: ischemic heart disease, percutaneous coronary intervention, physical activity questionnaire, treadmill stress test, echocardiography.

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CAD — coronary artery disease, ET — exercise test, HA — household activity, IHD — ischemic heart disease, LVEF% — left ventricular ejection fraction, LVESD — left ventricular end-systolic diameter, MET — increased metabolic cost, MI — myocardial infarction, MLTPAQ — Minnesota Leisure Time Physical Activity Questionnaire, PCI — percutaneous coronary intervention, RA — recreational activity, TST — treadmill stress test.

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МИННЕСОТСКИЙ ОПРОСНИК ФИЗИЧЕСКОЙ АКТИВНОСТИ В КАЧЕСТВЕ ДОПОЛНИТЕЛЬНОГО ИНСТРУМЕНТА ДЛЯ КЛИНИЧЕСКОЙ ОЦЕНКИ ПАЦИЕНТОВ С ИШЕМИЧЕСКОЙ БОЛЕЗНЬЮ СЕРДЦА ПОСЛЕ АНГИОПЛАСТИКИ

Zbigniew Nowak, Agata Nowak

Из многих методов, используемых для оценки физической активности, анкеты кажутся простым и недорогим методом оценки риска возникновения коронарной недостаточности. Однако количество клинических исследований, проведенных на применении анкетирования физической активности анкет, ограничено.

Цель. Целью настоящего исследования был анализ пригодности Миннесотского опросника физической активности (MLTPAQ) в оценке физической активности пациентов после чрескожного коронарного вмешательства (ЧКВ)

Материал и методы. Дизайн: перспективное исследование — до и через 6 месяцев после ЧКВ и корреляция между уровнем физической активности и физической способности, оцениваемой с помощью тредмил-теста с физической нагрузкой (ТТ), фракции выброса (ФВ ЛЖ%). Выполнено: в Медицинском центре Верхней Силезии, отделение кардиологии. Пациенты: 154 пациента в стационаре (средний возраст 56 лет), среди которых были пациенты с острым инфарктом миокарда (ИМ), ИМ в анамнезе и с ИБС без ИМ. Все пациенты были подвергнуты коронарографии с возможным ЧКВ. Все пациенты прошли этапы I и II сердечной реабилитации.

Опросник предлагался всем пациентам во время проведения ЧКВ и затем через 6 месяцев, как и тредмил-тест (TST) и эхокардиография (ЭХО).

Результаты. Общий расход энергии, рассчитанный с помощью MLTPAQ, остался на прежнем уровне и был низкой интенсивности (<4 MET, <2000 kcal/неделю) в 6 месяцев после ЧКВ. Отмечено увеличение физической работоспособности через 6 месяцев после первоначального ЧКВ: увеличение энергетических затрат (MET); максимального потребления кислорода (VO_{2max}); максимальный сердечный ритм (HR_{max}) был получен в ходе TST, снизилась частота пульса в спокойном состоянии (HRrest). ЭХО исследование показало улучшение ФВ ЛЖ,%.

Клиническое воздействие реабилитации: полезность исследования может быть использована в работе врачей-кардиологов или физиотерапевтов. Исследование позволит определить реальный уровень физической активности и физической выносливости пациентов, которые лечились с помощью ангиопластики. Кроме того, это самый простой и дешевый метод оценки.

Заключение. Несмотря на увеличение физической способности и улучшение сердечной гемодинамики в результате ЧКВ, пациенты показали одинаковый уровень физической активности через 6 месяцев после ЧКВ.

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Ключевые слова: ишемическая болезнь сердца, чрескожное коронарное вмешательство, анкеты физической активности, тредмил-тест, эхокардиография.

Introduction

In recent years there have been many papers published on the research methods aimed at measurement of physical activity. Some were based on monitoring of selected physiological parameters such as heart rate and whole body movements with the use of accelerometers or pedometers [1–3]. Other were aimed at assessment of energy expenditure derived from food, using direct and indirect calorimetry, kinematic analysis as well as doubly labelled water [4]. In epidemiological studies, the application of such methods is limited due to high costs, potential contraindications, advanced age of subjects, their health status and low reliability. It seems that a questionnaire constitutes a simple and inexpensive tool in assessment of physical activity [6–9]. In some questionnaires only occupational activity is of interest, in others, only leisure time exercise, but many seek information about activity both on and off the job.

The questionnaires assess the physical activity over a wide age range for various periods of time — the previous 24 hr, the previous week, month or even a year [7, 9].

The data obtained in this way allows for calculation of average energy expenditure of an individual, which informs us whether the form, frequency and intensity of physical activity reach the values required for prevention and treatment of many so-called civilization diseases.

Such measurement is of great importance, since the sedentary lifestyle is one of the risk factor responsible for occurrence of IHD and at the same time physical activity constitutes a major factor in treatment and secondary prevention of IHD [10, 11].

However, the number of studies done on the application of questionnaires for clinic purposes in patients with IHD is limited. We attempted to answer the following questions:

1. What is the average weekly amount of physical activity and energy expenditure calculated using the MLTPAQ in patients with coronary artery disease (CAD) before and after percutaneous coronary intervention (PCI)?

2. Do obtained questionnaire results correlate with the level of physical capacity [assessed with submaximal treadmill exercise test (ET)] and cardiac haemodynamical parameter — Ejection Fraction (evaluated with echocardiography), making it a usable tool in clinical studies?

3. Is there a correlation between the obtained questionnaire results and combined endpoint?

Material and methods

The study group consisted of 211 patients, aged between 32–74 years (mean age of 56±7), among which there were patients with acute MI, with history of past MI and with IHD without MI. Patients with post-MI complications such as cardiogenic shock, circulatory arrest, pericarditis, resting arrhythmias and heart conductivity disorders were excluded from the study. All patients were informed about the type and aim of the research and they gave written informed consent before participating in the study. Subjects were told that they may withdraw from the study at any time. The study was approved by the Senate Ethics Committee of the Academy of Physical Education in Katowice, Poland.

All subjects underwent coronarography procedure with optional percutaneous coronary intervention (PCI). Out of 154 patients 32 (20,77%) did not receive stent implantation, 108 subjects (70.12%) received one stent, while 8 (5,19%) two stents implantation. All patients underwent phase I, inpatient cardiac rehabilitation which lasted from 5 to 7 days. After hospitalization all patients were referred to phase II, 24-day cardiac rehabilitation in health resort (sanatorium). All subjects filled the MLTPAQ twice: first, at the time of hospitalization due to PCI procedure, and then for the second time after the lapse of 6 months. The MLTPAQ results enabled the calculation of the level of recreational physical activity and household activities during leisure time. The results were expressed in a weekly value [kcal/week] after dividing the calculated 6-month energy expenditure by 26 weeks. The following ranges of activity intensity were used: low [< 4 MET], medium [4 — < 6 MET] and high [≥ 6 MET], where 1 MET equals the resting metabolic rate, which is approximately 3.5 ml oxygen kg^{-1} body weight per min^{-1}. The value of total averaged weekly energy expenditure was calculated separately for recreational activity (RA) and household activity (HA) (shopping, cleaning, gardening, house remodelling and repairing). Additional categorization of weekly energy expenditure into 4 ranges was also made: ≤ 999, 1000–1999, 2000–2999, ≥ 3000 [kcal/week]. The MET for a given activity value was calculated according the Compendium of Physical Activities Tracking Guide [12]. In order to increase reliability of the questionnaire calculations (avoiding possible misunderstanding of some questions, especially those concerning the time of activity) the authors of this study read the questions of the MLTPAQ and filled in the questionnaires for patients during individual appointments.

The level of work capacity was assessed with the use of submaximal treadmill stress test (according to Bruce's protocol) performed 1–3 months before the initial PCI procedure and 6 months after. The following variables of stress test were subjected to statistical analysis: test duration [min], metabolic cost [MET], resting and the highest recorded value of heart rate [beats/min], maximal oxygen consumption VO_2max [ml] and the reason for stress test termination: submaximal value of HRmax (85%) calculated with formula: HR max = 208–07 x age, fatigue, stenocardia, changes of S-T segment in electrocardiogram (ECG), occurrence of arrhythmias, heart conductivity disorders and excessive increase in arterial blood pressure. The value of VO_2max was calculated according to the following formula [13]:

$VO_2max = 13,3–0,03\ (t) + 0,297\ (t^2) — 0,0077\ (t.^2) + 4,2\ (CHS)$,

where, t — time [minutes], CHS — cardiac health status, 1- patients with angina pectoris, after MI, after

Table 1

Results of treadmill stress test at the time of PCI and 6 months after

Parametr	at the time of PCI, N = 154	6 months after PCI, N = 150	P
Stress test time [min]	4,24±2,22	6,32±3,12	<0,001
MET	6,52±1,26	8,21±2,86	<0,001
VO_2max [ml]	28,23±5,94	32,52±8,25	<0,001
Resting HR [beats/min]	72±4,23	70±6,22	<0,001
HR_{max} at the test [beats/min]	118±14,52	129±16,47	<0,001

Abbreviations: PCI — percutaneous coronary intervention, MET — metabolic cost, VO_2max — maximal oxygen consumption, HR_{rest}.— resting heart rate, HR_{max} — maximal heart rate.

Table 2

Indications for treadmill stress test termination

Indications for stress test termination	at the time of PCI		6 months after PCI	
	N	%	N	%
Reaching submaximal HR	19	12,33	118	78,66
Other†	135	87,67	32	21,34
Total	154	100	150	100
	P <0,001			

Abbreviations: PCI — percutaneous coronary intervention, HR — heart rate. † stenocardia, S-T segment changes in ECG, occurrence of arrhythmias and heart conductivity disorders, excessive increase in arterial blood pressure.

Table 3

Echocardiography results

Parametr	at the time of PCI, N = 154	6 months after PCI, N = 150	P
LVEF%	50,45±7,21	51,36±6,12	<0,02

Abbreviations: PCI — percutaneous coronary intervention, LVEF% — left ventricular ejection fraction.

PCI, 0 — patients without clinical symptoms of angina pectoris, without history of MI or PCI.

Left ventricular ejection fraction (LVEF%) was analyzed. The assessment of heart structure was done with 2-dimennsional echocardiography (HP Sonos 1100) by a physician, cardiology specialist, after completion of echocardiography training.

All statistical analyses were performed using Statistica (v. 7.1) software, Statsoft USA and MedCalc software (v.8.0.0.1) by F. Schoonjans and included the calculation of means and standard deviations (SD) of variables. The distribution of means was evaluated with Wilk-Shapiro test for normality. A criterion of $p<.05$ defined statistical significance. Student's t-test for independent variables with normal distribution was used. This test was preceded by the Fisher's test for verification of the homogeneity of variance. In case the variance was not equal, Sattherwaite's test was used. Student's t-test for dependent variables was also used, as well as one-way variance analysis proceeded by Bartlett's test for verification of variance homogeneity. For variables with non-normal distribution, U Mann-Whitney test, Kruskall-Wallis ANOVA test and Sperman's rang correlation test were used.

Results

Out of 211 patients who initially underwent PCI procedure, there were 207 subjected to the second questionnaire administration (2 patients died due to coronary insufficiency in second and fifth month after the PCI, 2 patients resigned from the study due to general discomfort). Compared to the stress test performed at the time of the initial PCI procedure, the improvement of patients' physical capacity was noted during the treadmill stress test: increased metabolic cost (MET); maximal oxygen consumption (VO_{2max}); maximal heart rate (HR_{max}) obtained during the test and decreased resting heart rate (HR_{rest}) (Table 1). The number of patients who terminated the stress test due to pathological reasons reduced (Table 2).

After the 6-month period, there was a favourable tendency noted in the changes of heart hemodynamic, though only in the case of EF% statistical significance was observed (Table 3).

The total energy expenditure from the leisure time activities calculated with the MLTPAQ was higher 6 months after the angioplasty procedure (2829,52 vs 2799,92kcal/week). As far as physical activity of low intensity was concerned, there was an increase noted (1759,30 vs 1811,06 kcal/week). The values of activity of medium and high intensity dropped from 1300,99 to 1190,46 and from 714,63 to 491,73 kcal/week, respectively. Nevertheless, none of the above changes were statistically significant. The value of recreational activity was higher 6 months after the angioplasty for the range of low intensity (<4 MET) and in majority of patients did not exceed 3000 kcal/week. For the range of medium intensity (4–6 MET) it stayed under 2000 kcal/week in majority of patients. In the range of high intensity (>6MET) it did not exceed 1000 kcal/week in those few patients who presented with that level of intensity. In case of household activity, there was an increase noted in medium range of intensity (4–6MET) which did not exceed 3000 kcal/week in majority of patients. For the household activities of high intensity

Table 4

Types and ranges of physical activity energy expenditure calculated with the MLTPAQ

Parameter		below 999 kcal		1000–1999 kcal		2000–2999 kcal		over 3000 kcal		TOTAL		
		before PCI	6 months after PCI	before PCI	6 months after PCI	before PCI	6 months after PCI	before PCI	6 months after PCI	before PCI	6 months after PCI.	P
		Low intensity < 4 MET										
RA	Mean	498,18	521,75	1333,52	1451,66	2445,65	2512,62	4186,59	4105,97	1619,94	1707,99	<0,24
	SD	270,17	212,64	216,62	220,38	329,21	312,40	875,31	601,03	1232,93	1104,06	
	N	51	52	54	65	20	20	7	6	132	143	
HA	Mean	191,46	429,11	1210,46	—	2312,30	2403,93	4116,90	4000,07	1632,29	1320,53	<0,34
	SD	45,54	201,79	33,97	—	—	152,60	427,10	187,11	1611,22	1481,89	
	N	5	10	3	0	1	2	4	4	13	16	
Total	Mean	435,65	501,51	1235,39	1366,11	2568,12	2489,92	4452,98	4481,01	1729,10	1801,14	<0,31
	SD	292,09	232,50	233,37	222,51	307,08	309,43	1076,02	900,03	1421,13	1291,56	
	N	56	51	23	35	40	7	19	3	131	138	
		Medium intensity 4 — >6 MET										
RA	Mean	309,90	420,33	1318,01	1501,26	2500,76	2401,10	3048,04	4623,12	545,12	601,18	<0,11
	SD	253,55	261,49	324,92	223,30	190,19	288,27	—	—	534,81	641,21	
	N	84	85	22	10	9	4	4	2	119	101	
HA	Mean	371,91	524,22	1418,24	1495,28	2417,56	2484,60	4410,14	3765,73	1064,42	1011,12	<0,45
	SD	245,38	290,29	278,60	302,84	99,96	412,87	1295,59	531,09	1529,76	1129,48	
	N	65	66	21	28	5	5	13	11	104	110	
Total	Mean	415,37	515,90	1541,89	1352,59	2320,16	2355,92	4221,67	4112,71	1289,85	1088,42	<0,71
	SD	111,00	207,23	292,12	296,89	125,83	283,95	1007,42	568,86	1326,26	1198,55	
	N	74	81	34	29	12	15	12	8	132	133	
High intensity >6 MET												
RA	Mean	372,70	321,41	1226,15	1561,54	—	2225,00	3113,01	5226,14	511,94	643,90	<0,6
	SD	224,21	232,07	22,12	—	—	—	—	—	621,73	1005,01	
	N	24	21	3	1	0	1	1	1	28	24	
HA	Mean	332,15	231,94	1409,01	1206,15	2015,38	—	4644,61	—	723,74	195,34	<0,6
	SD	180,21	181,79	—	—	—	—	—	—	1220,53	252,87	
	N	18	25	2	2	1	0	5	0	26	28	
Total	Mean	361,61	281,26	1354,15	1396,15	2195,38	2068,45	4126,15	5106,14	700,63	391,73	<0,9
	SD	272,61	219,48	307,81	230,48	—	—	1293,36	—	1092,74	806,73	
	N	34	39	6	3	2	1	3	1	45	44	
Total energy expenditure	Mean	581,11	589,29	1449,74	1530,92	2477,41	2499,81	4796,96	4536,78	2363,11	2412,53	<0,6
	SD	292,31	199,13	154,43	110,69	100,83	154,70	1327,55	1107,28	1647,09	1599,55	
	N	28	23	45	42	37	48	44	37	154	150	

Abbreviations: PCI — percutaneous coronary intervention, RA — energy expenditure of recreational activity, HA — energy expenditure of household activity, Total — energy expenditure of either RA, HA or both forms of activity, SD — standard deviation.

(>6 MET) there was a significant drop of the energy expenditure noted in all ranges (Table 4).

There was a significant increase of work tolerance noted during the stress test 6 months after the angioplasty. There were considerable changes in values of all observed parameters. Patients, whose physical activity in leisure time was in the range of 2000–2999 and over 3000 kcal/week, obtained the most significant improvement during the stress test (Table 5).

The echocardiography examination performed 6 months after the angioplasty showed improvement of the heart structure dimensions. Statistically significant changes (within the normal range) considered the LVESD and LVEF% values. In the group of patients whose weekly energy expenditure was below 2000 kcal/week, there was a slight increase of the dimensions in majority of parameters, except for LVEF%, where there was a small decrease (within the normal range) observed in the group of patients with weekly energy expenditure under 999 kcal/week (Table 6).

There were weak correlations observed between total energy expenditure calculated with the MLTPAQ stress test parameters and ECHO results (Table 7 and Table 8).

Discussion

The average amount of weekly energy expenditure related to recreational activity, and therefore the one which is of great importance for prevention of cardiovascular

Table 5

Selected parameters of stress test in relation to the intensity ranges of activity calculated with the MLTPAQ

Parameter		below 999 kcal		1000–1999 kcal		2000–2999 kcal		over 3000 kcal		TOTAL		
		before PCI	6 months after PCI	before PCI	6 months after PCI	before PCI	6 months after PCI	before PCI	6 months after PCI	before PCI	6 months after PCI	P
Test duration [min]	Mean	5,70	5,64	5,71	7,16	5,31	7,35	6,15	8,18	4,24	6,32	<0,001
	SD	2,79	2,40	2,44	2,06	2,57	2,70	2,86	2,39	2,22	3,12	
	N	33	18	57	45	37	42	82	73	154	150	
Metabolic cost [MET`s]	Mean	7,51	7,70	7,68	8,95	7,01	9,26	7,73	9,66	6,52	8,21	<0,001
	SD	2,76	2,70	2,71	2,38	2,54	3,02	2,66	2,38	1,26	2,86	
	N	33	18	57	45	37	42	82	73	154	150	
VO2max [ml/kg/min]	Mean	28,93	27,16	28,54	32,90	27,70	34,54	30,49	37,94	28,23	32,52	<0,001
	SD	9,55	7,16	8,32	8,65	9,32	10,95	11,50	11,02	5,94	8,25	
	N	33	18	57	45	37	42	82	73	154	150	
HR resting [beats/min]	Mean	75,55	75,94	77,44	71,82	78,70	73,79	77,10	73,52	72,00	70,00	<0,001
	SD	8,53	8,63	9,40	10,13	9,11	10,46	9,41	9,72	4,23	6,22	
	N	33	18	57	45	37	42	82	73	154	150	
HR max [beats/min]	Mean	120,52	136,50	120,38	132,04	125,65	129,50	125,90	131,78	118,00	129,00	<0,001
	SD	15,56	11,64	18,89	15,02	18,23	15,51	16,09	14,85	14,52	16,47	
	N	33	18	57	45	37	42	82	73	154	150	
HR submax not reached	N/Σ	16/17	6/20	43/51	16/46	24/33	11/41	35/53	15/43	118/154	48/150	<0,001
	%	94,11%	30,00%	84,31%	34,78%	72,72%	26,82%	66,03%	34,88%	76,62%	32,00%	
Positive results of stress test	N/ Σ	21/30	8/23	33/41	11/30	26/32	16/37	41/51	7/60	121/154	42/150	<0,001
	%	70,00%	34,78%	80,48%	36,66%	81,25%	43,24%	80,39%	11,66%	78,57%	28,00%	

Abbreviations: PCI — percutaneous coronary intervention, MET — metabolic cost, VO_2max — maximal oxygen consumption, HR_{rest} — resting heart rate, HR_{max} — maximal heart rate: HR sumbax — HR calculated with formula: (220 — age) x 0,85; SD — standard deviation.

Table 6

Selected echocardiography variables, in relation to the intensity ranges of activity calculated with the MLTPAQ

Parameter		below 999 kcal		1000–1999 kcal		2000–2999 kcal		over 3000 kcal		TOTAL		
		before PCI	6 months after PCI	before PCI	6 months after PCI	before PCI	6 months after PCI	before PCI	6 months after PCI	before PCI	6 months after PCI	P<
LVEF% [%]	Mean	51,33	50,56	53,37	53,45	49,76	52,62	51,12	52,42	50,45	51,36	<0,02
	SD	9,12	9,85	8,03	8,00	7,64	7,21	10,26	8,69	7,21	6,12	
	N	33	27	57	47	37	47	82	81	154	150	

Abbreviations: PCI — percutaneous coronary intervention, LVEF% — left ventricular ejection fraction, SD — standard deviation.

diseases [12, 14, 15], did not exceed in our study the value of 2000 kcal/week before the first PCI and was mainly of low intensity — <4 MET (morning warm-up exercises, walking, fishing), or of moderate intensity, 4–6 MET (cycling, including stationary cycling, general conditioning exercises). The range of physical activity remained below the level of 1000 kcal/week.

Such low level of physical activity may result from limitation of exercise tolerance due to atherosclerotic process in coronary vessels or history of MI, but most likely from the sedentary lifestyle [13, 15, 16]. The majority of patients did not engage in any form of sport or recreational physical activity and even if they did, such activity was short-lasting and sporadic. There were however a few patients (6) who systematically participated in various forms of recreation (skiing, jogging, swimming); their weekly energy expenditure resulting from such activities very often exceeded the level of 2000 and sometimes even 3000 kcal per week.

That group of few patients included individuals who used to do sports in the past or who were really enjoying such activities. After the angioplasty procedure the increase of the level of physical activity as well as energy expenditure was anticipated. We assumed that one factor which would favourably affect patients' attitude to physical activity was the cardiac rehabilitation programme, both in hospital and in the health resort.

There was, however, no increase in total weekly energy expenditure noted after the PCI procedure; nor was there in the intensity or type of performed activities. During the 6-month period preceding the second PCI, patients engaged mainly in recreational activities of low intensity, in the range of 1000–1999 or 2000–2999 kcal/week, and in household activities of moderate intensity (4–6 MET).

The values of these activities however still remained at an unchanged level. We found an improvement in variables obtained at the second ET. The higher the increase in energy expenditure in relation to the initial examination, the more the improvement in selected ET parameters was noted. Patients who exceeded the value of 2000 kcal/week after the first PCI were able to exercise longer, resulting in higher values of obtained MET, VO2max and maximal HR. In this group of patients, there was a considerable increase in the number of patients reaching the level of submaximal HR and a decrease in the number of positive ET results. Similar findings were reported by Nowak et al [13]. The angioplasty procedure restores proper circulation in coronary arteries, improves work tolerance and thus allows patient to exercise longer and with increased intensity. The procedure resulted in improvement of left ventricle function of studied subjects (increase in EF%) what was also reported by other authors [17–20]. We also evaluated correlation between the delta of energy expenditure assessed in the questionnaire versus the delta of selected parameters of treadmill stress test and echocardiography examination. As far as stress test results were concerned we found weak correlation with the delta of test time and VO2 max. There was however no association with the delta values of echocardiography procedure. This situation may result from patients' fear of ischemic symptoms reproduction associated with considerable chest pain and perhaps from their unwillingness to physical effort in general.

Table 7

Correlation indices between total energy expenditure calculated with MLTPAQ, stress test parameters and ECHO results

	Exercise stress test	r	P
MLTPAQ*Δ†	Time Δ†	0,198	<0,002
MLTPAQ Δ	MET Δ	0,158	<0,057
MLTPAQ Δ	VO_2max Δ	0,255	<0,001
MLTPAQ Δ	Rest.HR Δ	0,159	<0,048
MLTPAQ Δ	HR max Δ	0,134	<0,087

*Minnesota Leisure Time Physical Activity Questionnaire; †Δ: the result of subtraction of the first and second examination and MLTPAQ values.

Table 8

Correlation indices between total energy expenditure calculated with MLTPAQ, and ECHO results (EF%)

	Echocardiography	r	P
MLTPAQ*Δ†	EF% Δ	0,028	<0,624

* Minnesota Leisure Time Physical Activity Questionnaire; †Δ: the result of subtraction of the first and second examination and MLTPAQ values.

Conclusion

Our findings suggest that MLTPAQ may be used as an additional tool in clinical assessment of patients undergoing PCI. The results obtained in this study indicate that the level of leisure time physical activity in studied subjects was below the value recommended for primary and secondary prevention of IHD. We assume that improvement of patients' clinical status 6 months after the PCI resulted from high effectiveness of that procedure and participation in two phases of cardiac rehabilitation.

Clinical Rehabilitation Impact

The helpfulness of the research may be used in the work of cardiologists or physiotherapists. The research will allow to estimate the actual level of physical activity and physical endurance of patients that were treated by angioplasty. Moreover, this is the simple and cheap method of estimation.

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FACTOR INFLUENCING LENGTH OF STAY (LOS) OF PATIENTS UNDERGOING BYPASS SURGERY AT SHAHEED MADANEE CARDIAC TEACHING HOSPITAL –TABRIZ — IRAN

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Aim. This study aimed to study the effect of patients' and physician's characteristics as a predictor of length of stay (LOS) in patients undergoing coronary bypass surgery.
Material and methods. This was a retrospective study conducted at Tabriz Shaheed Madanee Cardiac Teaching Hospital in Iran in 2010. The 349 patients who did undergo a bypass surgery during 2008–2010 were studied. Patients and physicians characteristic were collected from patients medical records using a researcher developed checklist. Independent Samples Test of ANOVA was conducted to compare LOS between categorical variables. Data was analyzed using the SPSS17 statistical package.
Results. The mean age of the patients was 59.7 years. Overall average LOS was 15.58 (10.02) days. The findings of this study indicate that older patients stayed in the hospital for a significantly longer period than did younger patients. Patients' stay at the hospital was statistically significant and longer than assessed expected length of stay estimated by physicians (P< 0.05). Patient admitted to the hospital through emergency department and patients with no hospitalization history stayed longer in the hospital (P≤0.01).).Early discharged patients and death cases also had a longer LOS (P ≤ 0.01).Patient whose attending physicians were working in private sector, in addition to Shaheed Madanee Hospital and had higher level of education stayed longer than those whose physicians worked only at Shaheed Madanee Hospital (P≤ 0.01).
Conclusion. Institutional characteristics –physicians practice both in private sector and public teaching hospital, physicians' level of education, discharge process guidelines, and admission protocols were most important factor in predicting LOS. The patient's hospitalization history whether patient was hospitalized before or not, was also a predictor.

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Key words: coronary arteries bypass surgery, Length of stay, Teaching Hospital.

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ФАКТОР, ВЛИЯЮЩИЙ НА ПРОДОЛЖИТЕЛЬНОСТЬ ПРЕБЫВАНИЯ (ПП) ПАЦИЕНТОВ, ПЕРЕНЕСШИХ ОПЕРАЦИИ ШУНТИРОВАНИЯ В КАРДИОЛОГИЧЕСКОЙ КЛИНИЧЕСКОЙ БОЛЬНИЦЕ SHAHEED MADANEE -ТЕБРИЗ — ИРАН

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Цель. Это исследование было проведено с целью изучения влияния на характеристики пациентов и врачей такого предиктора, как продолжительность пребывания (ПП) пациентов, перенесших коронарное шунтирование.
Материал и методы. Это был ретроспективный анализ, проведенный в Кардиологической клинической Больнице Shaheed Madanee города Тебриза в Иране в 2010 году. Было исследовано 349 пациентов, которые прошли шунтирование в течение 2008–2010 гг. Характеристики пациентов и врачей были извлечены из медицинских записей пациентов с помощью специального контрольного списка, разработанного исследователями. Тест независимых выборок ANOVA проводился для сравнения ПП между категориальными переменными. Данные были проанализированы с использованием статистического пакета SPSS17.
Результаты. Средний возраст пациентов составил 59,7 года. Средняя ПП была 15.58 (10.02) дней. Результаты этого исследования показывают, что пожилые пациенты оставались в больнице в течение гораздо более длительного периода, чем у молодые пациенты. Пребывание пациентов в больнице было статистически значимо и дольше, чем ожидаемой ПП по оценкам врачей (P<0,05). Пациенты, поступившие в больницу через отделение неотложной помощи, и пациенты без истории госпитализации задерживались в больнице дольше (P=<0.01). Ранее выписанные пациенты, а также случаи смерти, также имели длительную ПП (P=<0.01). Пациент, чьи лечащие врачи работали в частном секторе, помимо больницы Shaheed Madanee, и имели более высокий уровень образования, оставались дольше, чем те пациенты, чьи врачи работали только в больнице Shaheed Madanee (P=<0.01).
Заключение. Институциональные характеристики — практика врачей и в частном секторе и в государственной клинической больнице, высокий уровень образования врачей, выполнение требований рекомендаций, и прием протоколов были важными факторами в прогнозировании ПП. История госпитализации пациента, был ли пациент госпитализирован до или после, также является предиктором.

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Ключевые слова: коронарное шунтирование, срок пребывания в больнице.

Introduction

Coronary artery bypass surgery is a safe and accepted technique to treat coronary artery diseases [1], with its own costs implications [2]. The annual cost of it is more than 10 billion US dollars for 500,000 coronary bypass surgeries in the United States [3]. Because of the large number of surgeries performed, even modest reductions in bypass unit cost by rationalizing the length of stay could significantly reduce expenditures at both the hospital and national levels [3].

However it has been shown that length of stay is associated with resource use [4], additionally it is a sensitive and specific marker of inefficiency in using scarce resources of hospitals in inappropriate length of stay [4].

However, there does not appear to be much evidence in the literature to support the assumptions that there is a golden

standard of length of stay for patients undergoing coronary bypass surgery, but finding of studies indicates that longer preoperative hospital stay can be a risk factor for deep wound infection [4, 5], in addition longer preoperative hospital stay was associated with a increased risk of surgical site infections [5]. In recent years, there has been data published from several studies suggesting that the predictors of length of stay as a patient outcome can range from clinical mix [1, 6, 7], to patient, [6, 8–10] and care providers characteristics [6, 8]. Therefore the risk of prolonged length of stay on patient's outcome may be no different than clinical predictors of patient outcome in regards to service quality. However it seems possible to decrease coronary bypass surgery patients' length of stay with lower resource utilization and costs without adversely affecting patient's outcomes. It is not something out of sight, and it can be achieved with minor interventions in clinical and administrative procedures, processes, providers behaviour, and the guidelines, for instance, some studies show that the development of fast-track anaesthetic techniques for cardiac surgery has helped to decrease intensive care unit (ICU) and hospital length of stay (LOS) without adversely affecting mortality and morbidity [4, 11].Therefore this study aimed to study the effect of patients' and physician's characteristics as a predictor in length of stay of patients undergoing coronary artery bypass surgery at Shaheed Madanee Cardiac Teaching Hospital in Tabriz.

Material and methods

We used a retrospective-observational study at Tabriz Shaheed Madanee Cardiac Teaching Hospital to study 349 hospitalized patients who did undergo a bypass surgery in 2010. About 349 hospitalized patients who did undergo a bypass surgery were studied. Study data were collected using a researcher developed checklist from patient medical records during 2008–2010.

Trained personnel collected data using a standardized checklist on 349 patient's undergone coronary bypass surgery during 2008–2010. Patients in this study had a coronary bypass grafting surgery (CABG) as their principal procedure defined by International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code, according to their medical records. During years 2008–2010 we randomly selected 15 medical records every month out of those records showing that patient has undergone a bypass surgery

Study checklist included demographic information such as: patient's sex, occupation, patients insurance, marital status, type of admission, history of hospitalization, discharge status, physician specialties, physicians practice in private in addition to practice at Shaheed Madanee Hospital sector, and length of stay at the hospital. Furthermore, in regards to determining the assessment of physicians on expected length of stay of patients undergoing coronary bypass surgery data was collected from physicians who had enough experience in diagnosing and performing coronary bypass surgery. The pessimistic, optimistic and most likely length of stay for patients undergoing coronary bypass surgery at this hospital were collected though conducting interviews with physicians and then expected length of stay was calculated using the PERT (Program Evaluation and Review Technique) Weighted Average formula:

*Expected time = (Pessimistic value + 4*most likely value + Optimistic value) /6*

Frequencies and percentages were used to describe demographic information of patients. Independent Samples Test, ANOVA was conducted to compare LOS between categorical variables after testing the normality of their distribution and confirmation by a Kolomogrov-Smirnov test. One-Sample T Test was used to describe the differences between physicians' estimated and actual LOS derived from patients' records. Furthermore data was analyzed using the SPSS17 statistical package. The P values ≤ 0.05 were considered as statistically significant.

Results

Data were collected on all 349 patients undergone coronary bypass surgery. Overall average LOS derived from patients' records was 15.58 (±10.02) days. The mean age of the patients studied was 59.7 (9.8) years. Further analysis of the data indicates that older patients stayed in the hospital for a significantly longer period than did younger patients (P≤0.001). Table 1 summarizes the findings of the patients' characteristics according to gender, occupation, type of insurance (Insurance plan), mode of admission, history of hospitalization (previous hospitalization due to cardiac problems), discharge status, physicians' educational level, and their practice in private sector.

Study findings indicate females' LOS statistically was longer than male (p=0.014). There was no significant association between length of stay and patients' marital status and place of residence -rural or urban- (P>0.05). Significant association was observed between length of stay and type of admission and, hospitalization history, and physicians practice in private sector (P≤0.001), also, data related to practice in private sector for two physicians were not available. With the exception discharge status which was a little longer for partial recovery (P=0.049). Table 1 also reports the length of stay according to physicians status; patients whose physician was a specialist did stay one and half day longer than those whose physician was a sub-specialist, this difference wasn't statistically significant (P=0.061) (Table 1).

Table 2 indicates detailed pessimistic, optimistic and most likely length of stay according to physician's point of view. To calculate the expected length (time) of stay physicians were asked to estimate pessimistic, optimistic and most likely length of stay for patients undergoing coronary bypass surgery. Then the Expected length (time) of stay was determined using PERT Weighted Average formula.

The physicians estimated LOS was 10.72 days and actual LOS derived from patients' medical records was 15.58 days. The difference between estimated and actual LOS using One-Sample T Test was statistically significant (P≤0.05) (Table 2).

Table 1

Length of Stay according to Patient and Physician characteristics

Characteristics	No (%)	Mean of Length of Stay (SD)	Min_Max	p
Sex				
Male	246 (70)	14.77 (8.94)	3–60	0.014
Female	103 (30)	17.53 (10.79)	2–71	
Occupation				
Unemployed	109 (31.1)	17.56 (10.82)	2–71	0.052
Employee	33 (14.6)	13 (5.77)	6–31	
Technical worker	30 (5.9)	13.93 (6.22)	3–29	
Non-Technical worker	15 (8.6)	15.47 (9.07)	4–40	
Retired	51 (4.3)	17.56 (10.82)	4–46	
Farmer	34 (9.7)	15.68 (6.41)	3–33	
Other	77 (22)	14.10 (8.56)	3–60	
Patient Insurance type				
Health services	170 (48.7)	16.16 (9.48)	2–60	0.672
Social security	120 (34.4)	14.42 (8.81)	3–71	
Military insurance	40 (11.5)	16.55 (8.53)	4–54	
Private insurance	8 (2.3)	14.50 (3.85)	9–20	
Uninsured	11 (3.1)	14 (7.55)	5–27	
Patient Marital status				
Married	347 (99.5)	15.6 (9.86)	2–71	0.401
Single	2 (0.5)	13.5 (2.27)	6–21	
Type of admission				
Elective	261 (74.7)	14.11 (6.45)	2–60	<0.001
Emergency	88 (25.3)	19.94 (10.54)	2–71	
History of hospitalization (previous hospitalization due to cardiac problems)				
Yes	231 (66.2)	13.7 (9.09)	3–46	<0.001
No	118 (33.8)	19 (7.49)	2–71	
Discharge status				
Complete recovery	278 (79.7)	14.86 (7.59)	2–60	0.049
Partial recovery	42 (12)	15.57 (6.90)	4–36	
Death	29 (8.3)	22.30 (17.95)	4–71	
Physician's educational status				
Specialist	215 (61.6)	15.83 (7.24)	3–60	0.061
Sub-Specialists	134 (38.4)	14.35 (6.25)	2–46	
Physician's work in private sector				
Yes	106 (35)	13.45 (7.2)	3–60	<0.001
No	197 (65)	15.97 (8.35)	2–71	

Table 2

Physicians estimated LOS related to real LOS

Conditions	LOS (day)	p
Optimistic	5.64	
Pessimistic	20.34	
Most likely	9.59	
Te. (Expected Time)	10.72	< 0.05
Real LOS according medical record	15.58	

Discussion

Previous researchers have found that there is considerable variation in the resource use and LOS associated with bypass surgery. Our study examines the length of stay for a single regional specialist heart hospital in Tabriz. We found substantial associations between patients' and physician's characteristics and length of stay in this study. LOS was higher for patients, who were unemployed, retired, female, and had no hospitalization history due to cardiac problems, emergency admission patients, and death cases. These findings are generally consistent with prior studies that used medical records identify the predictors of length of stay [1, 2, 12]. Despite previous research findings failure to explain patients and physicians non clinical characteristics [7, 13] as predictors of variation of length of stay [1], our findings identify some association between institutional characteristics and length of stay as additional risk factors for prolonged length of stay which are consistent with previous findings [11, 14]. Length of stay differs due to many factors some of which may be modifiable such as discharge status and physicians practice in private and public sector at the same time [13, 14]. Therefore variation in pattern of staffing of physicians may affect the length of

stay [11, 14]. Research findings indicate that some hospitals adopted protocols to shorten the length of stay, which are being considered to be effective. These studies also revealed that hospital discharge policy, hospital size and managerial factor have a major role in LOS [11, 13, 14]. Furthermore several recent studies suggest using critical pathways, care maps, and a fast-track protocol is effective to increase the efficiency by reducing LOS [11, 14].

Our study provides such information that could be used to predict and distinguish patients who as a result longer period of stay in the hospital. Furthermore, we could determine that savings will be extended if we use integrated hospital and home care services. That is to say, since Shaheed Madanee Hospital is the only hospital serving a vast geographical area (more than three provinces in North West of the country) and most of the residents have difficulty in accessing the post-operative services, the providers and patients tend to prolong the hospital stay. Thereby offering post-operative services through home care can considerably reduce the LOS.

Further research is needed to address these issues, particularly in light of the trend toward shorter hospitalizations and resource utilization without sacrificing the quality of care [15].

On the other hand, due to non-linear pattern of hospital costs and revenue, most of the costs of hospitalization and profitable services for are incurred at the beginning of hospital stay, so, by reducing LOS hospital marginal profit's increase [16]. Along with this factor according to present study findings technical expectancy of LOS based on physician's estimation was significantly shorter than real LOS derived from medical records. In this regard, findings in the literature also indicate that other factors such as quality of care and hospitals volume can influence this issue [17].

Although we tried to limit the constraints of our study but there are still a number of limitations. First, our findings do not take into account the patients' residency and economic characteristics, although, these factors play an enormous role in LOS. In our study context due to lack of access to post-operative services in some setting some patient and provider prefer to longer LOS. Second, to be as an observational and retrospective study, the results were subject to documentation biases and missing data Third, We also had no access to and did not follow up transfer patients, thereby have no idea of their LOS. Fourth, we did not mention the other factor such as patient's co-morbidities and surgery condition that may influence LOS, due to incomplete medical records.

In summary, this research suggests that provider's characteristics — physician's practice both in private sector and public teaching hospital, discharge process guidelines, and admission protocols- were substantial predictors of length of stay. Patient non clinical characteristics such as gender, occupation, type of insurance and marital status did not play an important role in hospital stay except hospitalization history — those with no hospitalization history stayed for longer period. Furthermore the data from this study may be useful to administrators and physicians who are involved in the management of health programmers and hospital budget, to encourage shorter length of stay to reduce costs. Further research is needed to assess its impact on patient outcomes.

Conclusion

The factors that were significantly associated with length of stay were largely due to institutional characteristics — physicians practice both in private sector and public teaching hospital, physicians' level of education (specialist, subspecialist), discharge process guidelines, and admission protocols. The patient's hospitalization history was also a predictor (those with no hospitalization history stayed longer). The shorter length of stay seemed to be possible by administrative interventions to normalize the potential institutional predictors.

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SUCCESSFUL TREATMENT OF A PARAHISIAN WOLFF-PARKINSON-WHITE CASE WITH CRYOABLATION

Cenk Conkbayir, Kamil Gulsen

A 27-year-old patient with Parahisian Wolff-Parkinson-White Syndrome (WPW), who had very frequent tachycardia attacks and pre-syncope complaints, could not be cured with the RF ablation method previously. Since RF ablation may necessitate a permanent cardiac pacemaker, cryoablation was decided to be performed in another session. Herein, we report a successful treatment of a WPW case via cryoablation.

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Key words: Parahisian Wolff-Parkinson-White Syndrome, treatment, cryoablation.

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WPW — Wolff-Parkinson-White Syndrome.

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УСПЕШНОЕ ЛЕЧЕНИЕ СЛУЧАЯ ПАРАГИСИАЛЬНОГО СИНДРОМА ВОЛЬФА-ПАРКИНСОНА-УАЙТА КРИОДЕСТРУКЦИЕЙ

Cenk Conkbayir, Kamil Gulsen

27-летний пациент с парагисиальным синдромом Вольфа-Паркинсона-Уайта (WPW), у которого были очень частые приступы тахикардии и пресинкопе, ранее не мог быть вылечен методом радиочастотной аблации. Поскольку радиочастотная аблация может вызвать необходимость постоянной кардиостимуляции, было решено в этот раз выполнить криодеструкцию. В данном сообщении мы говорим об успешном лечении WPW с помощью криодеструкции.

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Ключевые слова: парагисиальный синдром Вольфа-Паркинсона-Уайта, лечение, криодеструкции.

Introduction

The recent developments in ablation treatment have revealed the possibility of transmitting the cryoenergy by the guidance of a catheter [1]. The first percutaneous cryoablation procedure was performed in 1999, and the cumulative results were reported in 2001 [2]. In 2003, FDA (Food and Drug Administration) approved the use of the cryoablation method, and subsequently the studies concerning the issue have gained acceleration. Cryoablation is also used in AVNRT cases with parahisian localization, where the RF ablation method has failed to succeed. Occasionally, when there is a close proximity to his bundle in patients with WPW syndrome where RF ablation is risky, cryoablation is used in order to prevent a possible cardiac pacemaker-dependence. Herein, we have reported the successful treatment of a case of parahisian wolff-parkinson-white with cryoablation.

Case Report

A 27-year-old male patient presented to our clinics due to frequent tachycardia attacks. Following the ECG (Fig. 1) monitoring and clinical evaluation, electrophysiological examination was planned due to suspicion of Wolff-Parkinson-White syndrome. The patient was taken into the electrophysiology laboratory after he had signed the informed consent. Diagnostic catheters were placed into superior right atrium, apex of the right ventricle, His bundle region and the coronary sinus. Following the electrophysiological study, a radiofrequency ablation procedure was planned. The site of ablation was decided according to the fluoroscopic and intracardiac activation mapping. Radiofrequency energy was applied onto the region adjacent to the His bundle. Meanwhile, it was observed that the temperature was as high as 51 °C. Despite the radiofrequency ablation procedure, the short PR and the delta wave of the patient did not disappear. Cryoablation was planned in another session due to the close proximity to his bundle, where there was a risk of permanent cardiac pacemaker installation. Following the arrangements, the patient was taken into the electrophysiology laboratory in another session, and a quadripolar electrophysiology catheter was placed through the right femoral vein into the superior right atrium, coronary sinus and his bundle. Following the mapping with a cryoablation catheter at –30 °C

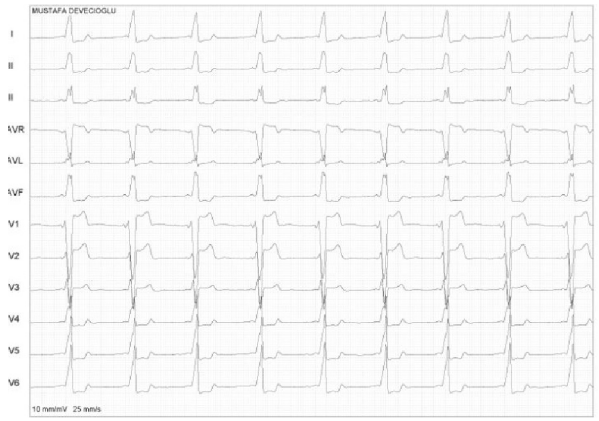

Figure 1. The ECG of a Parahisian Wolff-Parkinson-White case with 12 derivations (very short PR and intertwined delta waves).

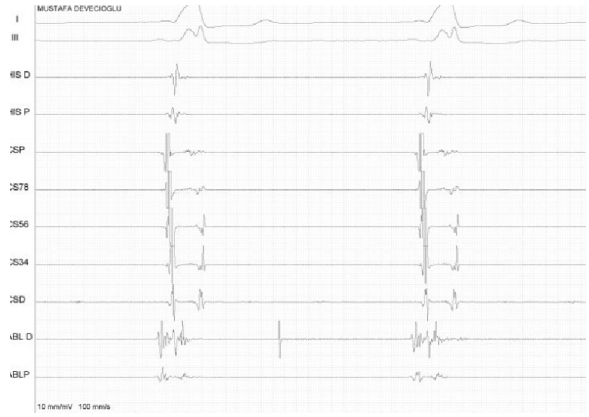

Figure 2. Parahisian-located accessory pathway during mapping with ablation catheter.

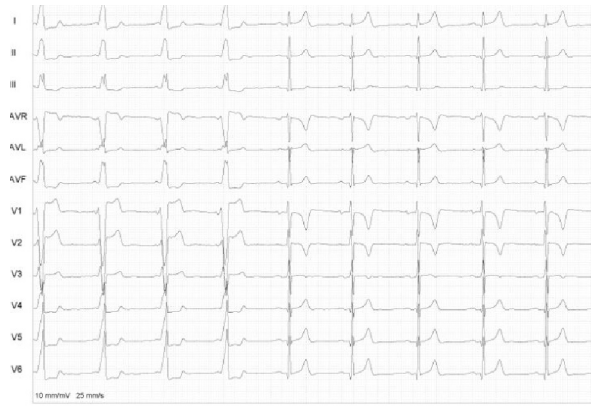

Figure 3. The successful disappearance of the delta wave and extension of the PR interval during cryoablation at –80 °C (ECG with 12 derivations).

(Fig. 2), cryoablations of 300 seconds at –80 °C were performed 3 times to the accessory pathway with close proximity to the his bundle. The accessory pathway was observed to be ablated. The delta waves in the ECG disappeared and the QRS interval was shortened (Fig. 3). The patient, who was seen to have no problems on the follow-up, was discharged and asked to return for a later control.

Conclusion

The theory of generating transmural heart lesions via cryoenergy was first attempted by Hass and Taylor [2] in 1948. Later, Lister and Hoffman [3] defined the generation of a reversible transmission block in the atrio-ventricular node, which is now known as cryo-mapping. Although there is no difference between the depths of the lesions generated by both the radiofrequency ablation and cryoablation, it has been claimed that the damage in regions where cryoablation was performed were to a lower extent with an intact tissue structure [4, 5]. In this case report, we have suggested that the cryoablation treatment can safely be used in Wolff-Parkinson-White cases with an accessory pathway of parahisian localization, where radiofrequency ablation is risky.

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CORONARY ARTERY VASOSPASM SECONDARY TO TYPE I VARIANT KOUNIS SYNDROME: A CASE SERIES OF MEN. IS THE GENDER DIFFERENCES IMPORTANT?

Cuneyt Kocas[1], Ahmet Cagri Aykan[2], Okay Abaci[1], Gokhan Cetinkal[1], Sukru Arslan[1], Mustafa Yildiz[1]

Kounis syndrome is a well-known cause of acute coronary syndrome and more than 100 cases are reported with allergic reactions to various drugs, animal and insect bites, even with drug eluting stents and endovascular devices. In this paper we report five-patients with Kounis syndrome related to different drugs. The main characteristic of patients is given in Table 1. All of them were male and their age was from 18 to 35. All patients presented with ST- elevation myocardial infarction. Coronary angiography was performed in all patients and revealed normal coronary arteries. From history of allergic exposure, electrocardiographic, laboratory (Total IgE and tryptase levels) and angiographic findings the diagnosis was Kounis syndrome type I for all patients and was treated with oral antihistamines and prednisolone. Despite Type 1 KS is not associated with atherosclerotic risk factors and CAD all patients in or report and many patients in literature are male. Gender differences in KS should be investigated in further studies.

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Key words: Kounis syndrome, gender.

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ВАЗОСПАЗМ КОРОНАРНЫХ АРТЕРИЙ СРЕДНЕГО ТИПА I ВАРИАНТ KOUNIS СИНДРОМА: СЕРИЯ СЛУЧАЕВ У МУЖЧИН. ВАЖНЫ ЛИ ГЕНДЕРНЫЕ РАЗЛИЧИЯ?

Cuneyt Kocas[1], Ahmet Cagri Aykan[2], Okay Abaci[1], Gokhan Cetinkal[1], Sukru Arslan[1], Mustafa Yildiz[1]

Kounis-синдром является известной причиной острого коронарного синдрома и сообщается о более 100 случаях заболевания при аллергических реакциях на различные препараты, укусы животных и насекомых, даже на стенты с лекарственным покрытием и эндоваскулярные устройства. В этой статье мы докладываем о пяти пациентах с синдром Kounis, по отношению к различным лекарствам. Главная характеристика больных приведена в Таблице 1. Все они были мужчинами, и их возраст от 18 до 35 лет. У всех пациентов представлен инфаркт миокарда с подъемом ST. Коронарная ангиография выявила у всех больных нормальные коронарные артерии. Из истории аллергического воздействия, электрокардиографических, лабораторных (Общий IgE и уровни триптазы) и ангиографических данных, был поставлен диагноз синдрома Kounis типа I для всех пациентов, которых лечили перорально антигистаминными препаратами и преднизолоном. Несмотря на то, что синдром Kounis типа I не связан с факторами риска атеросклероза и ИБС, все пациенты в отчетах, и многие пациенты, описанные в литературе, являются мужчинами. Гендерные различия синдрома Kounis должны быть изучены в ходе дальнейших исследований.

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Ключевые слова: Kounis синдром, пол.

Introduction

The first paper in the literature, examining the acute myocardial infarction (MI) related to prolonged allergic reaction was published in 1950 [1]. But the definition of Kounis syndrome (allergic angina) was in 1991 as ‘‘the coincidental occurrence of chest pain and allergic reactions accompanied by clinical and laboratory findings of classic angina pectoris caused by inflammatory mediators released during the allergic insult’’ [2]. In 1996 “allergic myocardial infarction” term was defined in literature [3]. As today, Kounis syndrome is a well-known cause of acute coronary syndrome and more than 100 cases are reported with allergic reactions to various drugs (antibiotics, analgesics, antineoplastics, contrast media, intravenous anaesthetics, no steroidal anti-inflammatory drugs, anticoagulants, proton pump inhibitors), animal and insect bites, even with drug eluting stents and endovascular devices [4, 5].

Case Descriptions

In this paper we report five-patients with Kounis syndrome related to different drugs. The main characteristic of patients is given in Table 1. All of them were male and their age was from 18 to 35. Main symptom was chest pain in all patients whereas dyspnoea was present in case 1 and pruritus was also accompanied in case 2. All patients presented with ST- elevation myocardial infarction, case 1,3 and 5 with anterior MI, case 2 inferior MI and case 4 with inferolateral MI. Troponin levels were increased in all patients, total immunoglobulin E (IgE) levels were also increased in all of them, tryptase level could be measured in two cases (Case 2 and 5) and elevated. Whole blood count, D-dimer, antithrombin III, serum cholesterol levels, C3 and C4 levels and antinuclear antibody, anti-DNA tests were within normal limits. The reasons of Kounis syndrome were metimazol sodium in case 1, gadopentetic acid in case 2, amoxicillin/clavulanic acid in case 3 and case 5, acetaminophen in case 4. The medical history for bronchial asthma, any allergic disease or coronary artery disease was negative. The serologic tests for viral aetiology were also negative. Coronary angiography was performed in all patients and revealed normal coronary arteries. From history of allergic exposure, electrocardiographic, laboratory (Total IgE and tryptase levels) and angiographic findings the diagnosis was Kounis syndrome type I for all patients and was treated with oral antihistamines and prednisolone. All symptoms electrocardiographic and echocardiographic findings were resolved by the time of discharge.

Table 1

The characteristics of patients with Kounis syndrome

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age, years	33	35	31	24	18
Sex	M	M	M	M	M
Atopy	No	No	No	No	No
CVRF	No	No	No	No	No
Symptoms	Dyspnoea, chest pain	Pruritis, chest pain	Chest pain	Chest pain	Chest pain
Allergic cause	Metamizol 500 mg	Gadopentetic acid 20 ml	Amoxicillin/ Clavulanic acid 1000 mg	Acetaminophen 500 mg	Amoxicillin Clavulanic acid 1000 mg
ST segment elevation	Anterior	Inferior	Anterior	Inferolateral	Anterior
Trop I (ng/ml)	40	13	15	46	50
Total IgE (0–100 IU/ml)	190	117	120	202	350
Tryptase (5.6–13.5 µg/L)	-	20	-	-	45
CAG	Normal	Normal	Normal	Normal	Normal

Abbreviations: CVRF — cardiovascular risk factors, Trop I — troponine I, CAG — coronary angiography.

Discussion

Kounis syndrome was defined as an acute coronary syndrome that manifests as unstable vasospastic or nonvasospastic angina, and even as acute myocardial infarction triggered by inflammatory mediators following exposure to an allergic insult. There are currently 3 variants of Kounis syndrome [6]. The first variant is observed in patients with no cardiovascular risk factors and normal coronary arteries in whom acute release of inflammatory mediators such as histamine and leukotriens can trigger coronary spasm [7]. In Type-II variant of KS include patients with pre-existing atheromatous disease in whom acute release of these mediators can induce coronary artery spasm or rupture of atheromatous plaque. Recently, Type- III variant of Kounis syndrome has been defined in subjects with drug eluting coronary stent thrombosis [4]. In this variant stent components (nickel strut, polymer or impregnated drug) may play a role as allergic insult [8]. All of our patients were Type 1 Kounis syndrome. Several pathophysiologic mechanisms have been described to explain the association between an allergic reaction and acute coronary syndrome [6]. Mast cell degranulation follows after antibody antigen complex or sometimes allergen itself may start degranulation. After mast cell degranulation vasoconstricting and collagen degrading mediators such as, histamine, neutral proteases (tryptase, chymase), platelet activating factor and newly synthesized mediators are released locally and in the peripheral circulation [9]. These mediators appear to affect the myocardium directly. Histamine, through its H1 receptors, mediates coronary artery vasoconstriction, and increases vascular permeability, whereas activation of H2 receptors causes inotropic, chronotropic effects [10, 11]. Histamine can also activate platelets and potentiates aggregatory response. Tryptase level was elevated in two patients but not applicable in other patients. Total IgE levels were increased in all patients and this result may be the reflector of an allergic reaction. All patients in our report are male. CAD frequency is higher in male compared to female but Type 1 KS is not associated with atherosclerosis and defined as KS with normal coronary arteries. Although previous reports have shown mortality or malignant course of Kounis syndrome [4], our patients had an uneventful in-hospital course.

Conclusion

Although the exact pathophysiologic mechanism of Kounis syndrome is not clear, the increasing number of reports published in the last few year's points that this syndrome should be kept in mind for consideration in the differential diagnosis of ischemic heart disease especially in young patients without cardiac risk factors and concomitant allergic symptoms. Gender differences in KS should be investigated in further studies.

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RARE CORONARY ANOMALY ASSOCIATED WITH MASSIVE ACUTE MYOCARDIAL INFARCTION

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Key words: anomalous, coronary, artery, infarction.

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РЕДКИЙ СЛУЧАЙ АНОМАЛИИ КОРОНАРНОЙ АРТЕРИИ, В СОЧЕТАНИИ С МАССИВНЫМ ОСТРЫМ ИНФАРКТОМ МИОКАРДА

Michael Patrick Flaherty[1], Todd Dorfman[2], Jon Resar[2]

Российский кардиологический журнал 2014, 4 (108), Англ.: 68–69

Ключевые слова: аномальный, коронарный, артерия, инфаркт.

Indeed, considerable variability exists in the anatomy of the left coronary artery, yet, the scientific record lists only roughly five cases of an anomalous PDA originating from the LAD [1] and ours is the second report of a PDA originating from the LAD whereby the LAD continues as the PDA across the left ventricular apex and into the posterior inferior interventricular groove with a non-dominant RCA [2]. Here we describe two cases of two separate patients presenting with disparate clinical syndromes both of which possess this extremely rare coronary anomaly.

CASE 1: A 68 year old man was referred for coronary angiography secondary to development of putative cardiogenic pulmonary edema. Coronary angiography revealed an especially unique variant (Figure 1). The patient was diagnosed with stage II diastolic dysfunction. He was treated for heart failure with preserved systolic function and discharged to home on a diuretic and a beta blocker.

CASE 2: A 51 year old male presented to the emergency department of a community hospital 1 hour following acute onset of severe substernal chest pressure, nausea and vomiting. He received thrombolytics and was transferred to our tertiary care institution. Figure 2A illustrates his electrocardiogram (ECG). The Flaherty, MP: "Anomalous PDA arising from the LAD" coronary angiogram during rescue PCI is shown in Figure 3. Stenting of the proximal LAD was performed. Echocardiography following percutaneous coronary intervention revealed severely reduced left ventricular systolic function with an EF of

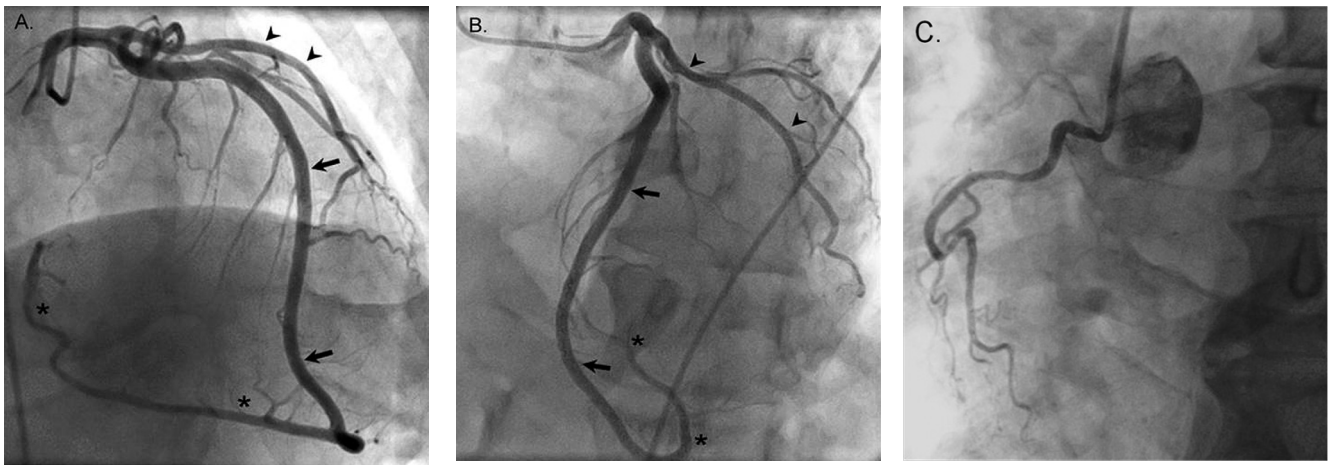

Figure 1. RAO and an LAO cranial views of the LCA **(A and B)** and an LAO view of the RCA **(C):** (i) the LCx is depicted by arrowheads and the LAD by arrows; (ii) note that the LAD wraps around the apex and gives rise to an anomalous large posterior descending artery (asterisk) that courses within the posterior inferior interventricular groove and gives rise to septal perforating branches before terminating at the level of the posterior atrioventricular groove; (iii) a small non-dominant right coronary artery originates from the right coronary cusp.

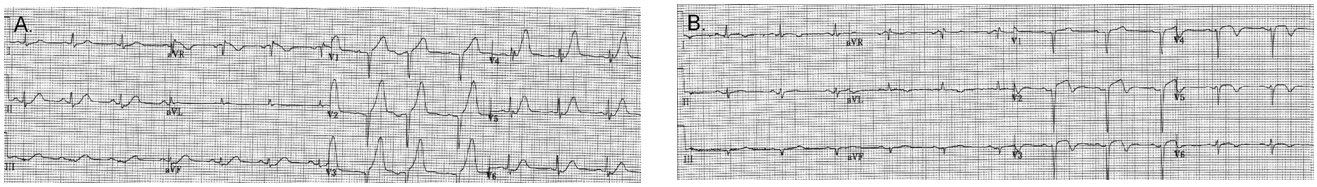

Figure 2. Electrocardiogram following thrombolytics **(A)** shows marked ST-segment elevation in leads V2-V3 with hyperacute T-wave in V4-V6 and greater than 1 mm of ST-segment depression in the inferior limb leads. A repeat electrocardiogram approximately 6 hours after PCI **(B)** reveals less ST-segment elevation in the anterior leads with biphasic T-waves and the new q-waves in the inferior leads.

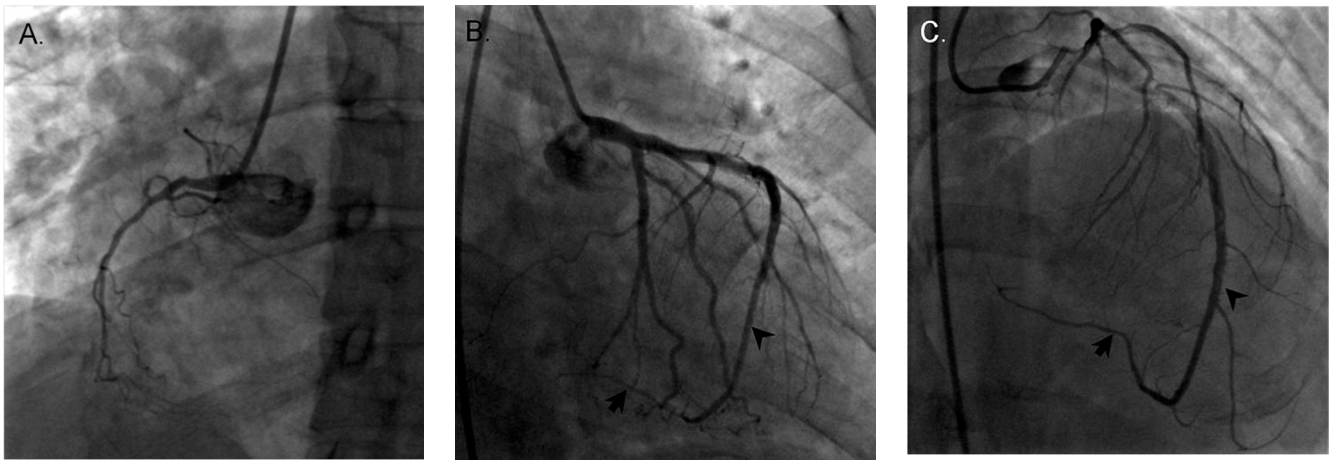

Figure 3. LAO view of the RCA **(A)** and RAO caudal **(B)** and cranial **(C)** views of the LCA: (i) a small non-dominant right coronary artery originates from the right coronary ostium; (ii) a large caliber LAD (arrowheads) is seen with a proximal filling defect consistent with thrombus and an underlying severe stenosis; (iii) note that TIMI II distal flow within the LAD distally shows the LAD wrapping around the apex (similar to Figure 1) giving rise to an anomalous large posterior Flaherty, MP: "Anomalous PDA arising from the LAD" descending artery (arrows) that courses within the posterior inferior interventricular groove and gives rise to septal perforating branches before terminating at the level of the posterior atrioventricular groove.

25–30% and akinesis of the distal anterior, apical, posterior and inferior walls and associated apical aneurysm; subsequent ECG also shows evidence of apical aneurysm and transmural anterolateral, apical and inferior wall infarctions (Figure 2B).

Discussion

Anomalous coronary anatomy occurs in 1% of the population, 60% of which involve either separate LAD and left *circumflex ostia* or the left circumflex artery originating from the right sinus or the proximal right coronary artery [3]. While considerable variability exists, the incidence of our especially unique variant is unknown [3], albeit rare, as only five cases of our anomaly exist in the literature [1, 2, 4, 5]. Regardless, the literature depicts an anomalous PDA arising from the distal LAD as a relatively benign entity. To our knowledge, this is the first reported case of a patient presenting with a massive left ventricular acute myocardial infarction as a result of this anomaly. Here, we hope to underscore the dire pathologic consequences owing to this particular anomaly should acute coronary thrombosis occur.

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CLINICAL GUIDELINES

2013 ESH/ESC GUIDELINES FOR THE MANAGEMENT OF ARTERIAL HYPERTENSION

The Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC).

Russ J Cardiol 2014, 1 (105): 7-94

NATIONAL RUSSIAN GUIDELINES ON APPLICATION OF THE METHODS OF HOLTER MONITORING IN CLINICAL PRACTICE

The joint working group for the management of guidelines of the Russian society of cardiology, Russian society for Holter monitoring and noninvasive electrophysiology, Russian Association of specialists in functional diagnosis, all-Russian scientific society of specialists on clinical electrophysiology, arrhythmology and pacing, Society of specialists in heart failure.

Russ J Cardiol 2014, 2 (106): 6-71

ESC GUIDELINES ON DIABETES, PRE-DIABETES, AND CARDIOVASCULAR DISEASES DEVELOPED IN COLLABORATION WITH THE EASD

The Task Force on diabetes, pre-diabetes, and cardiovascular diseases of the European Society of Cardiology (ESC) and developed in collaboration with the European Association for the Study of Diabetes (EASD).

Russ J Cardiol 2014, 3 (107): 7-61

EDITORIAL

METABOLIC SYNDROME: CHALLENGING AND UNRESOLVED ISSUES

Chumakova G. A.[1,2], Veselovskaya N. G.[1,3], Gritsenko O. V.[1,2], Ott A. V.[3]

Abstract

The paper focuses on the contradictory issues related to metabolic syndrome (MS), its criteria, and real-world prognostic value. Different types of obesity, which result from a variety of combinations of general and visceral obesity, are described. The authors emphasise the need for two separate definitions of MS (a wider one and a more specific one), which are characterised by different pathogenetic mechanisms and require different therapeutic approaches. The more specific MS definition could benefit from the inclusion of such criteria as fatty liver and polycystic ovary syndrome. More detailed definitions for the multiple risk factor cluster syndrome, as an alternative to the current MS definition, are proposed for further discussion.

Russ J Cardiol 2014, 3 (107): 63-71

Key words: metabolic syndrome, risk factor cluster, visceral obesity.

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ORIGINAL ARTICLES

VASCULAR AND CARDIAC REMODELLING AND COMBINATION THERAPY OF ARTERIAL HYPERTENSION IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Shpagina L. A.[1], Shpagin I. S .[1], Pospelova T. I.[1], Gerasimenko O. N.[1,2], Sukhaterina N. A.[1,2], Alicheva Ya.M.[1,2]

Abstract

Aim. To assess cardiac and vascular structure and function, blood flow parameters, endothelial dysfunction, and cytokine status in patients with arterial hypertension (AH) and chronic obstructive pulmonary disease (COPD), who were administered combination Co-renitec therapy.

Material and methods. The study included 37 patients with AH and COPD, who underwent laboratory, functional, and ultrasound examination.

Results. During the 6-month combination Co-renitec therapy, the parameters of clinical status, circadian blood pressure profile, and endothelial, vascular, and cardiac structure and function were assessed in patients with AH and COPD.
Conclusion. The combination Co-renitec therapy was associated with normalised blood pressure levels, improved clinical and hemodynamic status, cardiac and vascular structure and function, and blood flow and microcirculation, as well as with reduced levels of the markers of endothelial dysfunction and systemic inflammation.

Russ J Cardiol 2014, 1 (105): 95-100

Key words: arterial hypertension, chronic obstructive pulmonary disease, cardiac and vascular remodelling, endothelial dysfunction, systemic inflammation, therapy effectiveness.

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NEW APPROACH TOWARDS THE INTEGRAL ASSESSMENT OF CARDIOVASCULAR STATUS IN PATIENTS WITH ARTERIAL HYPERTENSION

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Abstract
Aim. To assess the potential of the integral assessment of cardiovascular system status in patients with arterial hypertension (AH), based on the evaluation of the parameters of microcirculation (non-invasive digital capillaroscopy) and macrocirculation (pulse wave velocity (PWV) and endothelial function).
Material and methods. The study included 188 people aged 40 years and older: 32 patients with systolic blood pressure (BP) levels 120–139 mm Hg ("PreAH" group), 36 patients with Stage 1–2 AH ("AH" group), and 85 AH patients who achieved target BP levels due to antihypertensive therapy ("Treated AH" group). The control group included 35 healthy volunteers, without any signs or symptoms of cardiovascular disease ("Healthy" group). All participants underwent clinical and laboratory examination, including office BP measurement, 24-hour BP monitoring, and echocardiography, the assessment of nailfold microcirculation, pulse wave velocity, endothelial function, as well as the measurement of BP and heart rate.
Results. There was an increase in remodelling coefficient (Cv/a) in the groups "PreAH", "AH", and "Treated AH", compared to the "Healthy" group. PWV levels were significantly higher in "PreAH" and "Treated AH" groups than in the "Healthy" group. Based on micro- and macrocirculation parameters assessed, the integral index of cardiovascular status was calculated. The values of this index were significantly higher in the "AH" group. Effective antihypertensive treatment was associated with a reduction in these values.
Conclusion. Based on the assessment of a range of micro- and macrocirculation parameters in AH patients, the integral index of cardiovascular status had been developed. This index satisfactorily reflects the dynamics of micro- and macrocirculation in treated AH and, therefore, can be used as an indicator of effective antihypertensive therapy. The complex assessment of macro- and microcirculation provides an opportunity for early AH detection.

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Key words: capillaroscopy, pulse wave velocity, endothelial function, integral index, prehypertension, arterial hypertension.

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CARDIAC MAGNETIC RESONANCE IMAGING AND POSITRON EMISSION TOMOGRAPHY IN THE PREDICTION OF LEFT VENTRICULAR DYSFUNCTION REVERSIBILITY IN PATIENTS WITH CHRONIC TOTALLY OCCLUDED CORONARY ARTERIES

Ryzhkova D. V.[1], Kostina I. S.[1,2]

Abstract
Aim. To compare the prognostic value of cardiac positron emission tomography (PET) and contrast-enhanced magnetic resonance imaging (ceMRI) for the prediction of reversibility of regional left ventricular (LV) dysfunction after endovascular recanalization of chronic totally occluded (CTO) coronary arteries (CA).
Material and methods. The study included 26 patients with chronic coronary heart disease and angiographically confirmed CTO CA. All participants underwent cardiac ceMRI and PET with ^{13}N-ammonia and ^{18}F-fluorodeoxyglucose (18F-FDG). Successful CTO CA recanalization was achieved in 20 patients. The standard for prognostic value assessment was the improvement of regional LV contractility at the control ceMRI.
Results. The values of scar tissue extension and scar tissue volume were significantly higher in the segments with irreversible dysfunction, compared to the respective values for viable myocardium (73,0±37% vs. 20,4±33,7% ($p<0,0001$) and 54,1±33,4% vs. 9,8±16,2% ($p<0,0001$), respectively). An opposite tendency was observed for the 18F-FDG uptake (51,8±17% vs. 67±11,6% ($p<0,001$)). The ROC analysis demonstrated that the maximal cut-off values of scar tissue extension and scar tissue volume, assessed by ceMRI (≤50% and ≤37,5%, respectively), predicted the improvement in the regional LV contractility with sensitivity, specificity, and accuracy of 80,2%, 78%,

79,6%, and 92,7%, 73,2%, and 86,9%, respectively. The minimal cut-off value of ≥56,4% for the ^{18}F-FDG uptake and the patterns of perfusion-metabolism match/mismatch provided sensitivity of 81,1% vs. 91%, specificity of 67,5% vs. 65,5%, and accuracy of 75,2% vs. 83,3%, respectively.
Conclusion. Compared to cardiac PET, ceMRI has superior prognostic value and accuracy in the prediction of reversibility of the regional LV dysfunction after endovascular revascularization of CTO CA. In patients with ceMRI contraindications, a complex PET assessment of myocardial perfusion and metabolism is recommended. PET with ^{18}F-FDG only is less effective in the prediction of the LV dysfunction reversibility, but can still detect the presence of viable cardiomyocytes in the severely affected myocardial segments.

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Key words: myocardial viability, cardiac magnetic resonance imaging, positron emission tomography, chronic total occlusion, left ventricular dysfunction.

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TISSUE DOPPLEROGRAPHY AND THE ASSESSMENT OF RIGHT HEART STRUCTURE AND FUNCTION IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Bart B. Ya.[1], Kulbachinskaya O. M.[2], Dergunova E. N.[2], Vartanyan E. A.[1]

Abstract
Aim. To assess the status of right heart structure and function in patients with mild chronic obstructive pulmonary disease (COPD).
Material and methods. The study included 56 COPD patients and 26 healthy volunteers. All participants underwent lung function assessment and echocardiography.
Results. Based on the analysis of the Doppler spectrum of transtricuspid flow, the signs of disturbed right ventricular (RV) relaxation were identified. A reduction in the total RV output was detected, based on the assessment of tricuspid annular amplitude and velocity.
Conclusion. In patients with mild COPD but without increased pulmonary vascular resistance or precapillary pulmonary hypertension, a silent global longitudinal (systolo-diastolic) RV dysfunction could be detected by tissue dopplerography.

Russ J Cardiol 2014, 2 (106): 79-83

Key words: COPD, echocardiography, right ventricular function.

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HEART-TYPE FATTY ACID BINDING PROTEIN-BASED EXPRESS TEST IN THE DIAGNOSTICS OF ACUTE MYOCARDIAL INFARCTION

Ryabov V. V., Kirgizova M. A., Markov V. A.

Abstract
Aim. To compare the effectiveness of two express tests — CardioFABP and Troponin I WB-Check-1 in the diagnostics of acute myocardial infarction (AMI).
Material and methods. The study included 38 patients who were hospitalised with the acute coronary syndrome (ACS) diagnosis within the first 12 hours after the pain onset. At the admission, the peripheral blood levels of CK-MB and troponin I were qualitatively assessed using the immunochemiluminescent analyser “Access-2” (Beckman Coulter, USA). In addition, the express test Troponin I WB-Check-1 (VEDALAB, France; sensitivity 1 ng/ml) was used. Qualitative assessment of hearttype fatty acid binding protein (hFABP) was performed with the express test “CardioFABP” (Biotest, Russia; sensitivity 15 ng/ml). For all tests, diagnostic sensitivity, diagnostic specificity, positive and negative predictive value, and diagnostic effectiveness were assessed.
Results. The express tests for hFABP and troponin I demonstrated high positive predictive value and diagnostic specificity (100%). However, both tests also had false negative results, and, therefore, negative predictive value was low for both the hFABP test (23,5%) and the troponin I test (17,4%). Diagnostic sensitivity was 35,4% for the troponin I express test and 57,6% for the hFABP express test. Diagnostic effectiveness was higher for the hFABP express test (62,2%). All positive results of the hFABP express test were confirmed by the other tests, which resulted in high positive predictive value (100%) and high diagnostic specificity (100%). In patients within the first 6 hours of ACS, diagnostic sensitivity of the hFABP express test was significantly higher than in those with a longer ACS duration (83,3% vs. 42,8%, respectively).
Conclusion. The higher diagnostic sensitivity and diagnostic effectiveness of the hFABP-based express test in the first 6 hours of ACS, compared to a qualitative assessment of troponin I and a later assessment of hFABP, agrees with the earlier obtained data and confirms the status of hFABP as the earliest marker of myocardial necrosis.

Russ J Cardiol 2014, 2 (106): 84-88

Key words: fatty acid binding protein, acute myocardial infarction, troponin I.

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INTERACTION BETWEEN SYMPATHO-ADRENAL ACTIVITY AND IMMUNE MEDIATORS IN PATIENTS WITH METABOLIC SYNDROME

Uzbekova N. R., Khuzhamberdiev M. A., Tashtemirova I. M.

Abstract

Aim. To investigate the interactions between the functional status of sympathoadrenal system and immune meditators in patients with metabolic syndrome (MS).

Material and methods. In total, 55 patients (age 35–57 years, mean age 46,7±2,1 years) were examined, including 30 individuals with MS. In all participants, the following parameters were assessed: carbohydrate metabolism parameters (fasting glucose and insulin), lipid metabolism parameters (total cholesterol (TCH), triglycerides, high-density lipoprotein CH (HDL–CH), and low-density lipoprotein CH (LDL–CH)), 24-hour urine excretion of free and conjugated catecholamines (CA), monoamine oxidase (MAO) activity, and cytokine status (interleukin-6 (IL-6), IL-10, and tumor necrosis factor α (TNF-α).

Results. MS patients demonstrated a significant increase in all CA fractions, particularly noradrenaline (NA). The total NA levels were elevated, compared both to the levels of other bioactive amines and to the respective levels among controls and hypertensive patients. There was a positive correlation between 24-hour NA excretion and glycemic index ($r=0,67$, $p<0,01$), as well as between NA levels and body mass index (BMI) values ($r=0,65$, $p<0,01$). Moreover, there was a positive correlation between 24-hour NA excretion and blood pressure (BP) levels ($r=0,62$, $p<0,01$). The elevated 24-hour CA excretion was accompanied by a significant reduction in MAO levels across all study groups. There was a negative correlation between MAO and 24-hour NA excretion in MS patients ($r= -0,68$, $p<0,01$). These patients also had elevated levels of IL-6 and TNF-α. There was a positive correlation between IL-6 levels and the following parameters: elevated BP ($r=0,67$, $p<0,01$), BMI ($r=0,59$, $p<0,01$), TNF-α levels ($r=0,53$, $p<0,01$), and increased 24-hour NA excretion ($r=0,65$, $p<0,01$).

Conclusion: Increased sympatho-adrenal activity disturbs humoral immune response, which is an important pathogenetic marker of MS progression. This emphasises the need for pathogenetically sound strategy of pharmacological treatment for these patients.

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Key words: sympatho-adrenal system, proinflammatory cytokines, metabolic syndrome.

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EPICARDIAL ADIPOSE TISSUE THICKNESS — AN ALTERNATIVE TO WAIST CIRCUMFERENCE AS A STAND-ALONE OR SECONDARY MAIN CRITERION IN METABOLIC SYNDROME DIAGNOSTICS?

Druzhilov M. A.[1], Beteleva Yu.E.[1], Kuznetsova T. Yu.[2]

Abstract

Aim. To assess the potential of echocardiographically assessed epicardial adipose tissue (EAT) thickness as a predictor of high cardiovascular risk (CVR) and subclinical target organ damage (STOD) in patients with abdominal obesity (AO).

Material and methods. In 132 normotensive AO patients (mean age 45,0±5,3 years), the following parameters were assessed: lipid and carbohydrate profile, glomerular filtration rate, microalbuminuria, and CVR levels by the SCORE scale. Triplex ultrasound of brachiocephalic arteries, echocardiography, bifunctional 24-hour blood pressure monitoring and arterial stiffness assessment were also performed.

Results. Mean levels of EAT thickness were significantly different across age groups (4,2±1,0 mm in those aged 31–45 years vs. 5,1±1,1 mm in those aged 46–55 years; $p<0,001$). Metabolic syndrome (MS) was diagnosed in 74 (56,1%) patients, based on the presence of AO and 2 additional criteria. In this group, the prevalence of STOD was relatively low. The combination of AO and EAT thickness ≥75% percentile for each age group (4,8 mm for 31–45-year-olds and 5,8 mm for 46–55-year-olds) was regarded as an alternative predictor of high CVR and STOD, observed in 38 (28,8%) patients. These individuals demonstrated a significantly higher prevalence of STOD (microalbuminuria, carotid atherosclerosis, carotid wall hypertrophy, left ventricular hypertrophy, and increased arterial stiffness). The alternative prognostic model was significantly more effective than the conventional one in terms of the identification of individuals with subclinical carotid atherosclerosis.

Conclusion. The alternative model for predicting high CVR and STOD in AO patients, which included the combination of such criteria of visceral obesity as AO and EAT thickness ≥75% percentile for each age group (4,8 mm for those aged 31–45 years and 5,8 mm for those aged 46–55 years), did not perform any worse than the conventional MS model. Of note, the alternative markers of visceral obesity were significantly more prevalent in patients who had both sets of criteria. AO patients with EAT thickness ≥75% percentile require further screening for carotid atherosclerosis.

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Key words: epicardial adipose tissue, metabolic syndrome, cardiovascular risk.

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ALTERNATIVE METHOD OF VISCERAL OBESITY ASSESSMENT IN THE DIAGNOSTICS OF METABOLIC SYNDROME

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Abstract
At present, the existing main and additional criteria of metabolic syndrome (MS) lack a clear justification, which warrants further research.
Aim. To assess the potential of waist circumference (WC) and epicardial adipose tissue (EAT) thickness as alternative main criteria of MS.
Material and methods. In order to compare the specific features of MS diagnosed by different criteria of visceral obesity (WC and EAT thickness), 186 male patients with general obesity were divided into two groups: MS by the EAT thickness-based criteria and MS diagnosed by the WC-based criteria. In all participants, main and additional metabolic risk factors were assessed. Systolic EAT thickness (mm) was measured at the B-mode echocardiography, in the parasternal long-axis view, behind the free right ventricular wall.
Results. In patients with MS by the EAT thickness-based criteria (EAT thickness ≥7 mm), the levels of insulin (11,2 μIU/ml; 95% confidence interval (CI) 5,2–19,9 μIU/ml), HOMA-IR index (2,6; 95% CI 1,1–4,6), resistin (12,8 ng/ml; 95% CI 8,1–16,7 ng/ml), and interleukin-6 (12,4 pg/ml; 95% CI 7,6–15,0 pg/ml) were higher than those levels in patients with MS by the WC-based criteria (WC ≥94 cm): 6,9 (3,5–14,2) μIU/ml (p=0,040); 1,8 (0,9–3,4) (p=0,041); 10,8 (6,6–16,1) ng/ml (p=0,044); and 9,8 (4,8–13,6) pg/ml (p=0,044), respectively.
Conclusion. Our results have demonstrated that the EAT thickness ≥7 mm is a more accurate non-invasive marker of insulin resistance and visceral obesity-related neurohumoral and proinflammatory disturbances, compared to the traditional WC criterion (≥94 cm in men). In our opinion, the EAT thickness ≥7 mm could be used as a clarifying criterion of visceral obesity in MS.

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Key words: epicardial adipose tissue thickness, waist circumference, metabolic syndrome.

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CLINICAL AND BIOCHEMICAL PREDICTORS OF DIABETES MELLITUS MANIFESTATION AFTER MYOCARDIAL INFARCTION

Barbarash O. L.[1,2], Gruzdeva O. V.[1], Akbasheva O. E.[3], Palicheva E. I.[1,2], Uchasova E. G.[1], Karetnikova V. N.[1,2], Fedorova T. S.[3]

Abstract
Aim. To identify the most informative parameters of carbohydrate and lipid metabolism which predict the manifestation of type 2 diabetes mellitus (DM-2) within one year after myocardial infarction (MI).
Material and methods. The study included 200 MI patients who underwent the assessment of glucose and insulin levels, insulin resistance (IR) index, and lipid profile at Days 1 and 12. The incidence of new DM-2 cases which manifested within a year after MI was assessed.
Results. After one year after MI, incident DM-2 was diagnosed in 14,5% of the patients. It was associated with concomitant cardiovascular risk factors, adverse clinical course of acute and longer-term MI periods, and lipid metabolism disturbances. A higher risk of incident DM-2 after MI was linked to IR and an elevation in free fatty acid (FFA) levels (9,5 times or higher) during the acute MI phase.
Conclusion. Important risk factors of incident DM-2 which manifested within a year after MI were IR (hyperglycemia and hyperinsulinemia) and elevated FFA concentration during the in-hospital MI period. FFA could be a promising marker for DM-2 risk stratification among MI patients.

Russ J Cardiol 2014, 3 (107): 87-94

Key words: diabetes mellitus, insulin resistance, myocardial infarction.

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GLYCEMIA CONTROL, INSULIN RESISTANCE, AND FUNCTIONAL ACTIVITY OF T-HELPER SUBPOPULATIONS IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

Kologrivova I. V., Koshelskaya O. A., Suslova T. E., Karpov R. S.

Abstract
Aim. To study the functional activity of T-helper subpopulations (pro-inflammatory T-helpers-17 (Th17) and T-helpers-1 (Th1) and immune-suppressing FoxP3+T-regulators (Treg)) and its association with clinical parameters, glycemic control levels, and insulin resistance severity among patients with arterial hypertension (AH) and Type 2 diabetes mellitus (DM-2).

Material and methods. The study included 35 patients (17 men and 18 women) with Stage 1–2 AH and DM-2, aged 47–63 years. The control group included 24 healthy volunteers, comparable by age and gender. All participants underwent standard clinical examination and assessment of carbohydrate and lipid metabolism parameters. Flow cytometry method was used for the ssessment of Treg levels and activated Th1 and Th17 numbers in the peripheral blood mononuclear cell fraction. Functional status of blood cells was assessed by the secretion levels of interleukin (IL) 1β, IL-2, IL-6, IL-17, IL-10, tumor necrosis factor (TFN) α, and interferon (IFN) γ.
Results. In diabetic patients, there was an increase in activated Th1 numbers and IL-17, IL-6, and TNF-α secretion, combined with a decrease in IL-10 secretion, FoxP3+ Treg numbers, and Treg/Th17 ratio, compared to the control group. In patients with HbA1c >7%, more pronounced abdominal obesity was associated with reduced Treg numbers and Treg/Th17 and Treg/Th1 ratios, as well as with elevated IL-17 secretion, compared to patients with adequate glycemia control. According to the cluster analysis results, DM-2 patients could be divided into two subgroups by the severity of insulin resistance and HOMA index levels. Among patients with higher HOMA levels, more pronounced abdominal obesity, hyperglycemia, and hyperinsulinemia were associated with increased Th1 numbers and pro-inflammatory cytokine (IL-2, IL-1β, and IL-17) secretion, compared to their peers with less severe insulin resistance.
Conclusion. Our results suggest an important association between insulin resistance, inadequate glycemia control, and functional dysbalance of T-helper subpopulations in patients with DM-2.

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Key words: Type 2 diabetes mellitus, T-helpers, insulin resistance, glycemia control.

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METABOLIC PHENOTYPES AND CARDIOVASCULAR RISK IN PATIENTS WITH TYPE 1 DIABETES MELLITUS

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Abstract
Patients with Type 1 diabetes mellitus (DM-1) represent a heterogeneous group with different phenotypes, which might include some individuals with genetic predisposition towards insulin resistance (IR) and metabolic phenotype (MPH) development. At present, the IR effects on cardiovascular risk development in DM-1 patients remain an understudied area.
Aim. To assess the prevalence of cardiometabolic risk factors (RF) and micro- and macrovascular complications by phenotype in patients with DM-1.
Material and methods. The study included 3371 DM-1 patients from the Altay Region Diabetes Register. All participants were divided into two groups, by the waist circumference/hip circumference ratio: those with normal phenotype (NPH) and those with metabolic phenotype (MPH). Overall and separately in two age groups (under 50 and ≥50 years), the prevalence of the following characteristics was assessed: overweight, obesity, arterial hypertension, diabetic retinopathy, diabetic nephropathy, diabetic polyneuropathy, acute myocardial infarction, stroke (S), angina, and lipid metabolism disturbances.
Results. MPH was registered in 46,5% of DM-1 patients. Overall, MPH patients were 7 years older than their NPH peers. The percentage of men was higher among MPH participants. Among DM-1 patients with MPH, the prevalence of all clinical conditions was significantly higher ($p<0,05$), with S as the only exception. The effect of MPH on macroangiopathy development was greater than that for microangiopathy development. MPH participants were characterised by a higher prevalence of hypercholesterolemia and hypertriglyceridemia ($p<0,01$); however, this difference was less obvious in older patients. In the age group of 50 years and older, the strength of the association between MPH and cardiovascular diabetic complications was different from that in younger patients.
Conclusion. In DM-1 patients, MPH is an additional RF of cardiovascular disease development, which should be taken into account while choosing the appropriate therapeutic strategy

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Key words: insulin resistance, metabolic and normal phenotype, macro- and microangiopathy.

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CLINIC AND PHARMACOTHERAPY

AFOBAZOLE EFFECTIVENESS IN THE COMPLEX TREATMENT OF PATIENTS WITH ARTERIAL HYPERTENSION

Chumakova E. A.[2], Gaponova N. I.[1], Berezina T. N.[3]

Abstract
Aim. To study the potential increase in the treatment effectiveness due to accounting for psychological and emotional status features of patients with arterial hypertension (AH).
Material and methods. Psychological status features were assessed in 300 patients with essential AH, aged 35 years and older, who attended the Moscow City Polyclinics No. 9. The main group (n=264) was administered antihypertensive therapy and Afobazole (30 mg/d),

while the control group (n=36) received only antihypertensive therapy. The number of ambulance calls and the regularity of antihypertensive pharmacological therapy over the last 3 years were assessed. The Spielberger-Khanin and Strelau scales were used for the questionnaire-based assessment of psychological and emotional status. All participants underwent Holter blood pressure (BP) monitoring at baseline and 6 and 18 months after the start of the treatment.
Results. Our variant of antihypertensive therapy was clinically effective and associated with normalised BP parameters, decreased levels of state and trait anxiety, and reduced number of hospital admissions due to the main disease and comorbidities.
Conclusion. Adding Afobazole to the long-term complex treatment of AH patients facilitates stable positive dynamics of BP parameters, normalisation of psychological characteristics, increased duration (up to 6–12 months) of clinical stability periods, and a halved number of hospital readmissions over the following 1,5 years.

Russ J Cardiol 2014, 2 (106): 89-95

Key words: arterial hypertension, psychological features, treatment, Afobazole.

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MODERN POTENTIAL IN THE TREATMENT OF METABOLIC SYNDROME PATIENTS — FOCUS ON ENDOTHELIUM

Mychka V. B.[1], Tolstov S. N.[2], Salov I. A.[2], Prokhorova Yu.V.[1], Uzueva E. I.[1], Vertkin A. L.[1]

Abstract
Numerous publications on the use of β-blockers in patients with arterial hypertension (AH) and metabolic syndrome (MS) have reported adverse effects of these medications on carbohydrate and lipid metabolism, as well as reduced cerebral perfusion. This review presents the benefits of a third-generation β-blocker — nebivolol (NebiletR) — in the treatment of MS patients. The authors refer to their own findings that demonstrate effectiveness and safety of nebivolol monotherapy in individuals with AH and MS. Nebivolol treatment resulted in a sustained reduction of systolic and diastolic blood pressure levels and also improved carbohydrate and lipid metabolism parameters, which beneficially differentiates nebivolol from all other known -blockers. Nebivolol treatment did not demonstrate any negative effects on thyroid hormone levels and reduced aldosterone levels. Nebivolol-induced increase in the endothelial production of nitric oxide resulted in a significant improvement of cerebral perfusion. Moreover, nebivolol treatment was associated with a reduction in mean 24-hour QT interval duration, which was increased at baseline. These findings suggest a beneficial effect of nebivolol on myocardial electrophysiology. Nebivolol appears to be a promising medication in the treatment of patients with MS and AH.

Russ J Cardiol 2014, 3 (107): 107-113

Key words: metabolic syndrome, arterial hypertension, nitric oxide, β-blockers, nebivolol.

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LITERATURE REVIEWS

WHETHER CONTROL OF THE HEAT RATE IN THE TREATMENT OF HYPERTENSION?

Nedogoda S.V.

Abstract
In this literature review indicates the importance of monitoring the heart rate in the selection and prescription of adequate antihypertensive therapy.

Russ J Cardiol 2014, 1 (105): 107-110

Key words: heart rate, blood pressure.

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LECTURE

QUANTITATIVE ANALYTICAL METHODS IN STRESS ECHOCARDIOGRAPHY

Bobrov A. L., Bobrov L. L.

Abstract

The paper discusses various methods of quantitative analysis used in stress echocardiography (EchoCG). For each method, its key characteristics, specifics of applications, strengths, and weaknesses are described. The emphasis is on the methods widely recommended by the professional community for routine use in stress EchoCG. The application of these methods provides an opportunity to qualitatively assess the degree of myocardial contractility and relaxation disturbances, to identify early sings of heart failure, to calculate coronary flow reserve, and to assess the status of cardiac valves.

Russ J Cardiol 2014, 2 (106): 96-103

Key words: stress echocardiography, quantitative analysis, coronary heart disease.

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DIABETES MELLITUS AND CARDIOVASCULAR COMPLICATIONS: FOCUS ON HEMOSTASIS

Petrik G. G.[1,2], Pavlishchuk S. A.[1], Kosmacheva E. D.[1,2]

Abstract
This literature preview presents modern evidence on the mechanisms of prothrombotic status development in diabetes mellitus, taking into consideration the association between metabolic disturbances, increased functional platelet activity, and hemocoagulation.

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Key words: hemostasis, coagulation, metabolic disturbances, diabetes mellitus, platelets.

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